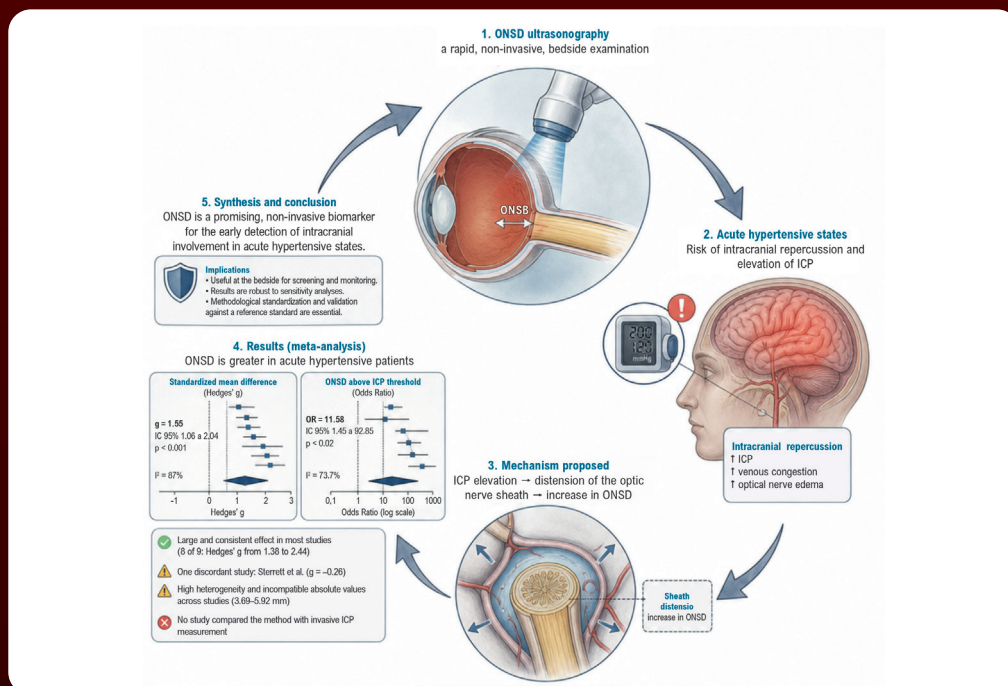




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Integrated Multiorgan Ultrasound for Assessment of Congestion in Heart Failure

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Introduction

Heart Failure (HF) is a complex clinical syndrome in which fluid overload and congestion play a central role in symptoms, hospitalization, and mortality. Traditional methods for assessing congestion, such as clinical examination and natriuretic peptide levels, often lack sensitivity and provide limited information about the distribution and severity of fluid accumulation.¹

Traditional bedside methods, such as auscultation for lung crepitations, chest radiography to detect overt pulmonary oedema, and palpation to grade pitting oedema, can help identify congestion. However, these approaches often only detect congestion after it is well established. In modern practice, echocardiography and focused ultrasound allow clinicians to identify congestion much earlier when applied systematically and evidence-based protocols. Echocardiography provides valuable information regarding Ejection Fraction (EF) and structural abnormalities that contribute to heart failure and fluid overload. Lung ultrasound, particularly the BLUE protocol with a B profile, can reveal early pulmonary congestion long before clinical signs become apparent, allowing timely intervention.^{2,3}

Beyond the lungs, targeted ultrasound of the venous system using VExUS can detect elevated venous pressures even before pitting oedema develops. This broader ultrasound-based assessment gives physicians a more sensitive and comprehensive assessment of a patient's congestive status.⁴

Integrated multiorgan ultrasound has emerged as a powerful, non-invasive tool that allows clinicians to visualise congestion across several key organs, including the lungs, heart, venous system, and kidneys. By combining findings from several ultrasound windows, this approach offers a more accurate and dynamic assessment of haemodynamic status than single-organ imaging alone. Consequently, integrated ultrasound has the potential to guide personalised therapy, optimize decongestion strategies, and reduce the risk of hospital readmission in patients with HF.

Keywords

Ultrasonography; Heart Failure; Echocardiography

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Lung Ultrasound

In heart failure, lung ultrasound enables early detection of pulmonary congestion, which presents as interstitial oedema resulting from elevated left ventricular filling pressures. Since pulmonary congestion is both a major driver of hospitalisation and a central feature of heart failure pathophysiology, lung ultrasound serves as an essential tool for diagnosis, ongoing monitoring, and therapeutic decision-making in congestive heart failure.

Patients are typically scanned across eight regions, with two anterior and two lateral zones on each side of the chest. Posterior views are generally not included unless there is a specific need to assess for pleural effusion. Positioning the probe at the level of the pleural line reveals the pleural line as a bright horizontal structure that moves with respiration, a finding known as lung sliding. Interstitial pulmonary oedema appears as bright vertical B-lines that arise from the pleural line and move in harmony with it. An increasing number of B-lines not only indicates a reduction in air content within the lung tissue but also identifies those at increased risk of subsequent heart failure readmission.^{1,5}

Cardiac Ultrasound

Transthoracic echocardiography is a cornerstone of non-invasive diagnosis and management in patients with clinical Heart Failure. Intracardiac filling pressures, chamber function, prognosis, and expected clinical outcomes can all be assessed using spectral Doppler.⁶ In addition, echocardiography enables assessment of mitral inflow patterns, mitral annular motion, and prompt identification of valvular abnormalities.⁷ It is an essential tool for classifying patients with HF into those with preserved ejection fraction (> 50%) and those with reduced ejection fraction (45-50 %), which is a critical distinction for guiding management.⁸

Systemic Venous Congestion Ultrasound

Systemic venous congestion is a defining feature of heart failure, yet it is frequently under-recognised despite its major contribution to fluid overload and its strong links with morbidity and mortality in critically ill patients. Evidence shows that excessive fluid administration can increase the risk of acute kidney injury.⁹ As venous pressures rise, the arteriovenous pressure gradient narrows, which reduces organ perfusion. Persistent elevations in capillary hydrostatic pressure, combined with endothelial barrier dysfunction, lead to interstitial oedema. Increasing systemic venous pressure further lowers organ perfusion pressure, placing encapsulated organs such as the brain and kidneys at particular risk of damage.¹⁰

Traditional haemodynamic monitoring has largely centred on maintaining adequate cardiac output and mean arterial pressure through fluid administration and the use of vasopressors or inotropes.¹¹ Although the importance of preventing, identifying, and treating congestion is increasingly recognised, the true prevalence of systemic venous congestion in ICU patients remains uncertain. Central venous pressure measurement is invasive, susceptible to error even in experienced clinicians, and carries inherent procedural risks.¹² Other approaches to assessing fluid responsiveness, including interpretation of the Frank-Starling curve, evaluation of peripheral oedema, and monitoring weight changes, have significant limitations and do not reliably reflect systemic venous pressure.¹³⁻¹⁵

The absence of a clear definition or reliable method for assessing venous congestion has posed major challenges, but several ultrasound-based parameters have now been established. Assessment of the hepatic portal pulsatility index, renal venous flow patterns, and inferior vena cava diameter allows clinicians to quantify and grade the severity of systemic venous congestion. The Venous Excess Ultrasound (VExUS) grading system applies colour Doppler and pulsed wave Doppler to visualise venous anatomy and evaluate blood flow patterns, providing a structured approach to identifying significant venous congestion.¹⁶

Preparation

With the patient lying supine, the inferior vena cava (IVC) and the hepatic, portal, and renal veins can be assessed using either a phased array transducer (2- 7.5 MHz) or a curvilinear transducer (2-5 MHz). The hepatic and portal veins are typically evaluated using standard cardiac or abdominal ultrasound approaches. Optimal imaging of the renal vessels often requires lowering the Nyquist limit by 10 to 15 cm/s and increasing the colour gain to enhance visualisation.

VExUS Protocol:

IVC Assessment

The first step in the VExUS assessment is the estimation of right atrial pressure through evaluation of the inferior vena cava (IVC) in spontaneously breathing patients. Using a subxiphoid view, the probe is positioned to obtain a long-axis image of the IVC about 2 cm below its junction with the right atrium. An IVC diameter under 2 cm usually indicates the absence of significant venous congestion and corresponds to a score of 0. In contrast, an IVC diameter greater than 2 cm suggests elevated right atrial pressure and possible venous congestion, prompting further evaluation of the hepatic veins.¹⁷

However, this method has important limitations, particularly in mechanically ventilated patients, in whom the relationship between right atrial pressure and IVC dilation is weak.¹⁸ Several additional factors can influence IVC measurements, including baseline dilation in endurance athletes, differences in body surface area that may require adjusted thresholds, and instances in which

elevated abdominal pressure leads to a small IVC despite high right atrial pressure. Taniguchi *et al.*, reported an optimal IVC cutoff of 1.7 cm for Asian patients with smaller body surface areas.¹⁹ To accurately distinguish the IVC from the abdominal aorta, clinicians should look for the aorta's bright hyperechoic wall and its characteristic pulsatile movement, which corresponds to the cardiac cycle.

Hepatic Vein Assessment

If a subxiphoid view is not attainable, a right lateral sonographic window can be used to evaluate all components of the VExUS exam, particularly the thin-walled hepatic veins draining into the IVC. The three hepatic veins (right, middle, and left) can be assessed for their Doppler flow patterns. Although any of these vessels may be used, the right and middle hepatic veins are usually the easiest to visualise. The left hepatic vein is often more difficult to assess because bowel or stomach gas may obscure the view. When the probe is positioned over a hepatic vein, colour Doppler typically displays a blue signal as blood flows away from the transducer. Pulsed-wave Doppler then reveals a waveform resembling right atrial pressure at the point where the hepatic vein enters the IVC. This waveform reflects the right heart's ability to accommodate venous return and contributes to the evaluation of venous congestion.

Hepatic vein Doppler waveforms normally show two antegrade waves: the systolic (S) wave and the diastolic (D) wave, both of which reflect changes in right atrial pressure. Under normal conditions, antegrade flow occurs twice: during ventricular systole as right atrial relaxation draws blood into the hepatic vein, and during diastole when the tricuspid valve opens. In healthy individuals, the S wave is larger than the D wave. As right atrial pressure increases, this pattern reverses, with the D wave becoming larger than the S wave, indicating mild hepatic vein abnormalities. In more advanced venous congestion, the S wave may become retrograde, signalling significant right heart dysfunction (Figure 1).

It is important to recognise that significant tricuspid regurgitation can limit the usefulness of hepatic vein Doppler assessment. Tricuspid regurgitation may cause S wave reversal even without marked venous congestion, which can lead to misinterpretation. Other conditions, such as liver cirrhosis, inferior vena cava stenosis, fatty infiltration, and hepatic lymphoma, can also blunt or distort hepatic vein waveforms, making accurate evaluation of venous congestion more difficult.⁴

Portal Vein Assessment

Placing the probe slightly upward along the right midaxillary line provides a clear view of the portal vein, which typically has a baseline velocity of about 20 cm/s. In this view, the main portal vein crosses over the IVC, while the hepatic vein drains directly into it. When colour Doppler is applied over the hyperechoic walls of the portal vein, red flow should appear, indicating blood moving toward the transducer.

In the absence of systemic venous congestion, both colour and pulsed-wave Doppler usually show minimal phasic variation or a largely monophasic waveform, as seen in Figure 2. When right atrial pressure rises, this pressure can be transmitted to the portal vein, producing portal vein pulsatility, which is a key marker of venous congestion. Pulsatility can be quantified using the Portal Vein Pulsatility Index: $((V_{\max} - V_{\min}) / V_{\max}) \times 100$, where $V_{\max}$ and $V_{\min}$ represent the maximum and minimum velocity during a cardiac cycle. Marked portal vein pulsatility indicates advanced right heart dysfunction and is associated with poor prognosis.

In lean individuals, some degree of portal vein pulsatility may occur even without raised right atrial pressure. As with hepatic vein Doppler, conditions such as cirrhosis or fatty liver can obscure or alter portal vein waveforms, potentially reducing the accuracy of congestion assessment in affected patients.

Renal Vein Assessment

The interlobar vessels are best assessed along the posterior axillary line to obtain an optimal view. The hilar veins and peripheral arcuate veins should be avoided, as they can give misleading velocity measurements that result in overestimation or underestimation. Intrarenal venous flow offers important information about the downstream impact of elevated right atrial pressure on the encapsulated

kidneys. With colour Doppler, both arterial flow in red and venous flow in blue can be visualised within the intrarenal vessels in the same imaging plane. Because these vessels are small, careful adjustment of the colour and pulsed-wave Doppler scales, along with increased gain, is essential for producing clear and reliable images. Asking the patient to briefly hold their breath can further improve visualisation.

In healthy individuals, renal interlobular venous flow appears as a monophasic waveform below the baseline on Doppler, representing blood moving away from the transducer. The arterial waveform, seen above the baseline, helps identify the phases of the cardiac cycle. As right atrial pressure rises, renal venous flow can become pulsatile, showing distinct S and D waves. In more advanced venous congestion, the S wave may reverse. However, this reversal can be obscured by the arterial waveform above the baseline, making only monophasic D waves visible (Figure 3).

Patients with congestive HF are susceptible to complications such as congestive renal failure, which contributes to the development of cardiorenal syndrome. Tricuspid regurgitation can further worsen renal congestion, resulting in a poorer long-term prognosis.⁴ Notably, Martin *et al.*, evaluated a modified version of the VExUS score that closely resembled the original but omitted the more technically challenging renal component. Their study suggested that this simplified approach may be more efficient in identifying elevated right atrial pressure.²⁰

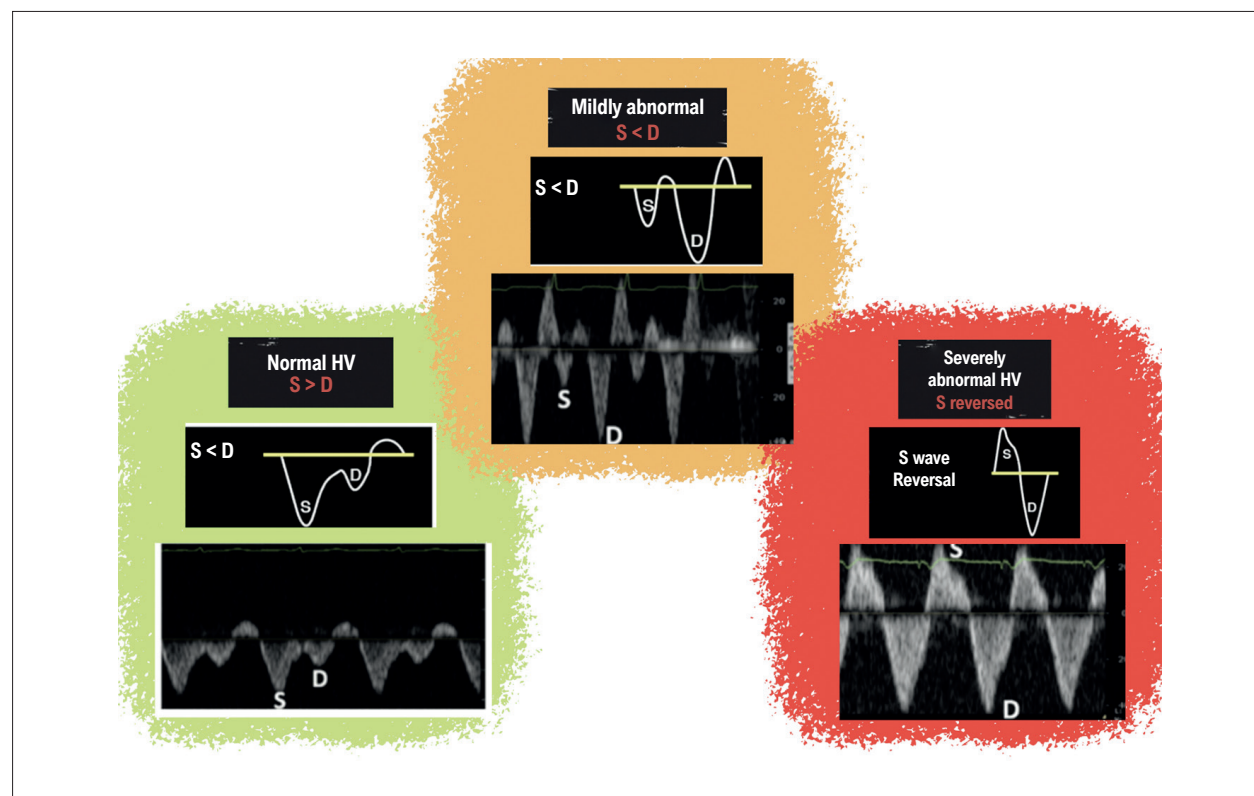


Figure 1 – Interpretation of Hepatic Vein Doppler. Created on Canva.

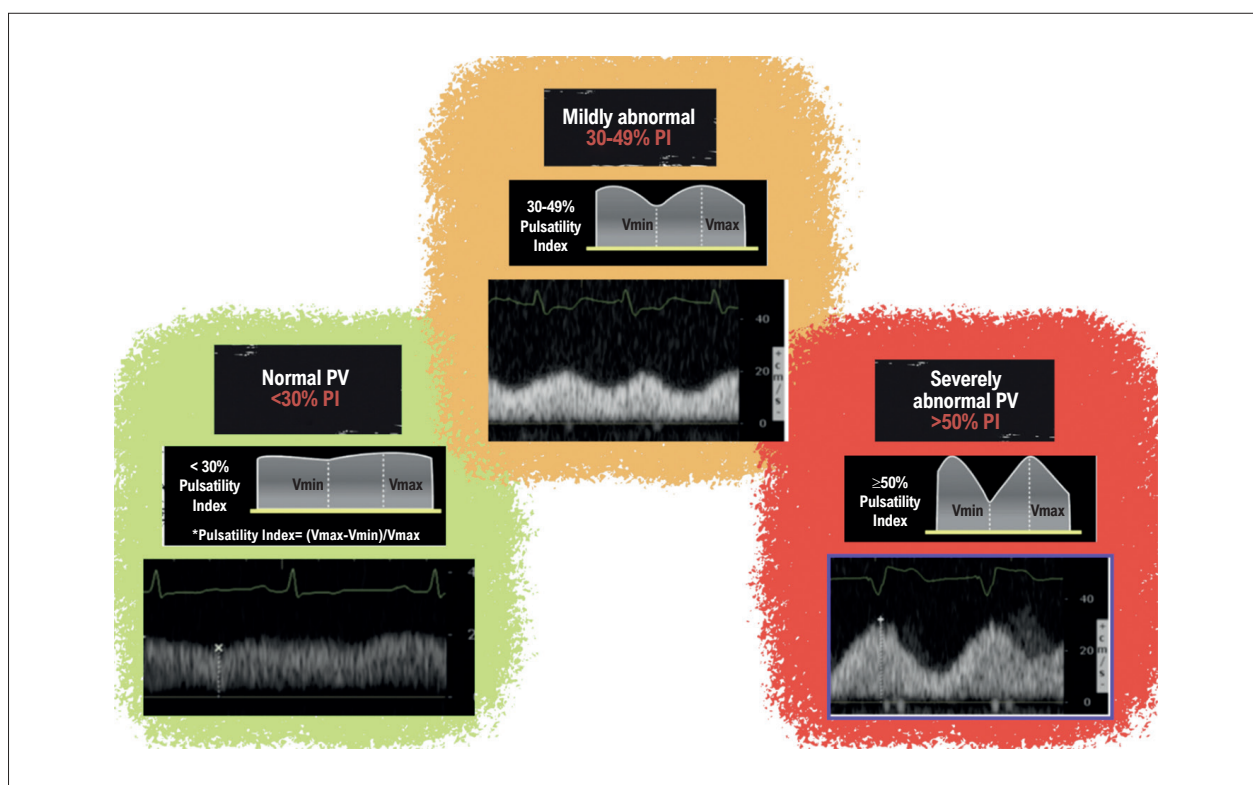


Figure 2 – Interpretation of Portal Vein Doppler. Created on Canva.

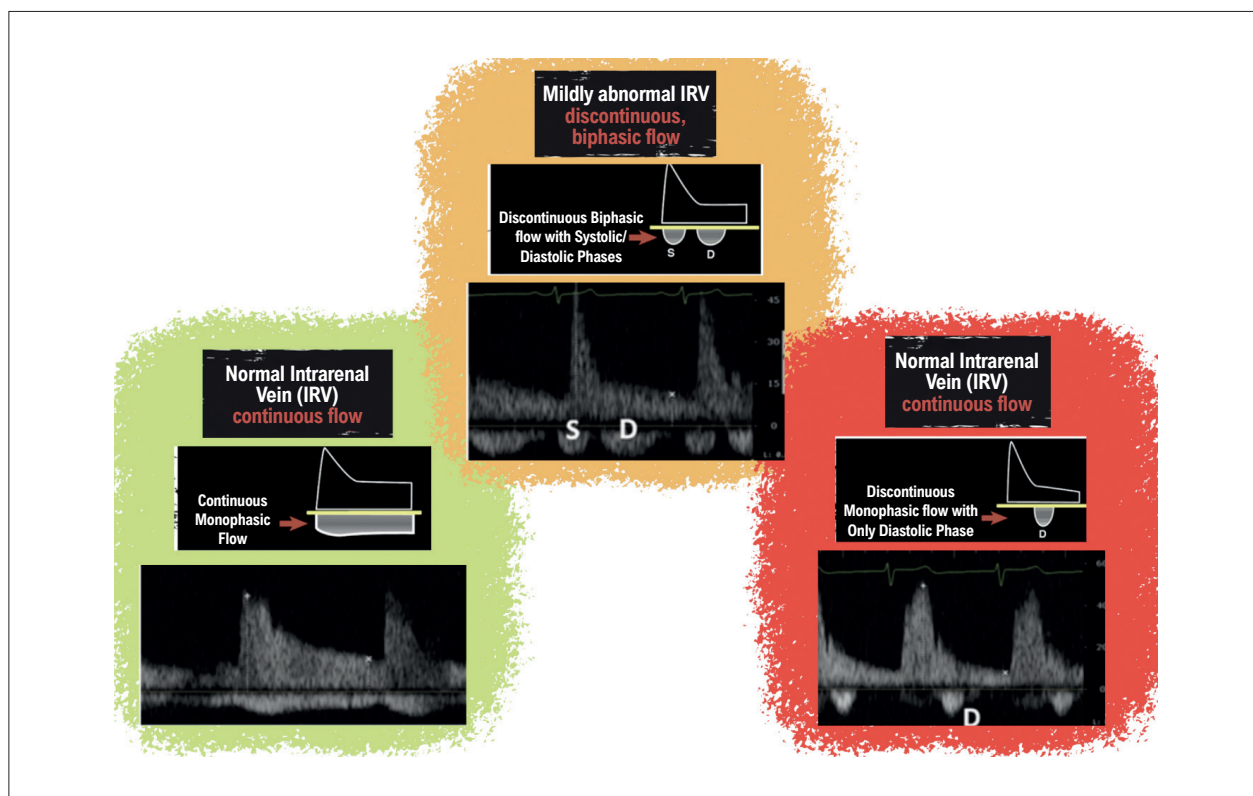


Figure 3 – Interpretation of Intrarenal Vein Doppler. Created on Canva.

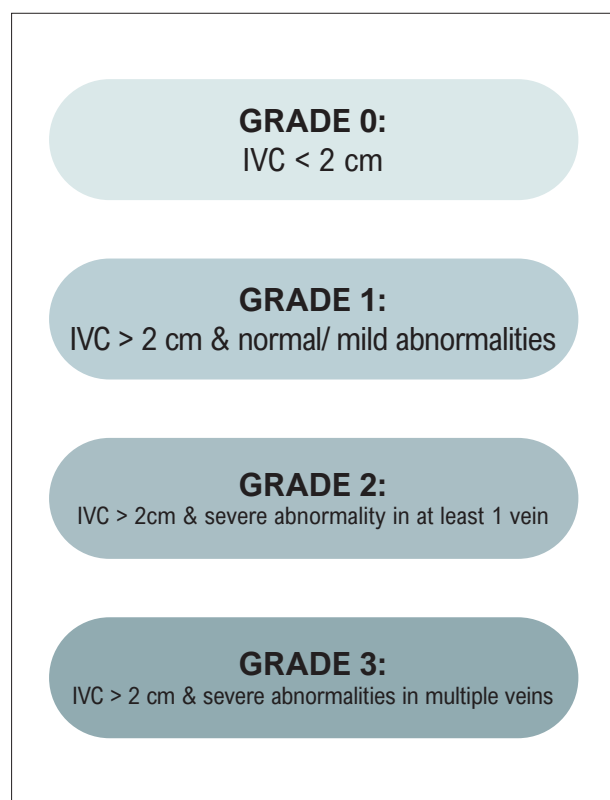


Figure 4 – VExUS Grading scores 0-3.

VExUS Score

The Venous Excess Ultrasound Score is a structured grading system used to determine the severity of systemic venous congestion through Doppler assessment of three key veins: the hepatic, portal, and intrarenal veins. Each vessel is evaluated for characteristic flow abnormalities that indicate rising levels of congestion, and the overall score ranges from Grade 0 to Grade 3 (Figure 4).

Grade 0 reflects no significant congestion, with normal Doppler patterns in all veins and an IVC diameter under 2 cm. Grade 1 represents mild congestion, defined by a dilated IVC and abnormal flow limited to the hepatic vein. Grade 2 indicates moderate congestion, with an IVC greater than 2 cm and abnormal waveforms in both the hepatic and portal veins. Grade 3 signifies severe congestion, characterised by a plethoric IVC and abnormal flow across the hepatic, portal, and intrarenal veins, consistent with marked right heart dysfunction.⁴ A higher VExUS score correlates with more advanced congestion and is associated with poorer clinical outcomes.

Conclusion

VExUS is a valuable tool for the assessment of systemic venous congestion and should be considered within the context of a comprehensive haemodynamic evaluation. As a bedside technique, it offers a practical way to identify, monitor, and assess critically ill patients with venous

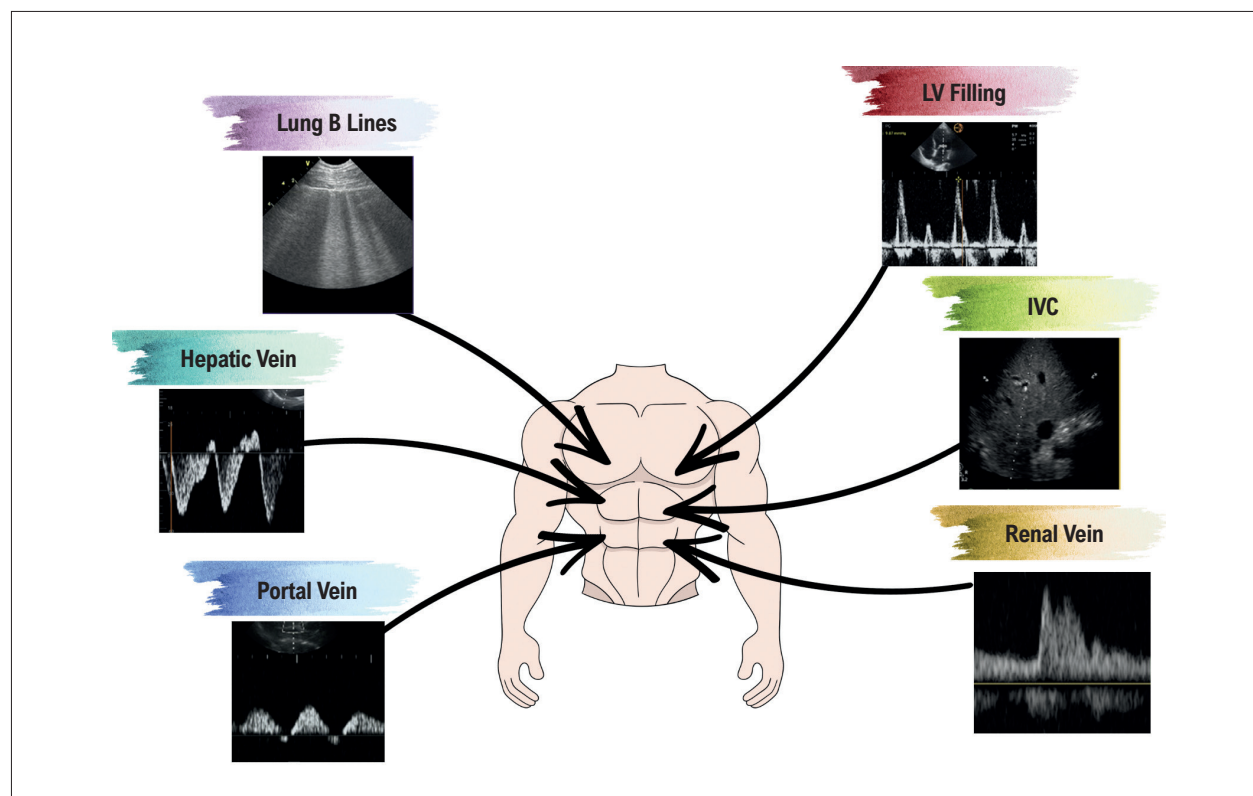


Figure 5 – Integrated multiorgan ultrasound for the assessment of congestion in heart failure.

congestion and to evaluate their response to treatment. Despite its value, VExUS has limitations. It cannot distinguish between right ventricular pressure overload and volume overload, so it should not be used as the sole guide for clinical decision-making. In addition, several conditions can alter VExUS waveforms, which may complicate interpretation.

For a complete evaluation of congestion in heart failure, VExUS should be integrated with cardiac ultrasound to assess intracardiac pressures and ventricular function, as well as lung ultrasound to detect early pulmonary oedema (Figure 5). For these reasons, a multiparametric approach is necessary for accurate assessment, diagnosis, and management.

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Right Ventricular Strain in Post-COVID Syndrome: Functional Recovery Does Not Always Mean Myocardial Recovery

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Among the various cardiovascular manifestations of post-COVID-19 syndrome, few remain as challenging as interpreting the persistent alterations in right ventricular mechanics. Although numerous studies have shown that the right ventricle is particularly susceptible to the overload imposed by the pulmonary circulation during the acute phase of infection, the clinical significance of the echocardiographic abnormalities that persist after recovery is still incompletely understood.¹

Its high sensitivity to variations in pulmonary afterload, hypoxia, vascular inflammation, and microvascular thrombosis explains the vulnerability of the right ventricle to SARS-CoV-2. This fact justifies the growing interest in the right ventricular free-wall longitudinal strain (RVFWLS), currently recognized as the most sensitive echocardiographic method for detecting subclinical impairment of right ventricular function before changes appear in conventional parameters.^{2,3}

The main merit of the present study does not lie merely in confirming the persistence of RVFWLS abnormalities after COVID-19 — a finding already described in previous investigations — but in shifting the discussion toward a conceptually more relevant question: does clinical recovery necessarily accompany the recovery of ventricular mechanics?^{4,5}

This change in perspective represents, in my view, the study's principal scientific contribution. Rather than treating strain solely as a marker of ventricular dysfunction, the authors introduce the possibility that it may represent a biomarker of myocardial recovery trajectory. This concept significantly broadens its clinical interpretation, positioning strain as a potential biomarker of the biological recovery of the right ventricle, allowing clinicians to track remodeling processes that do not necessarily manifest in the patient's clinical course.

Although previous studies have demonstrated persistent impairment of RVFWLS after COVID-19, most of them focused on describing the presence of these abnormalities. The present work goes beyond this descriptive approach by exploring the biological meaning of the persistence of altered right ventricular strain during clinical follow-up, shifting the

focus from simply identifying dysfunction to understanding myocardial recovery over time.^{4,5}

The study's results reveal an apparent dissociation between clinical evolution and the evolution of right ventricular mechanics. Despite objective improvement in functional capacity and pulmonary diffusion over approximately one year of follow-up, RVFWLS remained mildly reduced and essentially stable, while conventional parameters of right ventricular function remained preserved.

At first glance, the absence of a robust association between strain and functional recovery could suggest limited clinical utility of RVFWLS. However, this interpretation overlooks a fundamental issue: mechanical biomarkers do not necessarily follow the same timeline as clinical recovery. On the contrary, the findings suggest that functional recovery and myocardial recovery represent physiologically distinct dimensions of the cardiovascular repair process. From this perspective, the persistence of subtle RVFWLS abnormalities ceases to represent a mere residual echocardiographic finding and instead reflects a potential marker of the biological trajectory of ventricular remodeling.

In this perspective, RVFWLS may represent a persistent mechanical signature of prior cardiopulmonary injury rather than an isolated marker of the patient's current clinical status.

This interpretation is biologically plausible. Myocardial deformation likely reflects not only momentary ventricular contractility but also the structural consequences of the injury sustained during the acute phase of the disease. Remodeling of the extracellular matrix, reorganization of myocardial fibers, persistence of microvascular abnormalities, and prolonged adaptation to changes in pulmonary afterload may sustain subtle alterations in ventricular mechanics even after partial recovery of pulmonary function and functional capacity.^{1,5}

The study also reinforces a conceptual shift occurring in contemporary echocardiography. The debate is no longer about whether strain is superior to tricuspid annular plane systolic excursion (TAPSE) or fractional area change (FAC) — a question largely answered by the literature — but rather about understanding which physiological dimensions each parameter represents.^{2,3}

While TAPSE, FAC, and tricuspid annular systolic velocity reflect distinct components of ventricular function that depend on geometry and loading conditions, RVFWLS appears to capture earlier and more subtle changes in myocardial mechanics. Thus, strain should not be interpreted as a substitute for conventional parameters, but as a complementary component of a truly multiparametric assessment of right ventricular function, as emphasized by recent guidelines from the American Society of Echocardiography.^{2,3}

Keywords

Heart Ventricles; Post-Acute COVID-19 Syndrome; Echocardiography; Global Longitudinal Strain

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In other words, ventricular mechanical function and functional performance appear to represent distinct dimensions of post-COVID recovery.

From this perspective, the article significantly expands the potential role of RVFWLS. Instead of using it solely as a diagnostic or prognostic marker, it opens the possibility of employing it as a tool to monitor ventricular remodeling over time. This view brings the assessment of the right ventricle closer to the contemporary concept of ventricular reserve and right ventricle–pulmonary circulation coupling, areas that will likely represent the next major advance in functional echocardiography.²

Naturally, some limitations must be considered. The absence of pre-infection echocardiograms makes it impossible to assert that all observed alterations resulted exclusively from COVID-19, especially in a population with a high prevalence of obesity, hypertension, and diabetes. Moreover, the relatively small number of participants reduces the statistical power to detect subtle associations, and the lack of cardiopulmonary exercise testing or invasive hemodynamic assessment limits more robust pathophysiological interpretations.^{1,6}

Despite these limitations, the study offers an important conceptual contribution. It demonstrates that functional recovery may occur in parallel with the persistence of subtle

alterations in right ventricular mechanics, reinforcing that the evaluation of these patients must remain integrated and multiparametric. More than answering whether the right ventricle improves after COVID-19, the work suggests that we may be assessing distinct physiological phenomena: on one hand, the patient's clinical recovery; on the other, the structural and mechanical recovery of the myocardium.

This distinction may extend beyond the context of COVID-19 and become applicable to other conditions characterized by acute injury to the right ventricle, such as pulmonary embolism, acute respiratory distress syndrome, pulmonary hypertension, and heart failure. In this sense, the present study contributes not only to the understanding of post-COVID syndrome but also to broadening our interpretation of the true clinical meaning of right ventricular free-wall longitudinal strain.^{1,2}

The true advance of this study does not lie in demonstrating that RVFWLS remains altered after COVID-19. Its greatest merit is suggesting that ventricular mechanics follow their own timeline of recovery, partially independent of the patient's clinical evolution. This paradigm shift significantly expands the role of strain, which becomes interpreted not only as a marker of dysfunction but also as a potential biomarker of longitudinal myocardial remodeling.

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Multimodal Evaluation of Cardiac Myosin Inhibitor Response in Obstructive Hypertrophic Cardiomyopathy Using Echocardiography and Cardiopulmonary Exercise Testing: A Meta-Analysis

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Abstract

Background: Cardiac Myosin Inhibitors (CMIs), including mavacamten and aficamten, represent a novel class of targeted therapies for obstructive Hypertrophic Cardiomyopathy (oHCM). Their effects on echocardiographic parameters and cardiopulmonary performance across Randomized Controlled Trials (RCTs) have not yet been systematically synthesized.

Objectives: To conduct a systematic review and meta-analysis of RCTs in accordance with the PRISMA guidelines.

Methods: Primary echocardiographic outcomes included Left Ventricular Ejection Fraction (LVEF), Left Ventricular Mass Index (LVMI), Interventricular Septal Thickness (IVST), E/e' septal ratio, and resting, Valsalva, and post-exercise Left Ventricular Outflow Tract gradients (LVOT-G). Cardiopulmonary Exercise Testing (CPET) outcomes were also assessed. Data were pooled using random-effects models and reported as Mean Differences (MDs) or Standardized Mean Differences (SMDs), with 95% Confidence Intervals (CIs).

Results: Five RCTs comprising 767 participants were included. CMIs significantly reduced resting LVOT-G (MD: -37.59 mmHg), Valsalva gradients (MD: -46.45 mmHg), and post-exercise gradients (MD: -49.45 mmHg; all $p < 0.01$). Reverse cardiac remodeling was reflected by reductions in LVMI (MD: -11.96 g/m²), IVST (SMD: -0.98), and E/e' septal ratio (MD: -3.53), along with an expected modest reduction in LVEF (MD: -4.33%). CPET outcomes also improved significantly, including ventilatory efficiency (MD: -2.25), peak metabolic equivalents (METs) (MD: +0.45), peak circulatory power (MD: +482.78 mL/kg/min $\times$ mmHg), and exercise duration (MD: +0.88 min; all $p < 0.01$). Subgroup analyses revealed no significant differences between the agents.

Conclusion: CMIs promote reverse cardiac remodeling, improve hemodynamics, and enhance exercise tolerance in patients with oHCM, supporting their role as disease-modifying targeted therapies.

Keywords: Hypertrophic Cardiomyopathy; Echocardiography; Meta-Analysis.

Introduction

Obstructive Hypertrophic Cardiomyopathy (oHCM) is a prevalent form of hypertrophic cardiomyopathy characterized by asymmetric septal hypertrophy and dynamic Left Ventricular Outflow Tract Obstruction (LVOTO).^{1,2} This condition leads to symptoms such as exertional dyspnea, chest pain, fatigue, and syncope, often resulting in reduced functional capacity and increased morbidity.^{3,4}

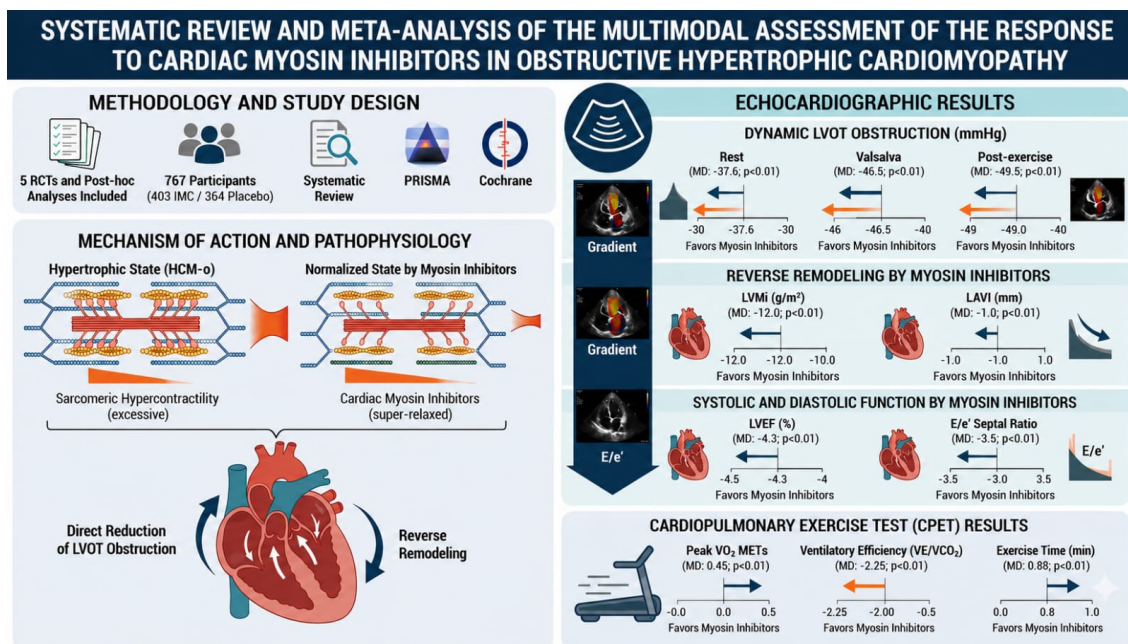
Traditional pharmacological therapies — including beta-blockers, calcium channel blockers, and disopyramide — aim

to alleviate symptoms by reducing contractility and LVOTO. However, their effects on disease progression and structural remodeling remain limited. Recently, Cardiac Myosin Inhibitors (CMIs), including mavacamten and aficamten, have emerged as targeted therapies capable of directly modulating sarcomeric function.^{5–7} Early clinical trials suggest that these agents improve hemodynamic parameters, relieve LVOT obstruction, and favorably affect cardiac structure and exercise capacity.

Cardiopulmonary exercise testing (CPET) plays a central role in assessing functional capacity in patients with oHCM by providing objective measures such as peak oxygen consumption (VO₂peak) and ventilatory efficiency, both of which closely correlate with symptom burden and exercise tolerance.^{8,9} Similarly, echocardiographic parameters — including septal thickness, left atrial volume, and LVEF — serve as key indicators of myocardial structure and function.^{10,11} Although early studies suggest that CMIs improve these parameters, the magnitude and consistency of these effects across randomized clinical trials remain to be fully established.^{12–14}

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Central Illustration: Multimodal Evaluation of Cardiac Myosin Inhibitor Response in Obstructive Hypertrophic Cardiomyopathy Using Echocardiography and Cardiopulmonary Exercise Testing: A Meta-Analysis A Meta-Analysis

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RCTs: Randomized Clinical Trials; CMIs: Cardiac Myosin Inhibitors; CPET: Cardiopulmonary Exercise Testing; oHCM: Obstructive Hypertrophic Cardiomyopathy.

This systematic review and meta-analysis aimed to synthesize evidence from randomized controlled trials (RCTs) evaluating the effects of CMIs on echocardiographic markers of left ventricular structure and function, as well as CPET outcomes, in patients with oHCM.

Methods

Protocol and Registration

This systematic review and meta-analysis was conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions and followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.^{15,16} The study protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD420251078060.

Eligibility Criteria

We included RCTs and pre-specified or clearly identified post hoc analyses derived from RCTs that evaluated the effects of CMIs compared with placebo on CPET outcomes and left ventricular structure and function in patients with oHCM. No restrictions were applied regarding publication date, language, or geographic location. Studies were excluded if they contained incomplete or unavailable data, were conference abstracts, letters, expert

opinions, case reports, review articles, duplicate publications, studies involving untreated patients, or animal studies.

Search Strategy and Study Selection

A systematic literature search was conducted in May 2025 using Cochrane CENTRAL, PubMed, and Embase. The search strategy included terms related to CMIs and oHCM (detailed in Supplementary Table 1). Study selection was performed in two stages using Rayyan. Titles and abstracts were screened first, followed by full-text assessment of potentially eligible studies. Both stages were conducted independently by two reviewers, with disagreements resolved by consensus or by consultation with a third reviewer.

Outcomes

CPET outcomes included ventilatory efficiency (minute ventilation [VE]/carbon dioxide output [VCO₂] slope during exercise), peak circulatory power (peak VO₂ × peak systolic blood pressure), peak metabolic equivalents (METs), and exercise duration. Left ventricular structure and function outcomes included changes from baseline in resting, Valsalva, and post-exercise left ventricular outflow tract gradients (LVOT-G), left ventricular ejection fraction (LVEF), left ventricular mass index (LVMi), interventricular septal thickness (IVST), and E/e' septal ratio. Subgroup analyses stratified according to study drug (mavacamten or aficamten) were performed whenever feasible.

Two investigators independently extracted the data into Microsoft Excel spreadsheets, followed by cross-checking of the extracted information.

Quality and Risk of Bias Assessment

The risk of bias of the included RCTs and eligible post hoc analyses derived from these trials was assessed using the Cochrane Risk of Bias 2.0 (RoB 2) tool for the specific outcomes of interest.¹⁷ For post hoc analyses, particular attention was paid to the pre-specification of outcomes and the potential for selective outcome reporting. Disagreements between reviewers were resolved through discussion or, when necessary, by consultation with a third reviewer. Given the limited number of included studies, publication bias was not formally assessed.

Statistical Analysis

Continuous outcomes were analyzed using Mean Differences (MDs) with corresponding 95% confidence intervals (CIs). Heterogeneity was assessed using restricted maximum likelihood (REML) estimation and the I^2 statistic, with $p < 0.05$ or $I^2 > 50\%$ considered indicative of substantial heterogeneity. Pooled analyses were performed using both the inverse-variance common-effect model and the DerSimonian–Laird random-effects model, with statistical significance defined as $p < 0.05$. Forest plots were generated to illustrate individual study estimates and pooled effect sizes. Meta-analyses were performed using RStudio (version 2023.12.1+402) and the meta package for data synthesis and visualization.

Results

Search Results

A total of 1,448 records were identified through database searching. After screening and eligibility assessment, five RCTs met the inclusion criteria, and their post hoc analyses were incorporated into the meta-analysis (Figure 1).^{18–27}

Study and Participant Characteristics

The included studies comprised a total of 767 participants, with 403 assigned to the CMI group and 364 to the placebo group (Central Illustration). All trials were published between 2020 and 2024, and their main characteristics are summarized in Table 1.

LVEF

LVEF was significantly reduced with CMIs (MD: -4.33%; 95% CI: -5.33 to -3.33; $p < 0.01$; $I^2 = 0\%$), as shown in Figure 2A. Aficamten was associated with a slightly greater reduction (-5.00; 95% CI: -6.50 to -3.50) than mavacamten (-3.80; 95% CI: -5.14 to -2.47), although the subgroup difference was not statistically significant ($p = 0.24$).

LVMI

A significant reduction in LVMI was observed in patients treated with CMIs compared with placebo (MD: -11.96 g/m²; 95% CI: -17.72 to -6.19; $p < 0.01$; $I^2 = 68.1\%$; Figure 2B). Subgroup analysis showed similar effects for aficamten (MD: -12.20; 95% CI:

-17.95 to -6.45) and mavacamten (MD: -11.49; 95% CI: -21.56 to -1.42), with no significant difference between groups ($p = 0.90$).

IVST

CMIs were associated with a moderate reduction in IVST (SMD: -0.98; 95% CI: -1.51 to -0.46; $p < 0.01$; $I^2 = 48.3\%$; Figure 3A). Aficamten (SMD: -1.00; 95% CI: -1.65 to -0.35) and mavacamten (SMD: -0.85; 95% CI: -1.91 to 0.22) showed no significant subgroup differences ($p = 0.81$).

E/e' Septal Ratio

A significant reduction in the E/e' septal ratio was observed (MD: -3.53; 95% CI: -4.35 to -2.71; $p < 0.01$; $I^2 = 0\%$; Figure 3B). Aficamten (-3.60; 95% CI: -4.75 to -2.45) and mavacamten (-3.45; 95% CI: -4.62 to -2.28) yielded comparable results ($p = 0.86$).

Resting LVOT-G

CMIs significantly reduced resting LVOT-G (MD: -37.59 mm Hg; 95% CI: -47.35 to -27.83; $p < 0.01$; $I^2 = 62.9\%$; Figure 4A). Sensitivity analysis (Supplementary Figure 1) confirmed the robustness of this finding, with pooled MDs ranging from -35.10 to -39.83 mm Hg across all leave-one-out iterations. Heterogeneity varied from low to moderate ($I^2 = 23.5\%$ to 71.1%), indicating that no individual study disproportionately influenced the overall effect estimate.

Valsalva LVOT-G

CMIs were associated with a significant pooled reduction in Valsalva LVOT-G (MD: -46.45 mm Hg; 95% CI: -60.86 to -32.05; $p < 0.01$; $I^2 = 76.6\%$; Figure 4B). Aficamten reduced the gradient by -40.05 mm Hg (95% CI: -60.79 to -19.31), whereas mavacamten reduced it by -51.83 mm Hg (95% CI: -75.49 to -28.17), with no significant difference between subgroups ($p = 0.46$). Leave-one-out analysis confirmed the robustness of the findings (Supplementary Figure 2), with pooled effect estimates ranging from -41.39 to -50.43 mm Hg. Heterogeneity remained moderate to high ($I^2 = 50.3\%$ to 83.4%) across all iterations.

Post-Exercise LVOT-G

CMIs were associated with significantly lower post-exercise LVOT-G (MD: -49.45 mm Hg; 95% CI: -74.93 to -23.98; $p < 0.01$; $I^2 = 84.6\%$; Figure 4C). Leave-one-out analysis confirmed the robustness of these findings (Supplementary Figure 3), with pooled effect estimates ranging from -56.99 to -37.10 mm Hg. Heterogeneity decreased substantially ($I^2 = 0\%$) after exclusion of the EXPLORER-CN study.

Ventilatory Efficiency

CMIs significantly improved ventilatory efficiency compared with placebo (MD: -2.25; 95% CI: -2.87 to -1.63; $p < 0.01$; $I^2 = 0\%$), as shown in Figure 5A.

Peak Circulatory Power

CMIs significantly increased peak circulatory power (MD: 482.78 mL/kg/min $\times$ mm Hg; 95% CI: 274.05 to 691.51; $p < 0.01$; $I^2 = 47.7\%$; Figure 5B).

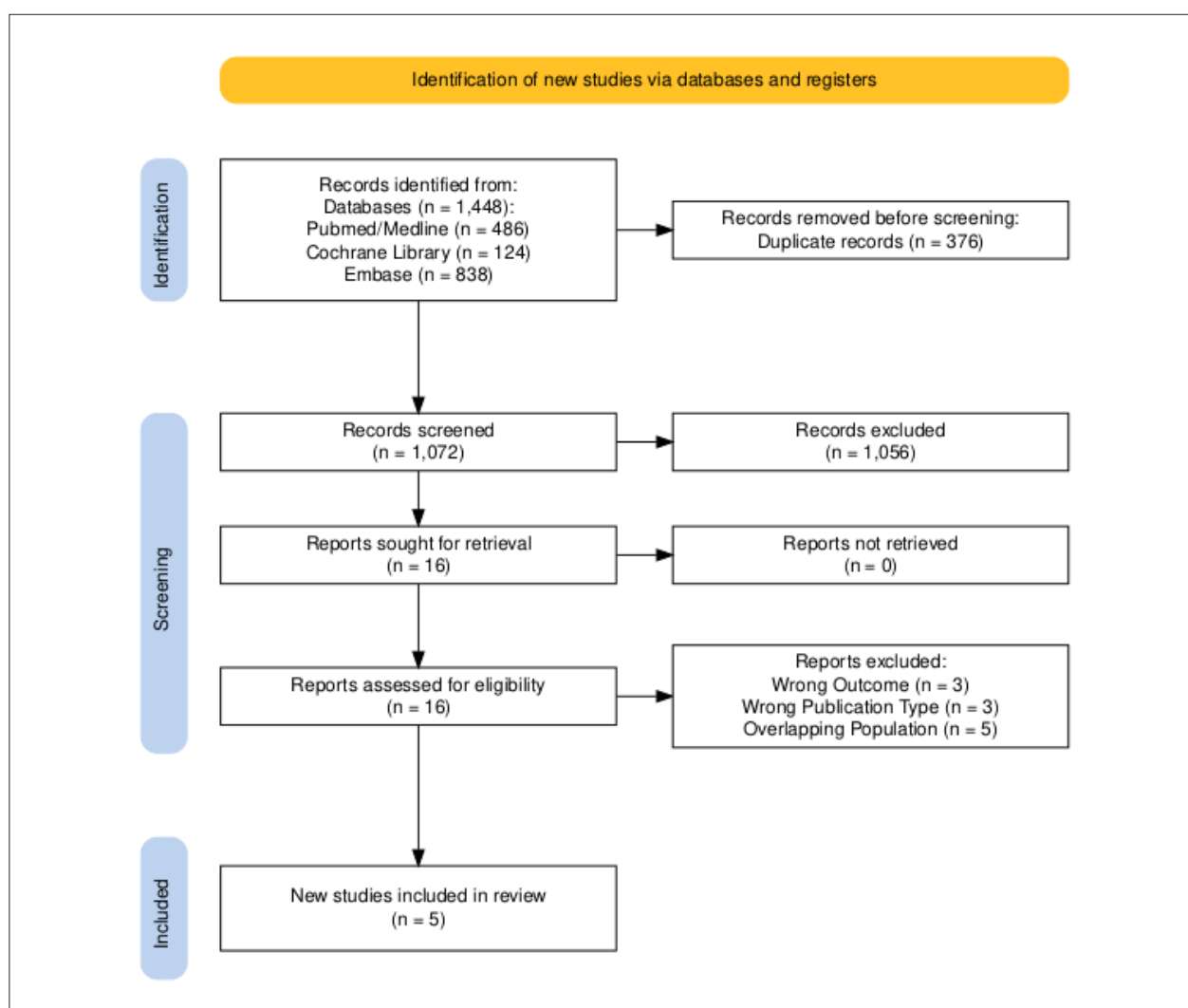


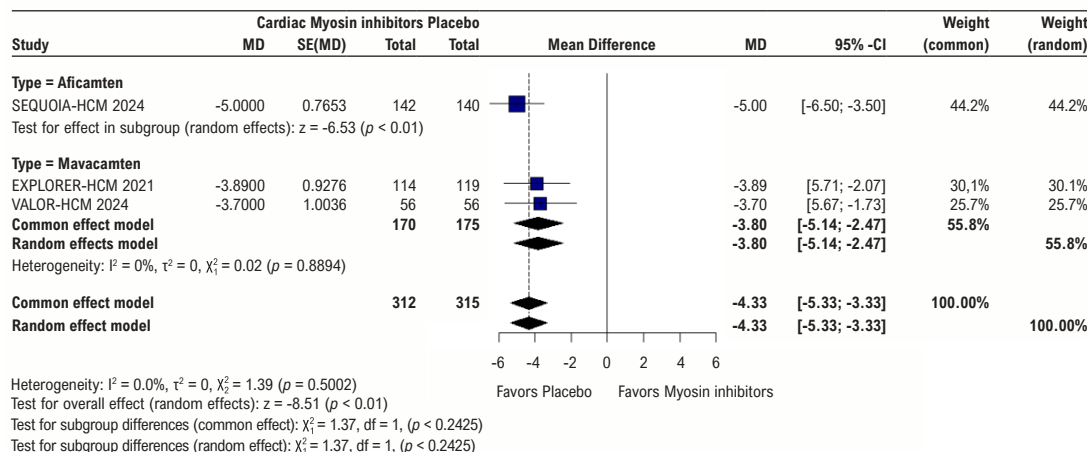
Figure 1 – PRISMA flow diagram of the systematic review and meta-analysis.

Tabela 1 – Características dos estudos incluídos e dados demográficos basais

Study	Number of Participants		Males, %		Age, years [†]		NYHA functional class II vs III, %		LVEF, % [†]		LVOT-G at rest, mm Hg [†]	
	CMI	Placebo	CMI	Placebo	CMI	Placebo	CMI	Placebo	CMI	Placebo	CMI	Placebo
EXPLORER-HCM	123	128	54	65	58.5	58.5	72 vs 28	74 vs 26	74	74	52	51
EXPLORER-CN	54	27	75.9	63.0	52.4	51.0	82 vs 18	67 vs 33	77.8	77.0	–	–
VALOR-HCM	56	56	51.8	50.0	59.8	60.9	7 vs 93	7 vs 93	67.9	68.3	51.2	46.3
REDWOOD-HCM	28	13	46	38	57	59	61 vs 39	85 vs 15	70 ^{††}	75 ^{††}	53 ^{††}	71 ^{††}
SEQUOIA-HCM	142	140	60.6	57.9	59.2	59.0	76 vs 24	76 vs 24	74.8	74.8	54.8	55.3

[†]Mean; ^{††}Median; CMI: Cardiac myosin inhibitor; LVEF: Left ventricular ejection fraction; NYHA: New York Heart Association; LVOT-G: left ventricular outflow tract gradient.

A) Left Ventricular Ejection Fraction



B) Left Ventricular Mass Index

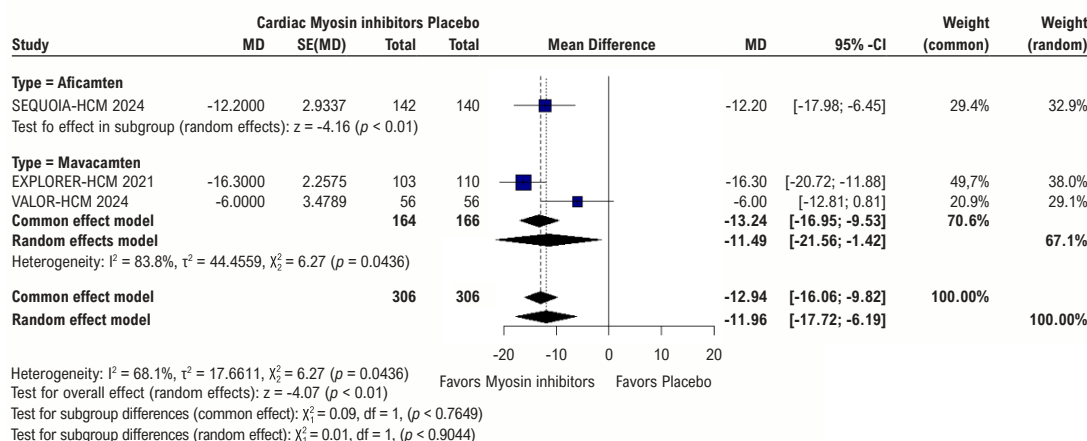


Figure 2 – Meta-Analysis of Left Ventricular Structural Outcomes. Results of the meta-analysis for (A) LVEF and (B) LVMI, comparing CMIs (aficamten and mavacamten) with placebo. Boxes are proportional to the weight of each study, and horizontal lines represent the corresponding 95% CIs. Diamonds represent the pooled MDs for each subgroup and the overall analysis, with diamond width corresponding to the 95% CI. Values to the left of the vertical line of no effect indicate reductions in these parameters, favoring treatment with CMIs. SE: Standard Error; MD: Mean Differences; CI: confidence intervals.

Peak METs

CMIs significantly increased peak METs (MD: 0.45 METs; 95% CI: 0.30 to 0.60; $p < 0.01$; $I^2 = 0\%$; Figure 5C).

Exercise Duration

Exercise duration was significantly longer in patients treated with CMIs (MD: 0.88 min; 95% CI: 0.53 to 1.24; $p < 0.01$; $I^2 = 0\%$; Figure 5D).

Risk of Bias Assessment

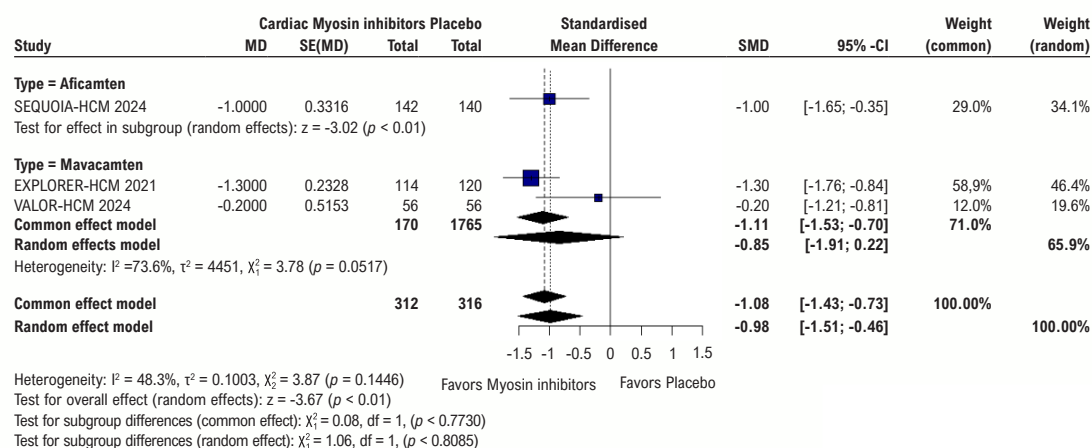
All included studies were judged to be at low risk of bias across all five domains assessed. Accordingly, the overall risk of bias was

considered low for all studies. A detailed visual summary of the risk-of-bias assessment is provided in Supplementary Figure 4.

Discussion

This meta-analysis synthesizes high-quality evidence from RCTs demonstrating that CMIs — namely mavacamten and aficamten — significantly improve cardiopulmonary performance and cardiac structural parameters in patients with oHCM. These findings support the disease-modifying potential of CMIs by directly targeting sarcomeric hypercontractility, a central pathophysiological mechanism in hypertrophic cardiomyopathy, rather than relying solely on negative chronotropic or vasodilatory effects.

A) Interventricular Wall Thickness



B) E/e' Septal Ratio

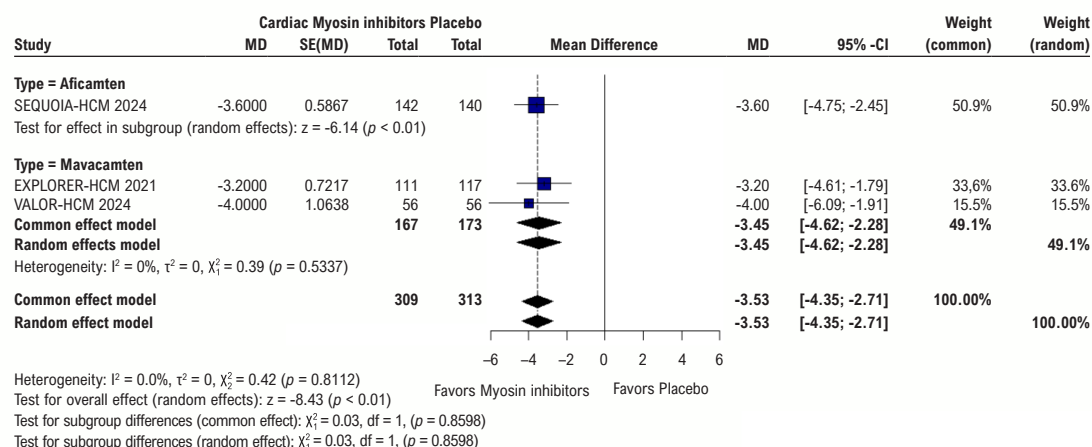


Figure 3 – Meta-Analysis of Interventricular Septal Structural Outcomes. Results of the meta-analysis for (A) IVST and (B) E/e' septal ratio, comparing CMIs (aficamten and mavacamten) with placebo. Values to the left of the vertical line of no effect indicate reductions in IVST and E/e' septal ratio, favoring treatment with CMIs. SMD: Standardized Mean Differences; MD: Mean Differences; CI: confidence intervals; HCM: Hypertrophic Cardiomyopathy; SE: Standard Error.

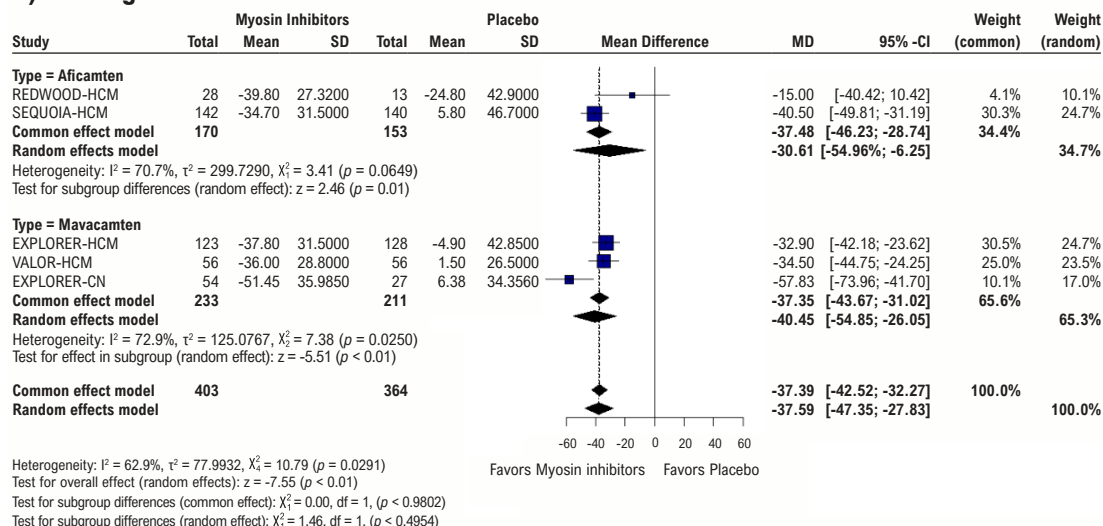
The molecular basis of oHCM is primarily driven by pathogenic sarcomeric variants — most commonly involving MYH7 and MYBPC3 — that increase the proportion of myosin heads in the Disordered Relaxed (DRX) state, leading to excessive actin–myosin cross-bridge cycling, increased myocardial ATPase activity, and augmented contractile force even at submaximal calcium concentrations.^{28,29} This hypercontractile phenotype contributes not only to resting and provoked LVOT-G but also to chronically increased wall stress, myocyte disarray, and maladaptive hypertrophic remodeling, particularly involving the basal interventricular septum.^{1,30}

CMIs bind allosterically to the catalytic domain of β -cardiac myosin, reducing the availability of myosin heads in the DRX state

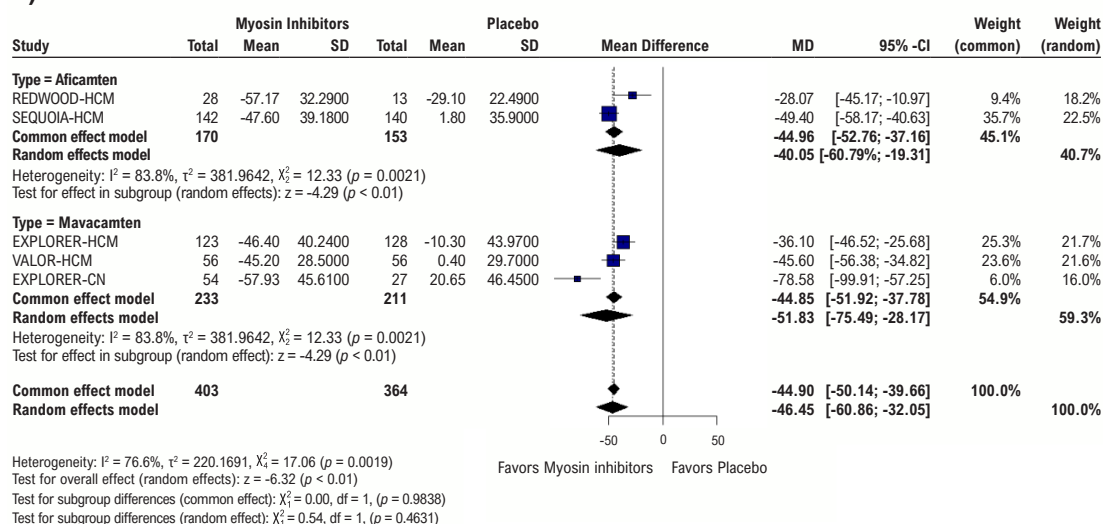
while promoting the super-relaxed state.^{31,32} This mechanism stabilizes sarcomeric energetics and directly attenuates contractile force without affecting calcium cycling.³³ Unlike conventional therapies, such as β -blockers and disopyramide, which reduce contractility indirectly through adrenergic or ionotropic modulation and may compromise systemic hemodynamics, CMIs act directly on the underlying molecular mechanism of disease.^{34,35}

The marked reductions in LVOT-G observed at rest, during the Valsalva maneuver, and after exercise demonstrate effective attenuation of the dynamic obstruction responsible for the hemodynamic burden of oHCM. The magnitude of gradient reduction (e.g., -37.6 mm Hg at rest and -46.5 mm Hg during the Valsalva maneuver) is comparable to that reported following

A) Resting Left Ventricular Outflow Tract Gradient



B) Valsalva Left Ventricular Outflow Tract Gradient



C) Post-exercise Left Ventricular Outflow Tract Gradient

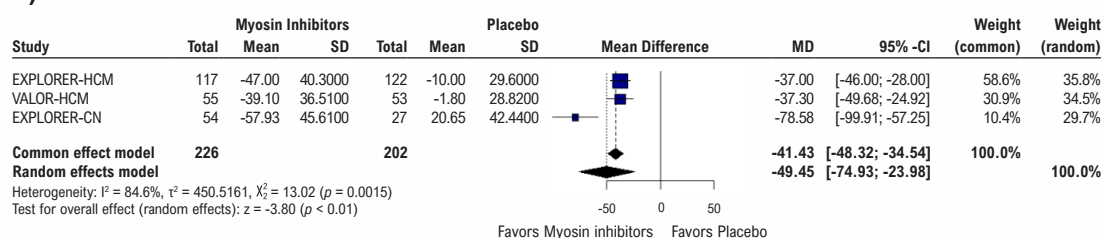


Figure 4–Meta-Analysis of LVOT-G Outcomes. Results of the meta-analysis for (A) resting LVOT-G, (B) Valsalva LVOT-G, and (C) post-exercise LVOT-G, comparing CMIs (aficamten and mavacamten) with placebo. Values to the left of the vertical line of no effect indicate lower LVOT-Gs, favoring treatment with CMIs. MD: Mean Differences; CI: confidence intervals; HCM: Hypertrophic Cardiomyopathy; SE: Standard Error.

septal reduction therapy. Furthermore, the consistency of these effects across different physiological conditions suggests sufficient suppression of basal hypercontractility to mitigate both resting and provokable gradients.^{36,37}

Importantly, this gradient reduction translates into enhanced exercise capacity. Peak METs, peak circulatory power, and exercise duration all improved significantly following CMI therapy, with minimal between-study heterogeneity. These CPET parameters reflect integrated cardiovascular performance, encompassing preload reserve, myocardial contractile reserve, chronotropic competence, and peripheral oxygen utilization.²⁵ Likewise, the improvement in ventilatory efficiency—a surrogate marker of pulmonary vascular coupling and left-sided filling pressures—suggests favorable effects on diastolic function and pulmonary vascular compliance.^{38–40}

Beyond their hemodynamic effects, CMIs produced statistically and clinically significant reductions in IVST and LVMI, reinforcing their capacity to promote reverse cardiac remodeling.⁴¹ The reduction in septal thickness supports true structural regression rather than merely transient functional unloading. These structural changes were accompanied by improvements in diastolic function, as evidenced by lower E/e' septal ratios, an echocardiographic marker of reduced left ventricular filling pressures and improved ventricular compliance.⁴² Given the well-established association between elevated filling pressures and symptom burden in oHCM, these findings indicate that CMIs favorably affect both the mechanical and diastolic components of the disease.⁴³

The modest reduction in LVEF observed with CMI therapy should be interpreted within the appropriate clinical context. Patients with oHCM frequently exhibit supranormal ejection fractions (> 70%), reflecting hypercontractile systolic mechanics rather than increased forward cardiac output.⁴⁴ CMIs normalize sarcomeric force generation, reducing LVEF toward the physiological range while preserving stroke volume. Importantly, none of the included studies reported reductions in LVEF below the pathological threshold (< 50%), indicating that this decrease reflects the intended pharmacological effect rather than myocardial dysfunction.⁴⁵ Although aficamten was associated with a slightly greater reduction in LVEF than mavacamten, this difference may be explained by its faster onset of action, shorter half-life (approximately 3 vs. 7 days), and lower interindividual pharmacokinetic variability.⁴⁶

Subgroup analyses revealed no significant differences between mavacamten and aficamten across structural and functional outcomes, suggesting a class effect attributable to their shared sarcomeric mechanism of action. Nevertheless, pharmacokinetic differences may influence clinical implementation, particularly with respect to dose titration, echocardiographic monitoring of LVEF, and potential drug–drug interactions.^{47,48} Heterogeneity was low to moderate across most analyses. The greater variability observed for Valsalva and post-exercise LVOT-G likely reflects differences in provocation protocols and baseline gradient severity among the included studies. Leave-one-out analyses confirmed the robustness of the pooled estimates, further supporting the internal validity of the findings.

Collectively, these findings reinforce the role of CMIs as upstream modulators of oHCM pathophysiology, offering a

pharmacological alternative to septal reduction therapy for patients with persistent gradients and symptomatic limitation despite guideline-directed medical therapy.^{49,50} Given their favorable effects on cardiac structure, function, and symptoms, CMIs may also hold promise as preventive therapy in genotype-positive individuals at high risk or in patients with early phenotypic expression, although this hypothesis remains investigational.⁵¹ In addition, CMIs may represent an attractive therapeutic option for patients who are ineligible for or unwilling to undergo septal myectomy or alcohol septal ablation.⁵² Nevertheless, because of the potential for excessive LVEF reduction, careful echocardiographic monitoring remains essential during dose titration.

Several limitations should be acknowledged. First, the number of included RCTs was relatively small, and follow-up periods were short, precluding conclusions regarding long-term outcomes such as heart failure progression, atrial fibrillation, or sudden cardiac death. Second, most studies excluded patients with advanced NYHA functional class, mid-ventricular obstruction, or apical variants, limiting the generalizability of these findings. Future studies should evaluate myocardial fibrosis and extracellular volume, incorporate genotype-stratified analyses, and investigate synergistic therapeutic strategies, including combinations of CMIs with RAAS inhibitors or antifibrotic agents. Finally, long-term registries will be essential to establish the long-term safety, cost-effectiveness, and durability of treatment response.

Conclusion

CMIs significantly improve functional capacity and promote favorable cardiac remodeling in patients with oHCM by directly targeting sarcomeric hypercontractility, the central mechanism underlying LVOTO and myocardial hypertrophy. This meta-analysis demonstrates that mavacamten and aficamten reduce LVOT-G, improve diastolic function, and enhance exercise capacity, with consistent effects across both agents. These findings support the incorporation of CMIs as disease-modifying therapy for oHCM, although additional studies are warranted to establish their long-term clinical benefits and broader applicability.

Author Contributions

Conception and design of the research, acquisition of data, and statistical analysis: Ramos JVO; analysis and interpretation of the data: Ramos JVO, Fernandes JVA; writing of the manuscript: Ramos JVO, Fernandes JVA, Fernandes LHC, Figueiredo VLFA, Estrela JVO; critical revision of the manuscript for intellectual content: Ramos JVO, Fernandes JVA, Fernandes LHC, Figueiredo VLFA, Estrela JVO, Tavares M; project administration and supervision: Tavares M.

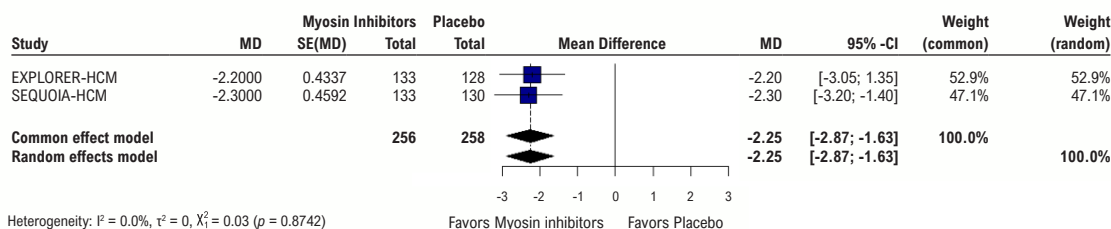
Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

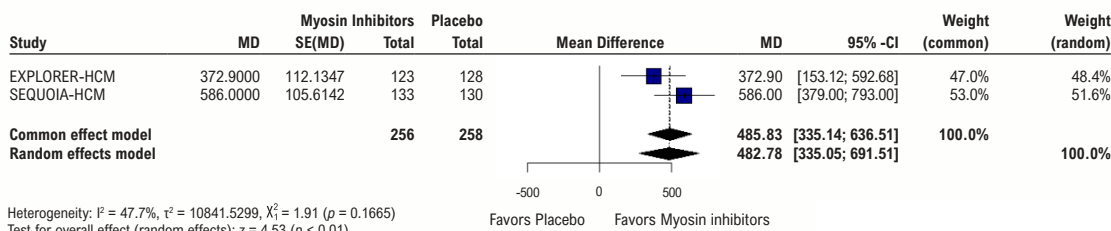
Sources of Funding

There were no external funding sources for this study.

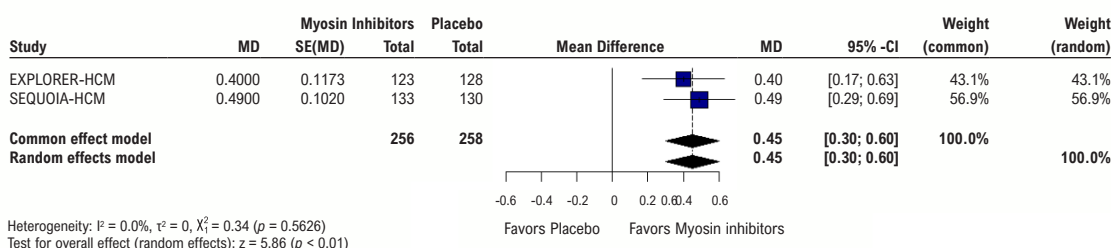
A) Ventilatory Efficiency



B) Peak Circulatory Power



C) Peak Metabolic Equivalents



D) Exercise time

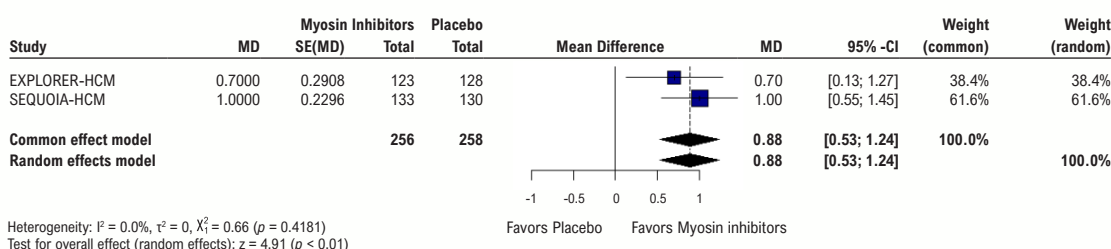


Figure 5 – Meta-Analysis of CPET Outcomes. Results of the meta-analysis for (A) ventilatory efficiency, (B) peak circulatory power, (C) peak METs, and (D) exercise duration, comparing CMIs with placebo. MD: Mean Differences; CI: confidence intervals; HCM: Hypertrophic Cardiomyopathy; SE: Standard Error.

Study Association

This study is not associated with any thesis or dissertation work.

Ethics Approval and Consent to Participate

This article does not contain any studies with human participants or animals performed by any of the authors.

Use of Artificial Intelligence

The authors did not use any artificial intelligence tools in the development of this work.

Availability of Research Data

The underlying content of the research is contained within the manuscript.

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*Supplemental Materials

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Correlating Invasive and Echocardiographic Hemodynamic Measures in Patients with Heart Failure with Reduced Ejection Fraction

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Abstract

Background: The management of heart failure with reduced ejection fraction (HFrEF) has advanced with the use of invasive hemodynamic markers such as cardiac power output (CPO) and pulmonary artery pulsatility index (PAPI). Simultaneously, interest has grown in noninvasive prognostic indicators, especially the left ventricular outflow tract velocity–time integral (LVOT-VTI).

Objective: This study aimed to assess the correlation between invasive and echocardiographic parameters, particularly CPO, PAPI, and LVOT-VTI, in patients with HFrEF.

Methods: This cross-sectional, single-center study included inpatients and outpatients with chronic stable or acutely decompensated HFrEF. Individuals with cardiogenic shock (CS) were excluded. Right heart catheterization (RHC) and echocardiography were performed on the same day. Statistical significance was defined as a two-sided p value < 0.05.

Results: Significant correlations were observed between invasive and echocardiographic CPO ($r = 0.737$, $p < 0.001$) and PAPI ($r = 0.604$, $p < 0.05$). LVOT-VTI showed significant correlation with CPO measured via pulmonary artery catheter (PAC) ($r = 0.469$, $p < 0.01$). Echocardiographic PAPI was measurable in only 16 patients. A sensitivity analysis of those receiving inotropes showed an even stronger correlation between invasive and echocardiographic CPO ($r = 0.812$, $p = 0.005$).

Conclusion: Echocardiographic and invasive hemodynamic parameters showed significant correlations in HFrEF, particularly CPO, supporting echocardiography as a potential alternative for hemodynamic assessment. However, the low feasibility of noninvasive PAPI measurement highlights important limitations in this population.

Keywords: Systolic Heart Failure; Hemodynamic Monitoring; Heart Rate; Echocardiography.

Introduction

Heart failure (HF) is a growing global health issue, affecting an estimated 60 million people worldwide. Advancements in cardiac care and improved patient survival have contributed to the rising prevalence of this syndrome.¹ The use of pulmonary artery catheter (PAC) for hemodynamic assessment remains a cornerstone in HF management. These invasive measurements are essential for diagnosing and optimizing treatment strategies in both chronic and decompensated HF, providing insights into disease progression and therapeutic response.^{2,3} PAC

use has increased in recent years, guided by a systematic approach that prioritizes parameters with the greatest prognostic impact, such as cardiac power output (CPO) and pulmonary artery pulsatility index (PAPI). These hemodynamic parameters have become essential tools in determining the need for mechanical circulatory support in patients with cardiogenic shock (CS).⁴ Although initially studied in CS, CPO and PAPI also have significant prognostic value in chronic and acutely decompensated heart failure with reduced ejection fraction (HFrEF).⁵⁻⁷

Research on noninvasive measures with prognostic value in patients with heart disease has also expanded, aiming to shorten evaluation time and improve safety. Among echocardiographic parameters, the left ventricular outflow tract velocity–time integral (LVOT-VTI) has demonstrated good prognostic value in observational studies.^{8,9} The LVOT-VTI is a Doppler-derived echocardiographic measurement that quantifies the distance blood travels through the LVOT during systole, serving as a key parameter in assessing stroke volume, cardiac output (CO) and overall hemodynamic status.^{10,11}

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Central Illustration: Correlating Invasive and Echocardiographic Hemodynamic Measures in Patients with Heart Failure with Reduced Ejection Fraction**Correlation between invasive and noninvasive hemodynamic assessments****34 patients with HFrEF evaluated on the same day
(inpatients and outpatients)****Echocardiography**

- eCPO
- ePAPI (feasible in 50%)
- LVOT-VTI

**RHC**

- CPO
- PAPI

Echocardiography	RHC	r
eCPO	CPO	0.73
*eCPO	CPO	0.82
ePAPI	PAPI	0.60
LVOT-VTI	CPO	0.46

Patients receiving inotropic support.*Strong correlation for CPO**

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CPO: cardiac power output; e-PAPI: echocardiography-derived pulmonary artery pulsatility index; PAPI: pulmonary artery pulsatility index; LVOT-VTI: left ventricle outflow tract velocity time integral.

The correlation between invasive and noninvasive measurements in acute decompensated HF-related CS has been recently investigated, revealing associations between CPO and PAPI measured via PAC and echocardiography.¹² Similarly, the relationship between PAC-derived and echocardiographic parameters has been explored in patients with chronic HF;^{13,14} however, these studies have not focused on parameters such as CPO, PAPI, and LVOT-VTI.

Therefore, the objective of this study was to evaluate the correlation between invasive and noninvasive measurements in inpatients and outpatients with chronic stable or decompensated HFrEF, with particular emphasis on CPO, PAPI, and LVOT-VTI. The main findings of this study are summarized in the Central Illustration.

Methods

This is a single-center cross-sectional study conducted at a university hospital in the South Region of Brazil. Participants indicated for routine evaluation by the HF team were recruited by actively searching outpatient and inpatient lists. Recruitment occurred between May 2023 and June 2024, using phone calls and direct contact with hospitalized patients. All patients were invited to undergo echocardiography before or after right heart

catheterization (RHC). The research protocol was approved by the institutional ethics committee, and written informed consent was obtained from all participants.

The study included patients aged 18 years or older with a diagnosis of HFrEF (left ventricular ejection fraction < 40%). Patients were excluded if there were technical difficulties in obtaining echocardiographic measurements or if RHC measurements could not be performed. Additionally, patients with CS, active infection, those on mechanical ventilation, or undergoing hemodialysis were excluded. Patients who received diuretics or vasodilators between the two evaluation methods were also excluded.

The study protocol involved performing a comprehensive echocardiographic assessment by two experienced echocardiographers (SVB and WRM) within the shortest possible time before or after the invasive hemodynamic evaluation using a PAC. All evaluations occurred within a six-hour interval between the two examination methods.

RHC

The invasive hemodynamic evaluation was performed using RHC with PAC inserted via micropuncture technique of the right basilic vein or the right internal jugular vein. The zero-reference

level was established at the mid-axillary line, and measurements were recorded at end-expiration. The operator performing RHC was blinded to the echocardiographic measurements.

CO was assessed using the thermodilution technique. Central venous pressure (CVP), pulmonary pressures, and pulmonary artery occlusion pressure (PAOP) were determined as the mean values over eight cardiac cycles. CPO was calculated using mean arterial pressure (MAP) according to the formula: $CPO = CO \times MAP / 451$. The PAPI was calculated as: $PAPI = (PASP - PADP) / CVP$, where PASP and PADP indicate pulmonary artery systolic pressure and pulmonary artery diastolic pressure, respectively. The remaining derived hemodynamic parameters were calculated using the formulas described in Table 1.

Echocardiography

Transthoracic echocardiography was performed by two experienced examiners (Berger SV e Menegazzo WR), blinded to the results of the RHC measurements. All examinations were performed using the Philips Epiq CVx system. To assess interobserver variability, a preliminary study was conducted in a subset of 10 patients, who were not included in the 34 patients of the study sample. The evaluation was performed by the two echocardiographers. Echocardiography was performed on the same day of the RHC, with the shortest possible interval between the two tests, and patients were required to rest for at least 10 minutes before the exam. Measurements obtained via echocardiography followed the guidelines established by the American Society of Echocardiography.¹⁰

CO was calculated using the formula: $CO = LVOT-VTI \times LVOT \text{ area} \times \text{heart rate}$. CPO was derived using the formula: $CPO = CO \times MAP / 451$, and PAPI was calculated using the formula: $PAPI = (PASP - PADP) / eRAP$ [estimated right atrial pressure], where eRAP indicates estimated right atrial pressure. CVP was estimated based on the maximum diameter of the inferior vena cava (greater or less than 2.1 cm) and its variability during inspiration (greater or less than 50%). Ejection fraction was assessed using Simpson's method. PASP, PADP, mean pulmonary artery pressure (MPAP), and other derived formulas are described in Table 2.

Statistical analysis

Table 1 – PAC-derived parameters

Parameter	Formula
CPO	$CO \times MAP / 451$
PAPI	$(PASP - PADP) / CVP$
TPG	$MPAP - PAOP$
PVR	TPG / CO

CO: cardiac output; CPO: cardiac power output; CVP: central venous pressure; MAP: mean arterial pressure; MPAP: mean pulmonary artery pressure; PADP: pulmonary artery diastolic pressure; PAOP: pulmonary artery occlusion pressure; PAPI: pulmonary artery pulsatility index; PASP: pulmonary artery systolic pressure; PVR: pulmonary vascular resistance; TPG: transpulmonary gradient.

The normality of continuous variables was assessed using histograms and the Shapiro–Wilk test. All continuous variables showed a normal distribution and were therefore expressed as mean $\pm$ standard deviation. Categorical variables were expressed as absolute and relative frequencies (n, %). Comparisons between groups were performed using the unpaired Student's t-test. For correlation analysis between invasive hemodynamic and echocardiographic measures, Pearson's correlation coefficient was used, as all continuous variables were normally distributed. Interobserver agreement was evaluated using intraclass correlation coefficient analysis, based on a two-way random-effects model, assessing consistency and average measurements. A statistical significance level of 5% ($p < 0.05$) was adopted. All statistical analyses were conducted using SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, United States).

A sample of 27 patients was required based on the correlation between LVOT-VTI and stroke volume measured by PAC of $r = 0.52$ (95%, $p < 0.01$) in a prior study,¹⁵ assuming an alpha value of 0.05 and a power of 80% to identify a similar correlation in our sample. The correlation between LVOT-VTI and CPO assessed via PAC was not utilized in the sample size calculation because such data were not available in the published literature at the time of the study design.

Results

Between May 2023 and June 2024, a total of 34 patients were included in the study. The mean age was 50.8 ± 6.2 years, 61.7% were male, and 82.4% of patients had nonischemic HF. The mean left ventricular ejection fraction was $21.1\% \pm 6.6\%$. The majority of the sample consisted of inpatients (67.4%), whereas 26.5% were receiving inotropic therapy at the time of the examinations. Table 3 provides an overview of the patient baseline characteristics and ongoing therapies.

All patients receiving inotropic support were classified as having INTERMACS III HF, as their mean serum lactate was 1.4 ± 0.2 mmol/L, and none of them were receiving vasopressor support (clinical characteristics in Supplementary Table S1).

Regarding clinical characteristics reviewed retrospectively in medical records, 24 of 34 patients underwent cardiopulmonary exercise testing, and the mean peak oxygen consumption was 15.9 ± 5.3 mL/kg/min; 9 patients (26.4%) underwent orthotopic heart transplantation, and 5 (14%) died.

PAC parameters

PAC measurements demonstrated elevated pulmonary pressures and impaired left and right ventricular hemodynamic parameters. Detailed invasive hemodynamic measurements are presented in Table 4.

Echocardiographic parameters

Echocardiography demonstrated marked left ventricular dilation and mild right ventricular enlargement, accompanied by severe biventricular systolic dysfunction. Pulmonary artery pressures were elevated, consistent with the advanced HF profile of the study population. Detailed echocardiographic structural, functional, and hemodynamic parameters are

Table 2 – Echocardiographic parameters

Parameter	Formula
CO	LVOT-VTI × LVOT area × heart rate
CPO	CO × MAP / 451
PAPI	(PASP – PADP) / eRAP
PASP	TR peak gradient + CVP
PADP	4 × (end-diastolic pulmonary regurgitation velocity) ² + CVP
MPAP	4 × (protodiastolic pulmonary regurgitation velocity) ² + CVP

CO: cardiac output; CPO: cardiac power output; CVP: central venous pressure; eRAP: estimated right atrial pressure; LVOT: left ventricular outflow tract; LVOT-VTI: left ventricular outflow tract velocity–time integral; MAP: mean arterial pressure; MPAP: mean pulmonary artery pressure; PADP: pulmonary artery diastolic pressure; PAPI: pulmonary artery pulsatility index; PASP: pulmonary artery systolic pressure; TR: tricuspid regurgitation.

Table 3 – Baseline characteristics and ongoing therapies

Parameter	Mean (SD) or Median (IQR)	n (%)
Age (years)	50.8 ± 6.2	34 (100)
Male sex (%)	61.7	34 (100)
Nonischemic HF etiology (%)		28 (82.4)
Heart rate (bpm)	78.2 ± 15.2	34 (100)
Systolic blood pressure (mmHg)	101.6 ± 17.9	34 (100)
Diastolic blood pressure (mmHg)	66.2 ± 13.2	34 (100)
MAP (mmHg)	73.4 ± 11.0	34 (100)
Weight (kg)	77.0 ± 18.9	34 (100)
Height (cm)	167.6 ± 10.6	34 (100)
Use of CRT-D (%)		3 (8.8)
ARNI (%)		10 (41.2)
ACE inhibitors/ARBs (%)		14 (38.2)
Mineralocorticoid receptor antagonists (%)		31 (91.2)
Beta-blockers (%)		31 (91.2)
Sodium-glucose cotransporter-2 inhibitors (%)		22 (64.7)
Digoxin (%)		17 (50.0)
Hydralazine plus nitrates (%)		6 (17.6)

ACE: angiotensin-converting enzyme; ARB: angiotensin II receptor blocker; ARNI: angiotensin receptor–neprilysin inhibitor; CRT-D: cardiac resynchronization therapy with defibrillator; HF: heart failure; IQR: interquartile range; SD: standard deviation; MAP: mean arterial pressure.

presented in Table 5.

Echocardiographic PAPI was successfully obtained in 16 of the 34 enrolled patients, whereas it was possible to estimate MPAP and PADP in 18 and 16 patients, respectively, owing to the absence of pulmonary regurgitation required for their calculation.

Interobserver agreement was excellent for CPO, LVOT-VTI, left ventricular ejection fraction, and E/e' ratio, whereas PAPI and fractional area change showed poor agreement (Supplementary Table S2).

Correlation between invasive and noninvasive

hemodynamic measures

This study demonstrated a correlation between the invasive and echocardiographic assessments of CPO (Figure 1). The CPO measured via PAC showed a positive correlation with CO obtained by echocardiography ($r = 0.616$, $p < 0.001$). Similarly, a positive correlation was observed between CPO measured via PAC and LVOT-VTI (Figure 2). There was also a positive correlation between CPO assessed by PAC and left ventricular ejection fraction, with a correlation coefficient of 0.365 ($p < 0.05$).

Regarding the assessment of right ventricular function,

Table 4 – PAC parameters

Measure	Mean ($\pm$ SD)	n (%)
CO (L/min)	4.2 $\pm$ 1.2	34 (100)
CI (L/min/m ²)	2.2 $\pm$ 0.5	34 (100)
PAOP (mmHg)	18.6 $\pm$ 6.2	34 (100)
CPO (W)	0.7 $\pm$ 0.2	34 (100)
PAPI	3.2 $\pm$ 1.5	34 (100)
RVSWI (mmHg-mL/m ²)	7.7 $\pm$ 2.9	34 (100)
CVP (mmHg)	7.7 $\pm$ 4.1	34 (100)
PASP (mmHg)	41.2 $\pm$ 10.3	34 (100)
MPAP (mmHg)	27.8 $\pm$ 7.7	34 (100)
PADP (mmHg)	20.8 $\pm$ 6.2	34 (100)
PVR (Wood units)	2.3 $\pm$ 1.5	34 (100)
Transpulmonary gradient (mmHg)	9.3 $\pm$ 4.7	34 (100)
CVP over PAOP	0.42 $\pm$ 0.2	34 (100)

CI: cardiac index; CO: cardiac output; CPO: cardiac power output; CVP: central venous pressure; MPAP: mean pulmonary artery pressure; PADP: pulmonary artery diastolic pressure; PAOP: pulmonary artery occlusion pressure; PAPI: pulmonary artery pulsatility index; PASP: pulmonary artery systolic pressure; PVR: pulmonary vascular resistance; RVSWI: right ventricular stroke work index; SD: standard deviation.

correlations were detected between PAPI assessed by PAC and by echocardiography (Figure 3). Furthermore, PAPI measured via PAC correlated with tricuspid annular plane systolic excursion (TAPSE), with $r = 0.553$ ($p < 0.01$), and right ventricular free wall strain, with a negative correlation coefficient of $r = -0.344$ ($p < 0.05$). Additionally, a positive correlation was observed between PAPI assessed by PAC and peak systolic velocity at the tricuspid annulus (S' wave), with a correlation coefficient of 0.356 ($p < 0.05$).

With respect to LVOT-VTI, in addition to the previously mentioned correlation with PAC-derived CPO, correlation was observed between LVOT-VTI and CO measured by PAC ($r = 0.538$, $p < 0.01$), as well as cardiac index measured by PAC ($r = 0.542$, $p < 0.01$).

Sensitivity analysis

A sensitivity analysis was conducted to evaluate the population receiving inotropic support. The correlation between invasive and echocardiographic CPO was higher in this subgroup compared to the overall population: $r = 0.812$ ($p = 0.008$). Additionally, a sensitivity analysis was also conducted in patients with CPO < 0.6 W. In this subset, the correlation between invasive and echocardiographic CPO was $r = 0.704$ ($p = 0.005$). In both groups, it was not possible to assess the correlation between invasive and echocardiographic PAPI because noninvasive PAPI measurement was feasible in only 3 of the 9 patients included in this subgroup.

Discussion

The assessment of correlations between invasive and noninvasive hemodynamic measurements aims to identify echocardiographic parameters that reliably reflect prognostically significant hemodynamic variables, such as CPO and PAPI. This approach intends to provide a more practical and safer diagnostic strategy for patients with advanced HF by minimizing the evaluation time and risks associated with invasive procedures.

As reported by Burstein et al., in a retrospective cohort study, noninvasive CPO demonstrated a prognostic role in patients admitted to cardiac intensive care units. The study analyzed nearly 5000 patients, with 50% presenting with decompensated HF. CPO below 0.89 ± 0.37 W was associated with greater hospital mortality.¹⁶ Echocardiographic PAPI also demonstrated prognostic value, being associated with 60-day mortality in acute decompensated HF-related CS (hazard ratio 2.96, 95% confidence interval 1.23–7.17, $p = 0.02$).¹² LVOT-VTI, as demonstrated by Kentzer et al. and Machado et al., also demonstrated significant prognostic value among cardiology patients, including those with HF and acute myocardial infarction.^{9,17}

In our study, regarding left ventricle function parameters, invasively measured CPO and CPO estimated by echocardiography showed the strongest correlation. This association was further enhanced in the subgroup of patients receiving inotropic support. Furthermore, CPO measured by PAC also demonstrated correlation with CO assessed through echocardiography and with the LVOT-VTI and left ventricular ejection fraction.

Table 5 – Echocardiographic measurements

Parameter	Mean (SD)	n (%)
LA diameter (mm)	48 (± 10.7)	34 (100)
LA reservoir strain	9.9 (± 7.2)	32 (94.1)
LA conduit strain	−6.7 (± 4.6)	32 (94.1)
LA contractile strain	−3.3 (± 4.8)	32 (94.1)
LV strain (%)	−6.6 (± 3.2)	34 (100)
LVDD (mm)	71.8 (± 7.7)	34 (100)
LVSD (mm)	64.8 (± 8.5)	34 (100)
LVDV (mL)	236.9 (± 69.7)	34 (100)
LVSV (mL)	189.2 (± 62.3)	34 (100)
LVEF (%)	21.1 (± 6.6)	34 (100)
CO (L/min)	3.6 (± 1.2)	34 (100)
CPO (W)	0.61 (± 0.35)	34 (100)
LVOT-VTI (cm)	12.8 (± 4.3)	34 (100)
E/e' ratio	18.0 (± 7.8)	32 (94.1)
PAPI	4.4 (± 3.7)	16 (47)
CVP (mmHg)	7.29 (± 4.8)	34 (100)
PASP (mmHg)	44.1 (± 14.8)	27 (79.4)
MPAP (mmHg)	28.8 (± 9.8)	18 (52.9)
PADP (mmHg)	20.2 (± 7.7)	16 (47)
TAPSE (mm)	16.1 (± 4.1)	34 (100)
S' wave velocity (cm/s)	8.8 (± 2.1)	34 (100)
RV free wall strain (%)	−14.0 (± 7.3)	33 (97)
FAC (%)	27.8 (± 9.3)	33 (97)
RV basal diameter (mm)	43.8 (± 8.4)	34 (100)

CO: cardiac output; CPO: cardiac power output; CVP: central venous pressure; E/e': ratio of early mitral inflow velocity (E) to early diastolic mitral annular velocity (e'); FAC: fractional area change; LA: left atrium; LV: left ventricle; LVDD: left ventricular diastolic diameter; LVSD: left ventricular systolic diameter; LVDV: left ventricular diastolic volume; LVSV: left ventricular systolic volume; LVEF: left ventricular ejection fraction; LVOT-VTI: left ventricular outflow tract velocity–time integral; MPAP: mean pulmonary artery pressure; PADP: pulmonary artery diastolic pressure; PAPI: pulmonary artery pulsatility index; PASP: pulmonary artery systolic pressure; RV: right ventricle; S': systolic velocity of the tricuspid annulus; SD: standard deviation; TAPSE: tricuspid annular plane systolic excursion.

Regarding PAPI, the results revealed correlation between its invasive measurement via PAC and its echocardiographic estimation, as well as with TAPSE. The correlations between PAPI and S' wave velocity and between PAPI and right ventricular free wall strain were weaker. Based on literature review, this appears to be the first study to evaluate the correlations between invasive CPO and PAPI with echocardiographic measurements in patients with HFrEF.

Stein et al. and Temporelli et al. reported a strong correlation between invasive and echocardiographic hemodynamic measurements in patients with chronic HF; however, CPO, PAPI and LVOT-VTI were not included

among the variables analyzed in these studies.^{13,14} Frea et al. published the largest study to date investigating the correlation between invasive and echocardiographic hemodynamic parameters in CS.⁹ Their population consisted of patients with CS secondary to decompensated HF. In our cohort, 26.5% of patients were receiving inotropic support and classified as having INTERMACS III HF. Although our population had normal lactate levels and were not on vasopressor therapy at the time of evaluation, these two populations may share similar pathophysiological conditions. In the study by Frea et al.,¹² correlation between the two methods showed a Pearson coefficient $r = 0.82$, $p < 0.001$ for CPO. The

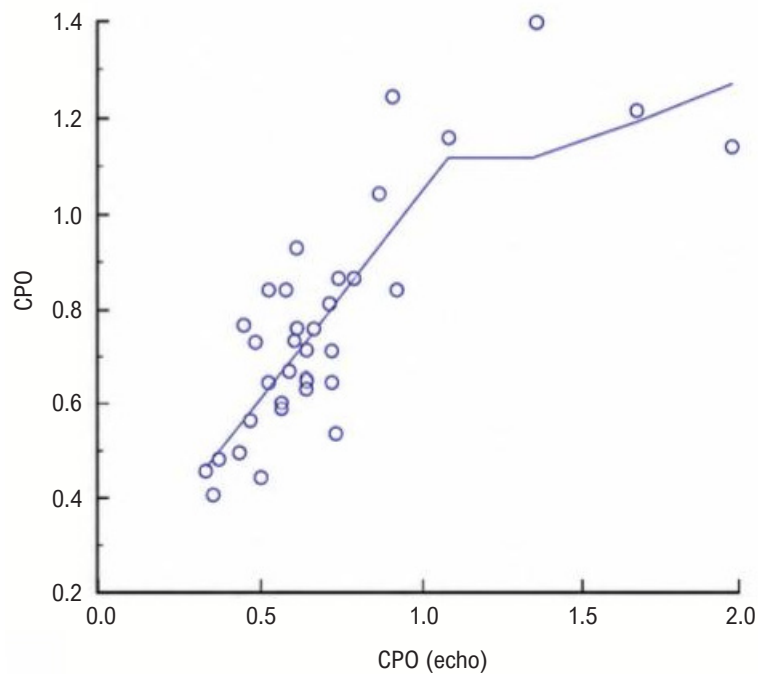


Figure 1 – Correlation analysis for CPO assessed by PAC and echocardiography. $r = 0.737$ ($p < 0.001$).

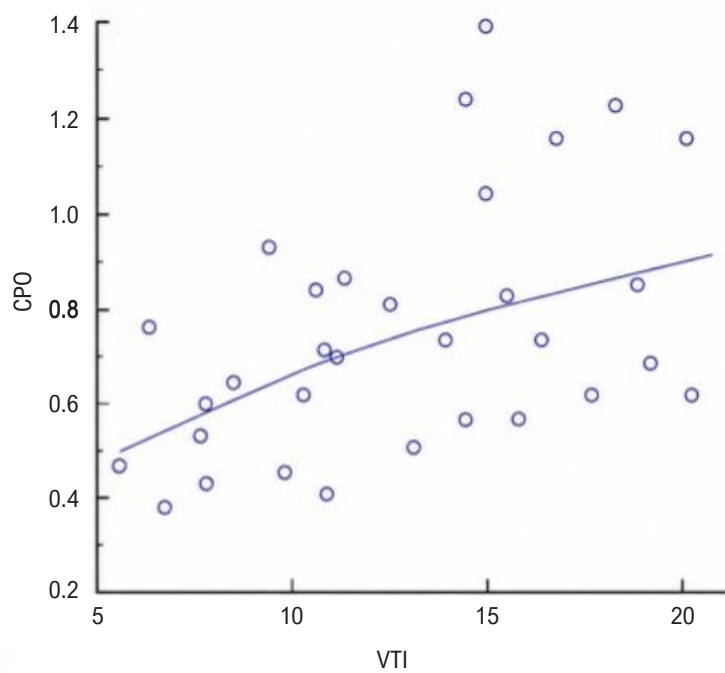


Figure 2 – Correlation analysis for CPO and LVOT-VTI. $r = 0.469$ ($p < 0.01$)

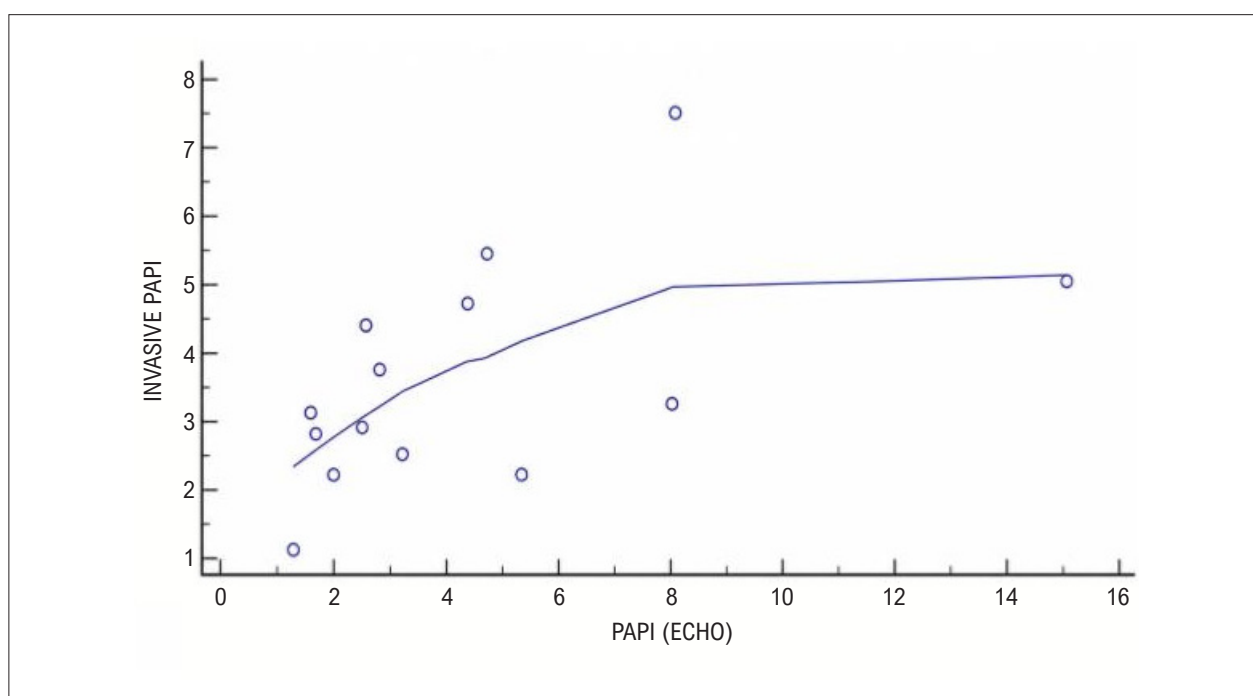


Figure 3 – Correlation analysis for PAPI assessed by PAC and echocardiography. $r = 0.604$ ($p < 0.05$)

results of our study were in line with these findings, especially among patient in INTERMACS III, given that CPO measured by PAC and echocardiography showed the strongest correlation between the two methods in our population ($r = 0.73$, $p < 0.001$), which was even greater in patients receiving inotropic support ($r = 0.81$, $p = 0.008$). Our study reaffirms the strength of correlation between invasive and echocardiographic CPO and its reproducibility, extending the findings observed in CS to patients with chronic and acutely decompensated HFrEF.

Frea et al.¹² also demonstrated a strong correlation between invasive and echocardiographic PAPI assessments. One notable difference between the two studies lies in the reproducibility of echocardiographic PAPI. In the cited study, PAPI estimation was feasible in 97 out of 101 patients, whereas in our study, it was achievable in only 16 of 34 patients. Pulmonary regurgitation is a rare finding on echocardiography in patients with pulmonary hypertension, consequently reducing the accuracy of methods that evaluate measures derived from it.¹⁸ There is also significant variability in PAC-derived PAPI thresholds capable of predicting adverse outcomes across different studied populations. Consequently, the cutoff values for PAPI differ between CS and HF.^{19,20} For this reason, low sensitivity of pulmonary regurgitation and the distinction in PAPI thresholds between different populations may have contributed to the differences in reproducibility observed between the two studies. Therefore, based on our findings, we conclude that echocardiographic PAPI may not be a reliable diagnostic parameter in patients with chronic and acutely decompensated HF due to its low reproducibility.

This study presents some limitations. First, the size of the analyzed population is a significant aspect to emphasize, especially after the publication by Frea et al.,¹² which occurred during the final recruitment phase of our study. Furthermore, the heterogeneity of our cohort represents another limitation, as our study includes individuals with diverse hemodynamic conditions and varying requirements for therapeutic support. To reduce population heterogeneity, we performed a sensitivity analysis among patients receiving inotropic support, attempting to exclude patients with less severe disease. The inability to obtain echocardiographic PAPI in part of the sample represents another limitation. Lastly, the extended interval between the two assessment methods may also be regarded as a potential limitation.

Conclusion

This study demonstrated significant correlations between invasive and noninvasive hemodynamic measures in patients with HFrEF, particularly for prognostic parameters such as CPO, PAPI, and LVOT-VTI. CPO showed the strongest agreement between methods, especially in patients receiving inotropic support. While PAPI correlated across techniques, its limited reproducibility by echocardiography reduces its clinical utility in this population.

Author Contributions

Conception and design of the research: Barbato JPR, Scolari FL, Berger SV, Menegazzo WR, Araujo GN, Valle

FH, and Wainstein RV; acquisition of data: Barbato JPR, Berger SV, Menegazzo WR, Crivelaro PAM, Amon AB; analysis and interpretation of the data: Barbato JPR, Scolari FL, Machado GP, Berger SV, Menegazzo WR, Amon AB, Araujo GN, Valle FH, Wainstein RV; statistical analysis: Barbato JPR, Scolari FL, Machado GP, Araujo GN; obtaining financing: Barbato JPR; writing of the manuscript: Barbato JPR, Scolari FL, Araujo GN, Valle FH, and Wainstein RV; critical revision of the manuscript for intellectual content: Barbato JPR, Scolari FL, Machado GP, Berger SV, Menegazzo WR, Crivelaro PAM, Amon AB, Araujo GN, Valle FH, and Wainstein RV.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of Hospital de Clínicas de Porto Alegre under the protocol number 5920490. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

Use of Artificial Intelligence

The authors did not use any artificial intelligence tools in the development of this work.

Availability of Research Data

The underlying content of the research text is contained within the manuscript.

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*Supplemental Materials

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Invasive Assessment of the Hemodynamic Profile of Critically Ill Patients: When Is Echocardiographic Assessment Alone Sufficient

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Short Editorial related to the article: Correlating Invasive and Echocardiographic Hemodynamic Measures in Patients with Heart Failure with Reduced Ejection Fraction

Assessing systemic and/or pulmonary congestion in patients with heart failure is fundamental to clinical management and prognosis. This congestive state is characterized by fluid accumulation in the body and represents the leading cause of hospitalization and hospital readmission in heart failure, both in patients with reduced or preserved ejection fraction, and directly contributes to increased mortality. Therefore, the early and accurate identification of fluid overload is indispensable for guiding therapeutic management, preventing complications, and optimizing clinical outcomes.¹ However, conventional clinical signs generally have low sensitivity and specificity, limiting their effectiveness when used alone for disease diagnosis and management and making complementary methods necessary to better define the clinical condition.²

Invasive tools to establish hemodynamic parameters are considered the gold standard for accurately determining the degree of congestion, assessing cardiac performance, and evaluating pulmonary and systemic vascular resistance. The use of invasive catheters, particularly right-sided catheters, has increased in recent years and has provided relevant prognostic information to guide appropriate treatment in patients with cardiac dysfunction and other diseases, particularly pulmonary hypertension.

Assessing the invasive hemodynamic profile with right heart catheterization is fundamental to managing heart failure. Although echocardiography can measure several noninvasive hemodynamic parameters, right heart catheterization remains indispensable in patients with symptoms refractory to medical treatment and when symptoms and objective findings are discrepant.

With the current establishment of the four-interface conceptual model proposed by Rola et al.,³ the role of echocardiography and its relationship with reliable hemodynamic parameters, particularly right ventricular-pulmonary arterial (RV/PA) and left ventricular-aortic (LV/Ao) coupling, becomes highly relevant for the assessment of systemic congestion and left cardiac function.

Assessing cardiac function in terms of contractile strength (i.e., cardiac power) and congestive processes, without integrating other interfaces, may lead to incomplete diagnoses and inappropriate clinical management. In this context, echocardiography stands out as an indispensable tool because it enables the combined assessment of LV/Ao coupling (Interface I), RV/PA coupling (Interface IV), and the capillary/venular compartment (Interface III) through the assessment of the inferior vena cava and systemic venous flows (hepatic, portal, and renal).

In the elegant study by Barbato et al.⁴ conducted with patients with systolic dysfunction, the relationship between cardiac power output (obtained by hemodynamic assessment) and echocardiographic parameters showed excellent correlation, particularly with the use of left ventricular outflow tract velocity time integral, which can be rapidly obtained even by non-echocardiography practitioners trained in advanced POCUS. The velocity time integral is directly associated with cardiac output, and values < 18 cm (particularly < 16 cm) are associated with impaired ventricular contractility. This parameter is particularly relevant for assessing patients awaiting heart transplantation and those receiving extracorporeal membrane oxygenation, in whom an increased value indicates recovery of ventricular function.

Although the pulmonary artery pulsatility index (PAPI) is fundamental for predicting right ventricular failure and adverse outcomes, translating it into a noninvasive method is challenging. Despite the positive statistical correlation observed ($r = 0.604$, $p < 0.05$), echocardiographic PAPI was obtained in only 16 of the 34 patients (47% of the sample).

The major limitation of the method is its technical dependence on pulmonary regurgitation. In the absence of a detectable pulmonary regurgitant jet with adequate Doppler quality, measuring pulmonary artery diastolic and mean pressures becomes impossible, precluding PAPI calculation. In these cases, the imaging specialist should rely on alternative right ventricular markers that showed correlations with invasive PAPI in the study, such as tricuspid annular plane systolic excursion ($r = 0.553$, $p < 0.01$) and right ventricular free-wall strain ($r = -0.344$, $p < 0.05$), which are complementary approaches when technical limitations of PAPI preclude its assessment.

Although limited by the small sample size, studies such as that by Barbato et al.⁴ are fundamental for defining the accuracy of echocardiography in hemodynamic assessment and its performance compared with invasive methods considered the gold standard. Future studies involving larger numbers of patients and additional centers may provide further information and establish the true role of echocardiography in comparison with hemodynamic assessment.

Keywords

Echocardiography; Catheterization; Heart Failure

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Table 1 – Summary of invasive and noninvasive findings and their correlations.

Hemodynamic correlation and feasibility matrix			
Parameter	Correlation (r)	Significance (p)	Clinical observation
CPO	0.737	p < 0.001	High reproducibility; excellent in critically ill patients.
PAPI	0.604	p < 0.05	Low feasibility (limited by pulmonary regurgitation).
LVOT-VTI	0.469	p < 0.01	Practical bedside marker of stroke volume.
CO (echo) vs. CPO (invasive)	0.616	p < 0.001	Strong correlation that supports echocardiographic flow estimation.

CPO: cardiac power output; PAPI: pulmonary artery pulsatility index; LVOT-VTI: ventricular outflow tract velocity time integral; DC: cardiac output.

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Ultrasound Measurement of Optic Nerve Sheath Diameter in Acute Hypertensive States For Detection of Intracranial Involvement: A Meta-Analysis

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Abstract

Background: Detection of intracranial involvement in acute hypertension traditionally relies on fundoscopy, a method with limited applicability at the bedside. Ultrasonographic measurement of the optic nerve sheath diameter (ONSD) has emerged as a rapid, non-invasive alternative.

Objective: To synthesize evidence on ONSD in adults and pregnant women with acute hypertensive states, assessing the difference in measurements between groups and its diagnostic performance for elevated intracranial pressure (ICP).

Methods: Systematic review and meta-analysis following PRISMA guidelines. Three databases were searched through July 2026, including observational studies. The primary outcome was the standardized mean difference (Hedges' g) in ONSD between hypertensive and control groups, using a random-effects model.

Results: Fourteen studies (995 participants) were included. Nine studies (426 hypertensive and 283 control participants) provided combinable continuous data: ONSD was significantly higher in hypertensive patients ($g = 1.55$; 95% CI 1.06 to 2.04; $p < 0.001$; $I^2 = 87.0\%$). Excluding a single discordant study reduced heterogeneity and strengthened the effect ($g = 1.77$; 95% CI 1.50 to 2.04; $I^2 = 51.8\%$). In five studies with observed counts, the odds of ONSD above the threshold were higher in hypertensive patients (OR 11.58; 95% CI 1.45 to 92.85; $I^2 = 73.7\%$). No study included ONSD with invasive ICP measurement.

Conclusion: ONSD is consistently higher in acute hypertensive patients, with a robust effect. However, substantial heterogeneity, reliance on statistical conversions, the presence of a discordant study, and the absence of validation against the invasive gold standard warrant caution, underscoring the need for methodological standardization and dedicated validation.

Keywords: Optic Nerve; Ultrasonography; Intracranial Pressure; Pre-Eclampsia; Hypertensive Crisis.

Introduction

Arterial hypertension is one of the leading causes of cardiovascular morbidity and mortality worldwide, and its acute presentations – hypertensive emergencies and urgencies, hypertensive encephalopathy, posterior reversible encephalopathy syndrome (PRES), spontaneous intracerebral hemorrhage, and the hypertensive disorders of pregnancy, including pre-eclampsia and eclampsia – may course with acute elevation of intracranial pressure (ICP) and potentially severe neurological repercussions. Early bedside recognition of this repercussion traditionally relies on fundoscopic examination for papilledema. However, this assessment is

difficult to perform outside the ophthalmologic setting: it requires mydriasis and patient cooperation, shows limited interobserver agreement when performed by non-specialists, and, importantly, papilledema may appear only hours to days after ICP elevation, delaying decision-making in urgent scenarios. These limitations justify the search for a rapid, objective, and reproducible marker.

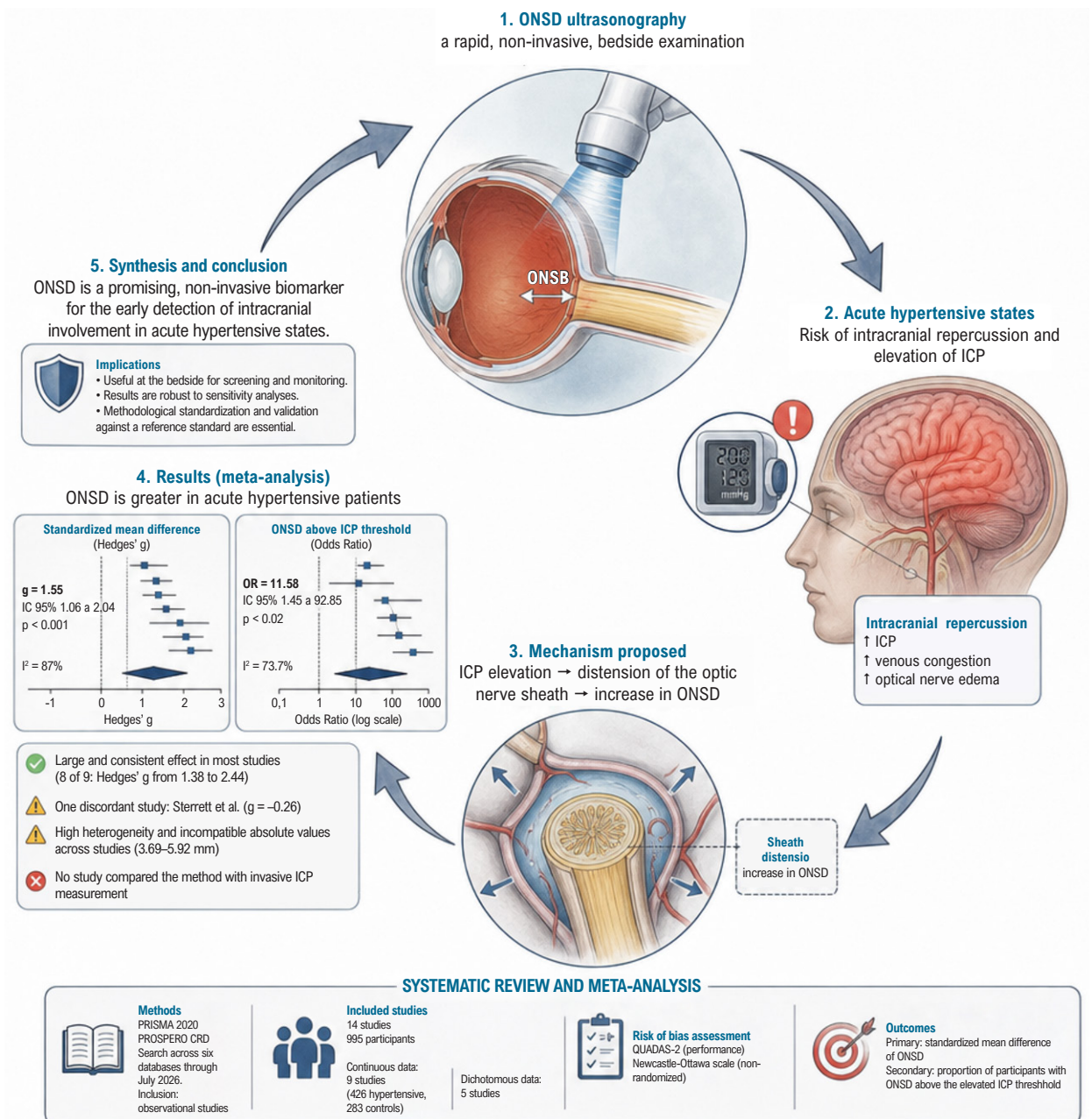
The optic nerve sheath diameter (ONSD) measured by transorbital ultrasonography has been proposed for this purpose. The subarachnoid space surrounding the optic nerve is contiguous with the intracranial subarachnoid space; thus, elevations in ICP are transmitted through the distensible nerve sheath, increasing its diameter. Studies comparing ONSD with direct invasive ICP measurement have confirmed this correlation, and meta-analyses in neurocritical populations have demonstrated good diagnostic accuracy of the method for intracranial hypertension.^{1,2} Because it is non-invasive, low-cost, and can be performed within minutes, the technique is particularly attractive when fundoscopic examination is impractical.

It is important to note that papilledema itself is an indirect sign of intracranial hypertension, not the target condition. The perineural subarachnoid space is contiguous with the

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Central Illustration: Ultrasound Measurement of Optic Nerve Sheath Diameter in Acute Hypertensive States For Detection of Intracranial Involvement: A Meta-Analysis



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ONSD: optic nerve sheath diameter; ICP: intracranial pressure.

intracranial compartment, and ICP elevation affects the optic nerve through two distinct pathways: mechanical distension of the sheath, which increases ONSD, and stasis of axoplasmic flow at the optic nerve head, which produces disc edema. These two findings are therefore parallel – both downstream

manifestations of the same process – and not sequential. The second pathway depends on progressive accumulation of axoplasmic material and appears later, helping explain why papilledema may be absent in the first hours of ICP elevation and why the sensitivity of fundoscopic examination

is described as limited in the acute setting.³ This leads to the central question of this review: the goal is not to determine whether ONSD reproduces the fundoscopic finding, but whether it provides information about the underlying condition reflected by both signs.

In acute hypertensive states, failure of cerebral autoregulation and endothelial dysfunction promote cerebral edema and increased ICP – a pathophysiological substrate common to hypertensive encephalopathy and PRES. In hypertensive patients, ONSD increases and subsequently decreases after blood pressure control,⁴ and among pregnant women, pre-eclampsia and eclampsia are associated with higher ONSD values compared with normotensive women.⁵⁻⁷ The relevance of this topic to cardiovascular imaging is reinforced by the recognition that hypertensive disorders of pregnancy are predictors of future cardiovascular disease.

Despite this growing body of evidence, studies evaluating ONSD in acute hypertensive states are heterogeneous in terms of population, reference standard, and diagnostic threshold, and are dispersed across small samples. Available systematic reviews focus on other populations, such as traumatic brain injury and non-traumatic neurocritical patients, without a synthesis dedicated to the hypertensive scenario.¹ This study aimed to systematically review this evidence, quantifying the difference in ONSD compared with controls and its performance in detecting elevated ICP.

Methods

Protocol and registration

This systematic review was conducted and reported in accordance with the PRISMA 2020 guidelines.⁸ The protocol was prospectively registered in PROSPERO (No. CRD420261459770) before the initiation of data extraction.

Eligibility criteria

Eligible studies included observational designs, namely case-control, cross-sectional, and prospective cohort studies, that evaluated ultrasound measurement of the ONSD in adults (≥ 18 years), as well as in pregnant or postpartum women presenting with acute hypertensive disorders. These conditions were defined as preeclampsia with or without severe features, eclampsia, hypertensive encephalopathy, PRES, spontaneous hypertensive intracerebral hemorrhage, hypertensive emergency or urgency, and severe acute hypertension.

The index test was ONSD measured by transorbital B-mode ultrasonography using a high-frequency linear probe, with measurements obtained approximately 3 mm posterior to the globe. Accepted comparators or reference standards included normotensive controls (the basis for the primary outcome), ICP monitoring, lumbar puncture opening pressure, neuroimaging findings consistent with elevated ICP, and the clinical diagnosis of eclampsia.

Case reports, case series, reviews, editorials, letters, and conference abstracts without extractable data were excluded. Studies conducted exclusively in healthy volunteers or animal models, as well as studies involving non-hypertensive

neurocritical populations when results could not be separated, were also excluded.

Information sources and search strategy

The following databases were searched from inception to July 2026, without language restrictions: MEDLINE (via PubMed), Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL). The search strategy combined three groups of terms using the Boolean operator AND: (1) the condition of interest (preeclampsia, eclampsia, acute hypertension, hypertensive emergency and urgency, hypertensive encephalopathy, and PRES); (2) the imaging modality (ultrasonography, ultrasound, sonography); and (3) the index test (ONSD). The search was supplemented by manual screening of the reference lists of included studies and relevant previous reviews. The complete search strategy for each database is provided in the Supplementary Material.

Study selection and data extraction

Two reviewers independently screened titles and abstracts, followed by full-text assessment of potentially eligible studies. Disagreements were resolved by consensus or, when necessary, by consultation with a third reviewer. Data extraction was performed independently in duplicate using a standardized, pilot-tested form. Extracted variables included study identification, country, study design, hypertensive etiology, number of participants per group, ONSD measurement technique and threshold, reference standard, and, depending on the analysis, mean and standard deviation of ONSD for each group and/or event counts by group. All extracted values were verified against the tables reported in the original articles before analysis.

Risk of bias assessment

Risk of bias was assessed independently by two reviewers using the tool appropriate for each study design: QUADAS-2⁹ for diagnostic accuracy studies and ROBINS-1¹⁰ for comparative observational studies. Disagreements were resolved by consensus or by a third reviewer.

Data synthesis

The primary outcome was the standardized mean difference (Hedges' g)¹¹ in ONSD between patients with acute hypertensive conditions and controls, estimated using a random-effects meta-analysis with the DerSimonian-Laird estimator.¹² The pooled standard deviation was calculated as the weighted average of the sample variances according to their respective degrees of freedom. Heterogeneity was quantified using Cochran's Q test and the I^2 and τ^2 statistics.¹³

As a secondary outcome, the proportion of participants with ONSD above the threshold for intracranial hypertension was synthesized as an odds ratio, restricting the analysis to studies reporting observed event counts. For contingency tables with zero events, a continuity correction of 0.5 was applied. Studies with paired within-subject designs or lacking an independent control group were not included in the independent-group meta-analytic models and were instead summarized through

a structured narrative synthesis. Publication bias was assessed using funnel plot inspection and Egger's test,¹⁴ with the explicit acknowledgment that these methods have low statistical power when fewer than ten studies are available. All analyses were performed in Python 3 (NumPy and SciPy libraries) using direct implementation of the statistical formulas, with a two-sided significance level of 5%.

Diagnostic threshold analysis

No statistical pooling of the reported cutoff values was performed for two prespecified reasons. First, the thresholds derived from receiver operating characteristic (ROC) curve analyses in the primary studies were intended to distinguish preeclampsia from normotension, rather than to diagnose intracranial hypertension. Second, the fixed thresholds used in other studies had been adopted from neurocritical care populations without local validation. Pooling sensitivities and specificities obtained against different diagnostic targets would therefore produce an estimate without a clearly defined clinical reference.

To assess whether a single threshold might be transferable across studies, an exploratory analysis was conducted in which each proposed cutoff was applied to all studies. Expected sensitivity and specificity were calculated from the mean and standard deviation of each group under a normal distribution assumption. Using the same approach, the threshold that maximized the Youden index was estimated for each study. These estimates represent modeled projections rather than observed event counts and are identified as such in the Results section. In addition, under the assumptions of normality and homoscedasticity, the area under the ROC curve (AUC) is related to the standardized mean difference through the identity $AUC = \Phi(g/\sqrt{2})$, which was used to estimate overall discriminative performance independently of any specific cutoff definition.

Harmonization of reported data

The included studies reported ONSD in different formats, requiring standardization before data synthesis. Values reported in centimeters were converted to millimeters; because the standardized mean difference is dimensionless, it is unaffected by the unit of measurement. When ONSD was reported as a median with interquartile range, the mean and standard deviation were estimated using the method of Wan et al.^{6,15} When reported as a median with a confidence interval, the standard deviation was estimated from the confidence interval width and sample size.⁵

In one study,⁷ the dispersion values reported in the outcome table (± 0.02 and ± 0.03 cm) were, by magnitude, incompatible with standard deviations. These values were therefore interpreted as standard errors and converted using the relationship standard deviation = standard error $\times \sqrt{n}$. However, another table in the same study reported eye-specific standard deviations (± 0.05 cm in the eclampsia group and ± 0.03 cm in the control group) that were internally consistent with the corresponding standard error column, but did not match either interpretation of the main outcome table. This ambiguity was addressed through sensitivity analyses. For

studies with multiple hypertensive groups compared against a common control group (Dikmetaş 2020, Singh 2018, and Sterrett 2022),^{4,16,17} the hypertensive arms were combined into a single group to avoid double-counting the shared control group.

Sensitivity and Subgroup Analyses

Sensitivity analyses were conducted by successively excluding the discordant study, the study with ambiguous dispersion, and all studies requiring dispersion conversion, in addition to a leave-one-out influence analysis. Subgroups were prespecified according to gestational condition and etiology.

Results

Study selection and characteristics

The process of identification, screening, and selection is summarized in the PRISMA 2020 flowchart (Figure 1). Fourteen studies^{4-7,16-25} with 995 participants were included in the systematic review (Central Illustration). Of these, nine provided means and standard deviations of ONSD per group – either directly or after conversion – and were included in the meta-analysis of the primary outcome, totaling 426 patients with acute hypertensive states and 283 controls (Table 1).

Five studies could not be incorporated into the independent-groups model: Assu et al.²⁴ ($n = 30$) and Rani et al.²⁵ ($n = 47$) are single-arm studies with paired measurements before and after magnesium sulfate; Mowafy & Elsayed²¹ ($n = 54$) compared paired measurements before and after delivery; Ortner et al.²⁰ ($n = 95$) is a single-cohort study of preeclampsia without a control group, reporting a mean ONSD of 5.4 ± 0.5 mm and 27 participants (28%) above 5.8 mm; and Brzan Simenc et al.¹⁸ presented ONSD only in a box plot, with no numerical values in the text. The latter, however, reported observed counts and was included in the binary secondary outcome.

Most studies evaluated preeclampsia and eclampsia; only one study⁴ included non-pregnant hypertensive individuals. Control groups were heterogeneous – normotensive pregnant women, asymptomatic normotensive adults, and postpartum women admitted to intensive care for other causes – which represents a relevant source of variability.

Primary outcome: difference in ONSD

The pooled standardized mean difference in ONSD between patients with acute hypertensive states and controls was $g = 1.55$ (95% CI 1.06 to 2.04; $p < 0.001$), indicating higher ONSD in the hypertensive group, with substantial heterogeneity ($Q = 61.4$; $df = 8$; $p < 0.001$; $I^2 = 87.0\%$; $\tau^2 = 0.485$; Figure 2).

Study-level effects were consistent and large in eight of the nine studies, ranging from $g = 1.38^5$ to $g = 2.44^{17}$ and discordant in a single study,¹⁶ $g = -0.26$ (95% CI -0.80 to 0.28) – the only one not showing a difference between groups. In that study, the mean ONSD of controls (5.92 ± 0.84 mm) was numerically higher than that of patients with preeclampsia (5.67 ± 0.98 mm), an inverse pattern compared with all other

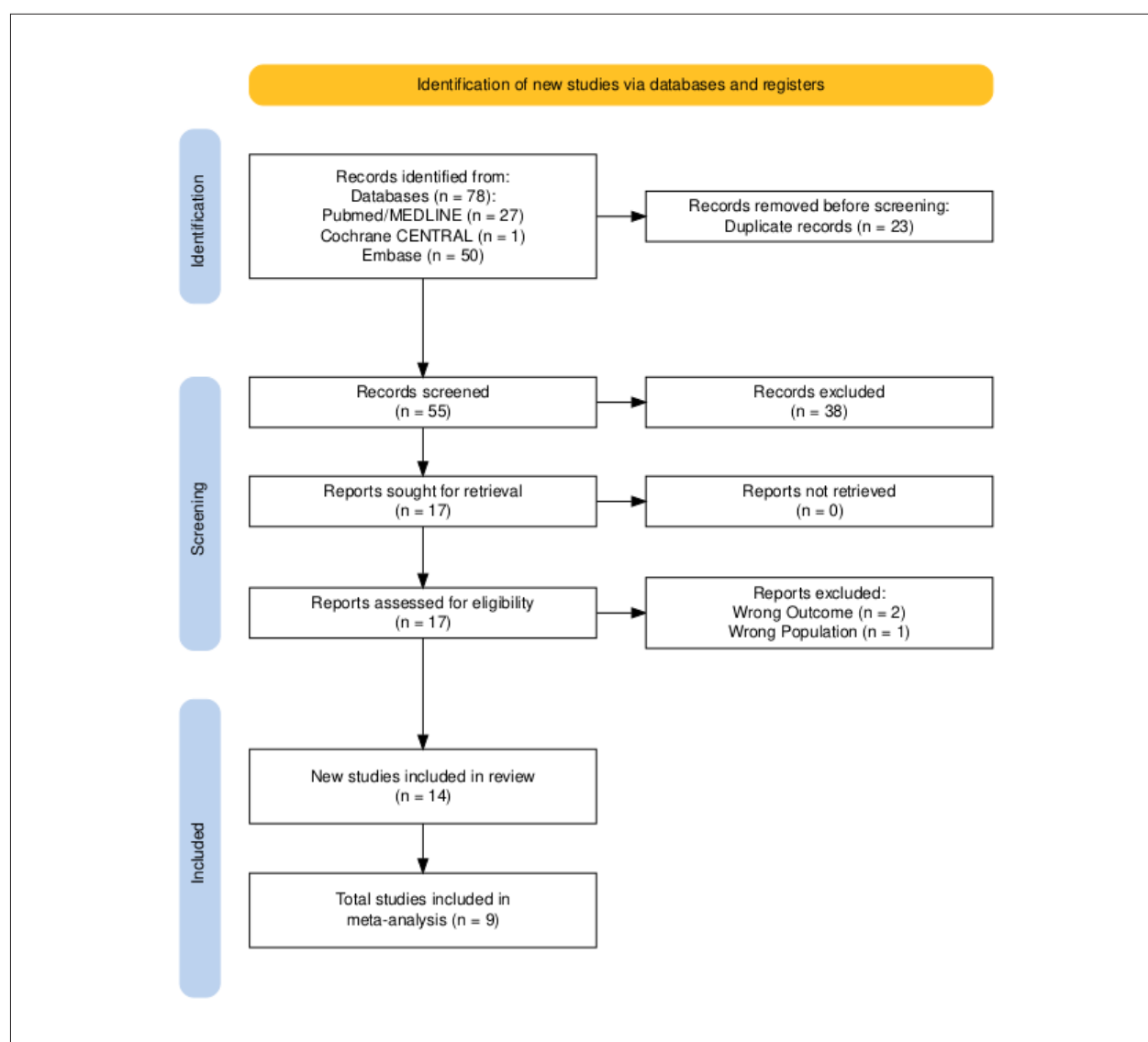


Figure 1 – Study selection flowchart (PRISMA 2020).

studies, and confirmed upon checking the original table, which reports adjusted differences that are likewise null or negative across all arms.

Influence analysis showed that heterogeneity was concentrated almost entirely in this study: its exclusion increased the pooled effect to $g = 1.77$ (95% CI 1.50 to 2.04) and reduced heterogeneity from $I^2 = 87.0\%$ to 51.8%. Excluding any other study individually changed the pooled effect by less than 0.11 and did not substantially modify I^2 (Table 2).

The effect remained stable and of large magnitude across all sensitivity analyses, including restriction to the six studies that did not require any dispersion conversion ($g = 1.55$; 95% CI 0.82 to 2.27) and the alternative interpretation of dispersion in Bala et al.⁷ ($g = 1.82$; 95% CI 1.21 to 2.43). In the gestational subgroup (eight studies), the effect was $g = 1.56$

(95% CI 0.98 to 2.15); the non-gestational subgroup included a single study and could not be meta-analyzed, preventing formal subgroup comparison.

Secondary outcome: proportion above the threshold

Five studies reported observed counts of participants with ONSD above the intracranial hypertension threshold (Figure 3). The odds of elevated ONSD were higher in the hypertensive group (OR 11.58; 95% CI 1.45 to 92.85; $p = 0.021$; $I^2 = 73.7\%$). Excluding Sterrett et al.¹⁶ the estimate was OR 29.54 (95% CI 6.98 to 124.99) with $I^2 = 0\%$. Four of the five studies recorded no events in the control group, requiring continuity correction and resulting in very wide confidence intervals; these results should therefore be interpreted as evidence of the *direction* of the effect, not its precise magnitude.

Tabela 1 – Características dos estudos incluídos na meta-análise do desfecho primário

Study (year)	Population / etiology	n (hip./ctrl)	ONSD (mm) hypertensive	ONSD control (mm)	Reporting form	Hedges' g (95%CI)
Arzpeyma et al. ¹⁹	Preeclampsia	38 / 38	5.37 ± 0.96	4.26 ± 0.55	mean ± SD	1.40 (0.91; 1.90)
Kumar et al. ⁷	Eclampsia (ICU)	24 / 22	6.40 ± 0.98 ^a	4.50 ± 1.41 ^a	SE → SD	1.55 (0.90; 2.20)
Biswas et al. ⁶	Preeclampsia	60 / 30	5.17 ± 0.84 ^b	3.69 ± 0.80 ^b	median+ IQR	1.78 (1.27; 2.28)
Dikmetaş et al. ⁴	Acute hypertension (non-pregnant)	99 / 50	5.25 ± 0.61	4.42 ± 0.39	mean ± SD	1.51 (1.13; 1.89)
Dubost et al. ⁵	Preeclampsia	26 / 25	5.40 ± 0.65 ^c	4.50 ± 0.64 ^c	median + 95%CI	1.38 (0.77; 1.98)
Nagpal et al. ²³	Preeclampsia	35 / 35	5.06 ± 0.46	4.24 ± 0.38	mean ± SD	1.92 (1.36; 2.48)
Singh et al. ¹⁷	Severe preeclampsia + eclampsia	49 / 25	5.70 ± 0.38	4.70 ± 0.46	mean ± SD	2.44 (1.82; 3.05)
Sterrett et al. ¹⁶	Preeclampsia	44 / 18	5.67 ± 0.98	5.92 ± 0.84	mean ± SD	-0.26 (-0.80; 0.28)
Su et al. ²²	Preeclampsia	51 / 40	4.34 ± 0.18	3.96 ± 0.14	mean ± SD	2.30 (1.77; 2.83)

ONSD: optic nerve sheath diameter; SD: standard deviation; SE: standard error; IQR: interquartile range; ^a Standard deviation obtained from the reported standard error ($SD = SE \times \sqrt{n}$); ^b Mean and SD estimated from median and IQR using the method of Wan et al.¹⁵ ^c SD estimated from the width of the confidence interval; Values converted from centimeters to millimeters in Kumar et al.⁷ and Dikmetaş et al.⁴ Multiple arms combined in Dikmetaş et al.,⁴ Singh et al.,¹⁷ and Sterrett et al.¹⁶

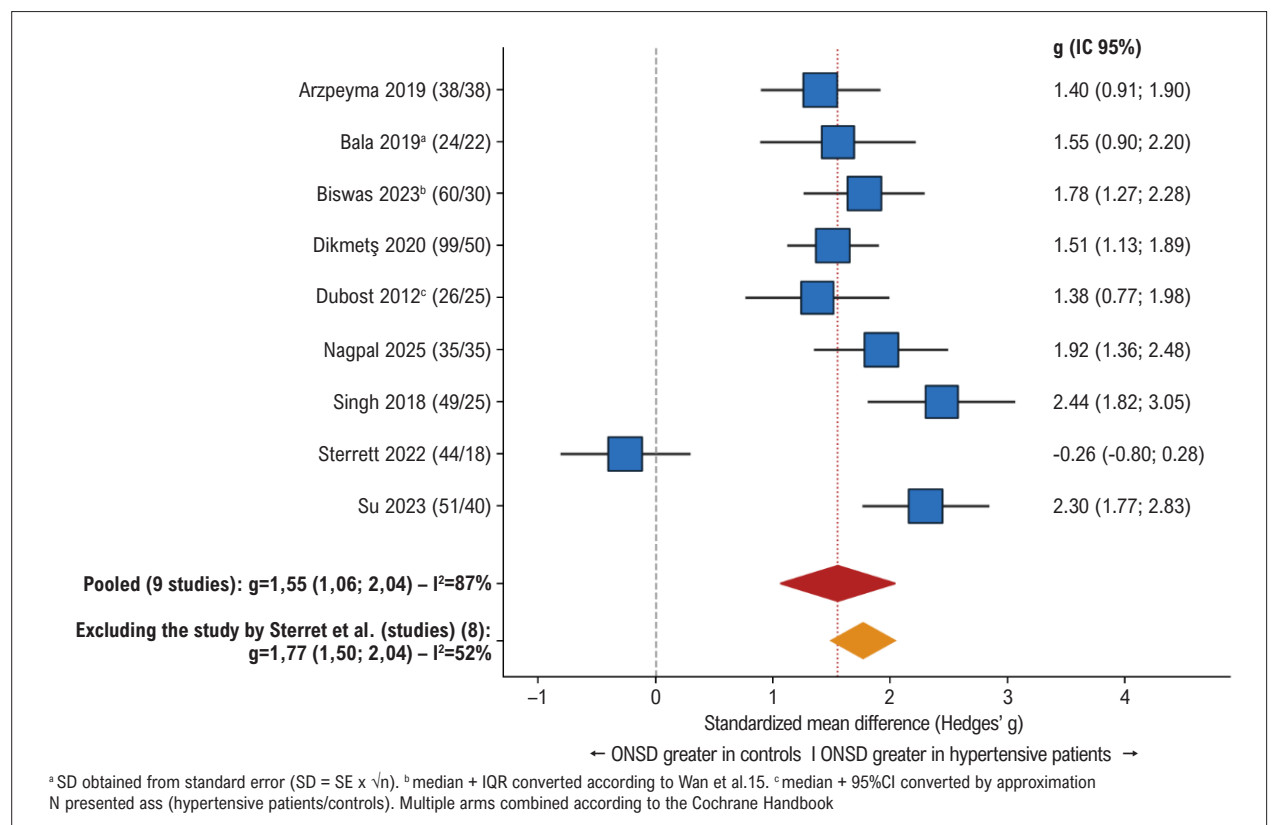


Figure 2 – Meta-analysis of the standardized mean difference (Hedges' g) in ONSD between patients with acute hypertensive states and controls, using a random-effects model (DerSimonian-Laird). Squares: study-specific estimates, with area proportional to weight; horizontal lines: 95% CI; diamonds: pooled effect of the main model (nine studies) and of the sensitivity analysis excluding the discordant study (eight studies).

Table 2 – Sensitivity and subgroup analyses of the primary outcome

Analysis	k	Pooled g (95%CI)	I ² (%)	τ ²
Main model (all combinable studies)	9	1.55 (1.06; 2.04)	87.0	0.485
Sterrett et al. ¹⁶ excluded (discordant)	8	1.77 (1.50; 2.04)	51.8	0.078
Bala et al. ⁷ excluded (ambiguous dispersion)	8	1.55 (1.01; 2.10)	88.6	0.541
Only studies without dispersion conversion	6	1.55 (0.82; 2.27)	91.7	0.745
Bala et al. ⁷ with the reported per-eye SD	9	1.82 (1.21; 2.43)	91.0	0.760
Subgroup: gestational	8	1.56 (0.98; 2.15)	88.6	0.630
Subgroup: non-gestational	1	1.51 (1.13; 1.89) ^d	—	—

k: number of studies; g: standardized mean difference (Hedges' g); I²: proportion of variability attributable to heterogeneity; τ²: between-study variance. ^d Single study; 4 estimate from the study itself, without pooling.

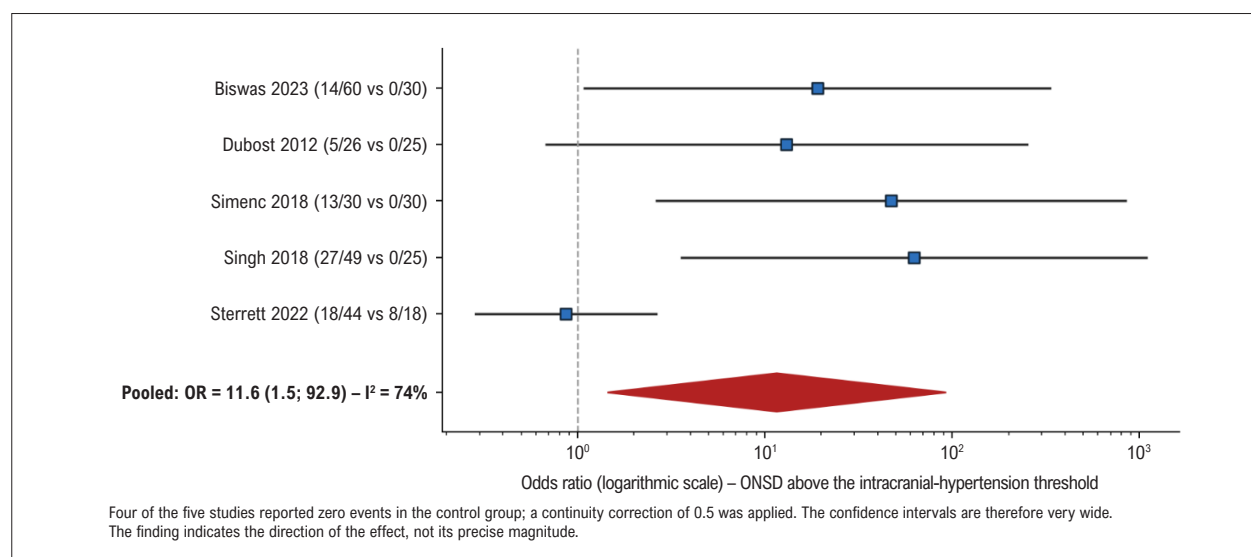


Figure 3 – Proportion of participants with ONSD above the intracranial hypertension threshold, expressed as odds ratios (logarithmic scale), restricted to studies with observed counts; a continuity correction of 0.5 was applied to tables with zero events.

Counts derived from sensitivity and specificity reported in three studies^{19,22,23} were not included in this synthesis because they do not represent observed counts; using them would amount to introducing reconstructed events into the model.

Diagnostic accuracy and reference standard

It was not possible to fit a bivariate model or estimate a summary ROC curve. None of the fourteen included studies compared ONSD with invasive ICP measurement or CSF opening pressure. The available ROC curves discriminated preeclampsia from controls – a diagnostic target distinct from intracranial hypertension – with areas under the curve of 0.82 (Arzpeyma et al.,¹⁹ cutoff 4.55 mm), 0.958 (Su et al.,²² cutoff 4.10 mm), and 0.907 (Nagpal et al.,²³ cutoff 4.65 mm). Because they involve a different diagnostic target and highly heterogeneous thresholds, these values are presented descriptively and were not pooled.

Risk of bias assessment

All fourteen observational studies were evaluated using the ROBINS-I tool. In this instrument, most studies show critical or serious risk in the initial domains – especially D1 (confounding) and D2 (selection of participants) – which severely compromises the overall quality of the evidence. Domains D3 (classification of interventions), D4 (deviations from intended interventions), and D5 (missing data) were frequently rated as low or moderate risk.

The QUADAS-2 tool was applied to six diagnostic accuracy studies, revealing high risk of bias, particularly in D1 (patient selection) and D2 (index test). As a result, the overall classification of most included studies was rated as critical or serious, indicating a high risk of bias that limits confidence in the conclusions (Figures 4A and 4B).

Diagnostic thresholds

The thresholds used in the included studies fell into two distinct ranges: values from 4.10 to 4.65 mm, derived from

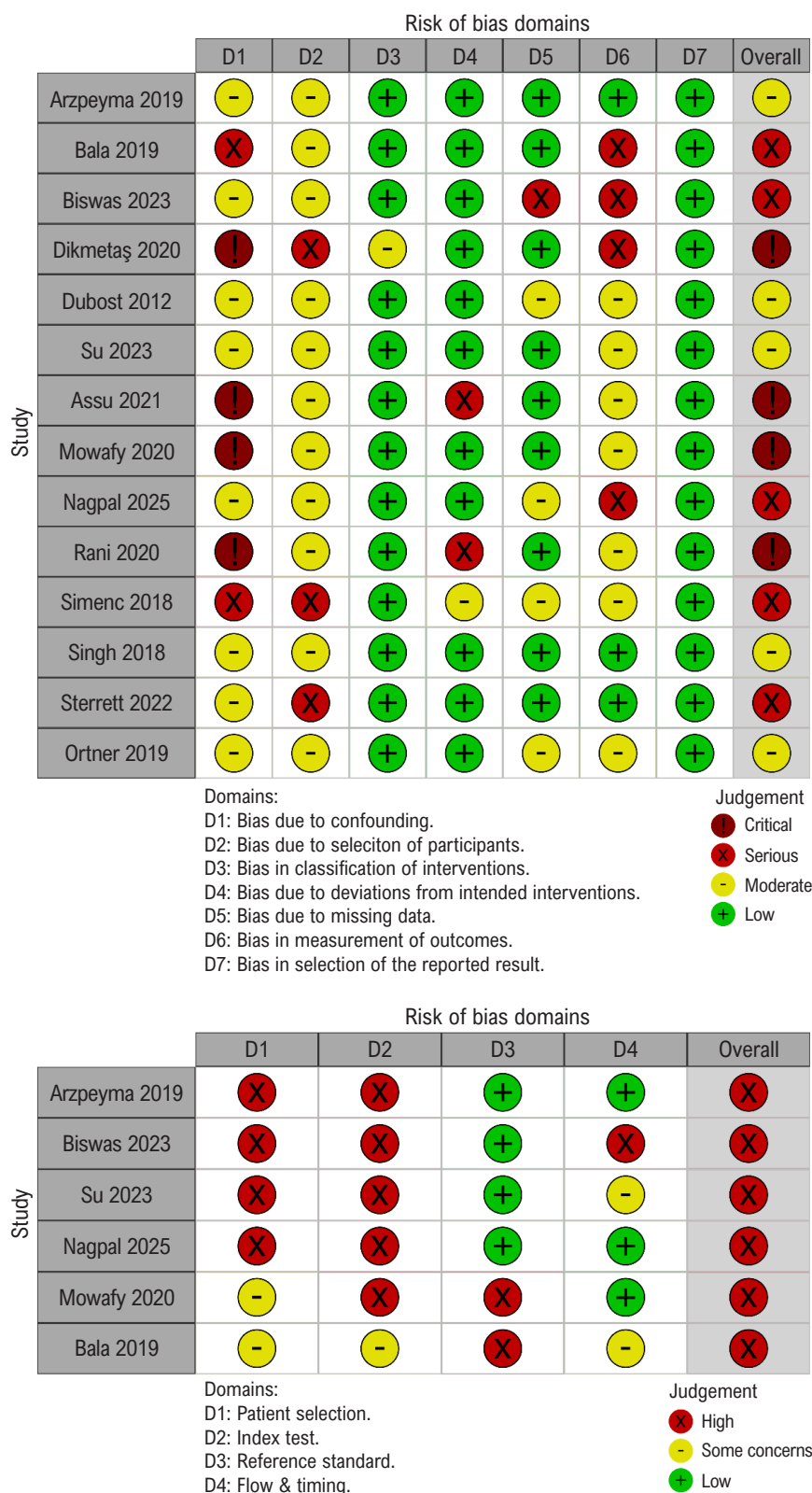


Figure 4 – Assessment of the risk of bias in the included studies (ROBINS-I for comparative observational studies and QUADAS-2 for studies with accuracy data).

ROC curves designed to discriminate preeclampsia from normotension, and values from 5.7 to 5.8 mm, imported from neurocritical populations and applied as presumed markers of intracranial hypertension.

Absolute ONSD values were incompatible across studies, preventing the transferability of any single threshold. Control-group means ranged from 3.69 mm⁴ to 5.92 mm³, a span of 2.23 mm, which exceeds the mean difference between hypertensive and control groups in most studies. The mean ONSD of controls in Sterrett et al.¹⁶ (5.92 mm) was higher than the hypertensive-group means in Su et al.²² (4.34 mm), Nagpal et al.²³ (5.06 mm), and Fallah Arzpeyma et al.¹⁹ (5.37 mm), meaning that participants classified as normal in one study would be classified as abnormal in another (Supplementary Material S2).

Cross-application of thresholds confirmed this incompatibility. The 4.10 mm cutoff – optimal in Su et al.²² – would yield 84% specificity in that study but only 2% in Sterrett et al.¹⁶ Conversely, the 5.80 mm cutoff would produce zero sensitivity in Su 2023²² and 22% in Biswas et al.⁶ When applied to control groups using observed counts, the 5.80 mm threshold was not reached by any participant in four studies (0/30 in Biswas et al.,⁶ 0/25 in Dubost et al.,⁵ 0/30 in Brzan Simenc et al.,¹⁸ and 0/25 in Singh et al.¹⁷ – the latter using a 5.7 mm cutoff), but was reached by 8 of 18 controls (44%) in Sterrett et al.¹⁶

The thresholds that would maximize the Youden index in each study ranged from 4.14 mm to 7.79 mm – a span of 3.64 mm (Table 3) – with no central value approaching optimal performance in more than a handful of studies. For this reason, no pooled cutoff was estimated.

As an estimate of the global discriminative ability independent of any threshold, the identity $AUC = \Phi(g/\sqrt{2})$ applied to the pooled standardized mean difference corresponds to an AUC of 0.863 (95% CI 0.773 to 0.925), or 0.895 when the discordant study is excluded (Figure 5). It should be reiterated that this estimate refers to the distinction between acute hypertensive state and normotensive control, not to the detection of elevated ICP.

Exploration of heterogeneity through meta-regression was not informative: the models were dominated by a single influential study, and the apparent associations disappeared once that study was excluded. In addition, mathematical coupling occurred when the covariate was the control-group mean, such that the results are presented solely as a diagnostic indication of non-interpretability given the number of studies available (Supplementary Material S3).

Narrative synthesis of non-poolable studies

The four paired-design studies converge in showing a reduction in ONSD after intervention or delivery. In Rani et al.²⁵ ($n = 47$), ONSD decreased from 5.56 ± 0.30 mm at baseline to 4.79 ± 0.13 mm four hours after magnesium sulfate ($p = 0.01$), remaining at 4.76 ± 0.11 mm at 24 hours. In Assu et al.²⁴ ($n = 30$), the reduction was more gradual, from 6.02 ± 0.77 mm to 5.64 ± 0.81 mm at 24 hours postpartum. In Mowafy et al.²¹

($n = 54$), ONSD decreased from 5.84 ± 0.82 mm before delivery to 5.24 ± 0.73 mm 24 hours later, with a strong correlation between ONSD and the lung comet score ($r^2 = 0.96$ before delivery). In Brzan Simenc et al.,¹⁸ 13 of 30 patients with severe preeclampsia (43%) had ONSD above 5.8 mm before delivery, compared with none of the 30 controls, with normalization within four days in most cases. This pattern of reversibility is consistent with the hypothesis that ONSD reflects a dynamic phenomenon of ICP elevation, but none of these studies allows estimation of the difference relative to independent normotensive controls.

Publication bias

With nine studies in the primary outcome – below the recommended threshold of ten – the methods for assessing asymmetry have low power. Egger's test did not indicate asymmetry (intercept 1.33; SE 6.19; $p = 0.836$), a result that, given the number of studies, should not be interpreted as evidence of absence of bias. The funnel plot is provided solely for transparency (Supplementary Material S1).

Discussion

This systematic review compiled the available evidence on ONSD ultrasonography in acute hypertensive states and showed that ONSD was, on average, higher in hypertensive patients than in controls, with a large effect size.

The pooled standardized mean difference was $g = 1.55$ (95% CI 1.06 to 2.04) and, excluding the single discordant study, $g = 1.77$ (95% CI 1.50 to 2.04), with a substantial reduction in heterogeneity. The finding proved robust: no sensitivity analysis – including restriction to studies that did not require dispersion conversion – shifted the effect below $g = 1.5$, and the influence analysis did not identify dependence on any individual study other than Sterrett et al.¹⁶ However, diagnostic performance against an objective ICP reference standard could not be established.

Contrary to what might be assumed from the neurocritical-care literature, none of the studies identified in the hypertensive setting compared ONSD with invasive ICP measurement. In our view, this is the most consequential finding of the review: the current body of evidence consistently demonstrates that ONSD differs between hypertensive and normotensive individuals, but does not establish that this difference reflects objectively measured intracranial hypertension. This distinction is important because the thresholds currently used in practice – particularly the 5.8 mm cutoff – are derived from neurocritical populations and have not been validated in the hypertensive context.

From a cardiovascular imaging standpoint, ONSD expands the bedside ultrasound arsenal beyond the heart and great vessels, offering a non-invasive window into the intracranial repercussions of hypertensive crises. This positioning is particularly relevant in hypertensive disorders of pregnancy, whose association with future cardiovascular risk reinforces the relevance of the topic for cardiologists and imaging specialists.

Table 3 – Thresholds that would maximize the Youden index in each study (modeled projection)

Study (year)	Optimal threshold (mm)	Sensitivity (%)	Specificity (%)	Youden index
Su et al. ²²	4.14	86.3	90.4	0.77
Biswas et al. ⁶	4.43	81.0	82.4	0.63
Nagpal et al. ²³	4.65	81.3	86.0	0.67
Dikmetaş et al. ⁴	4.86	73.6	87.5	0.61
Arzpeyma et al. ¹⁹	4.90	68.8	87.8	0.57
Dubost et al. ⁵	4.95	75.3	76.2	0.52
Singh et al. ¹⁷	5.21	90.1	86.8	0.77
Kumar et al. ⁷	5.37	85.4	73.2	0.59
Sterrett et al. ¹⁶	7.79	1.6	98.7	0.00

Estimated values derived from the means and standard deviations of each group under a normal-distribution approximation; they do not represent observed counts nor thresholds reported by the original authors. The diagnostic target is the distinction between acute hypertensive state and control, not intracranial hypertension. In Sterrett et al.,¹⁶ the absence of separation between groups renders the Youden index null and the threshold practically indeterminate.

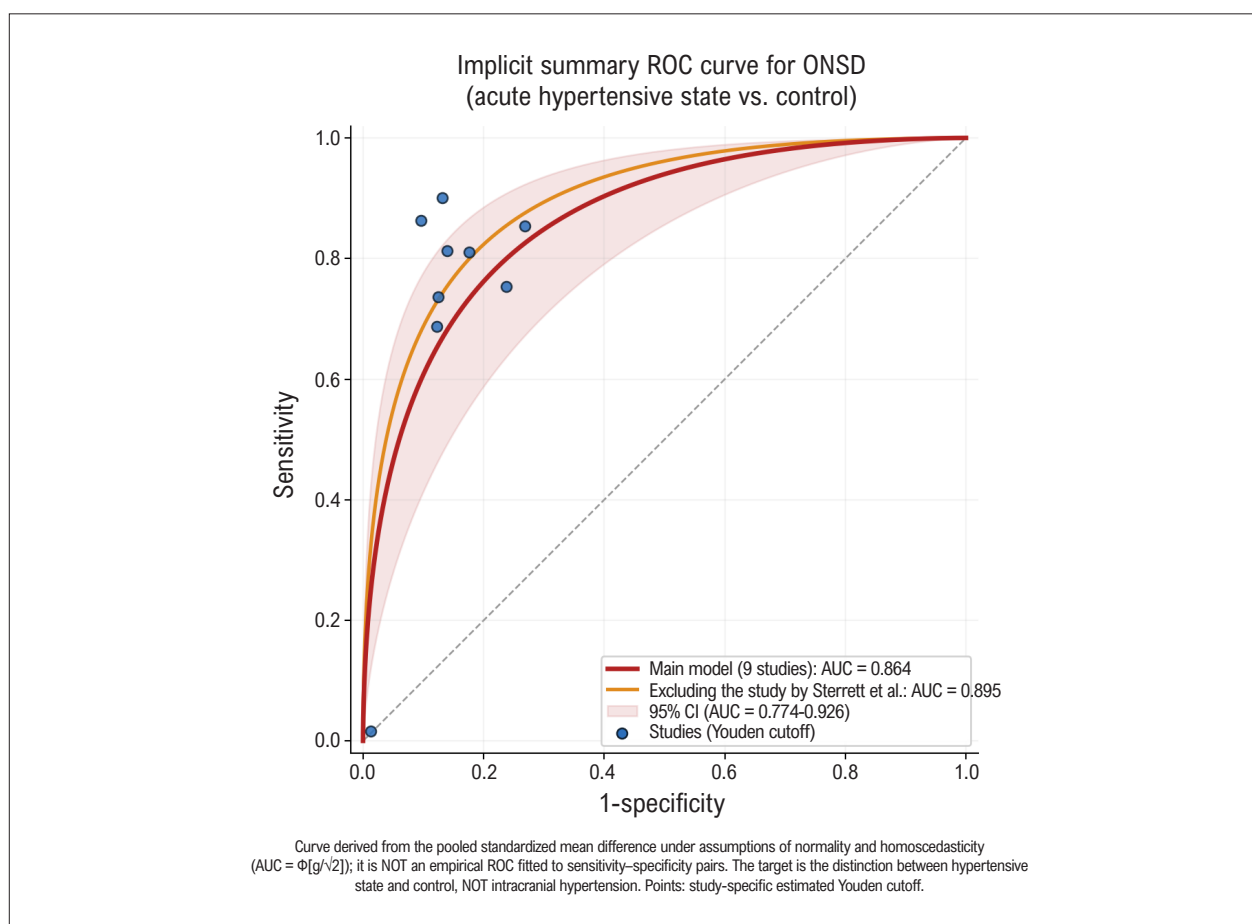


Figure 5 – Implicit summary ROC curve for ONSD in distinguishing acute hypertensive state from control, derived from the pooled standardized mean difference under assumptions of normality and homoscedasticity [$AUC = \Phi(g/\sqrt{2})$]. Red line: main model (nine studies; AUC 0.864); orange line: sensitivity analysis excluding the discordant study (AUC 0.895); band: 95% confidence interval; points: operating point of each study at the estimated Youden cutoff. The curve is not an empirical ROC fitted to sensitivity–specificity pairs; the target is the hypertensive-versus-control distinction, not intracranial hypertension.

The discordant study warrants specific consideration. In Sterrett et al.,¹⁶ the control group exhibited a higher mean ONSD than patients with preeclampsia, and the absolute values across all groups (5.5 to 5.9 mm) were substantially higher than those in the other studies, where control values ranged from 3.7 to 4.7 mm. This systematic shift suggests differences in acquisition technique or in the definition of the measurement point rather than a true absence of effect, and illustrates why methodological standardization is essential for comparability across studies.¹⁶ Technical differences described in the literature – internal versus external dural measurement, chosen axis, interocular asymmetry, and the ratio between ONSD and globe diameter – influence absolute values and thresholds and help interpret the observed heterogeneity.

The issue of a diagnostic cutoff deserves separate treatment, because the clinical question actually contains two distinct questions with opposite answers. A threshold intended to detect intracranial hypertension is, within this body of evidence, structurally underivable: a cutoff only exists in relation to a measured target, and none of the studies measured ICP. A threshold intended to distinguish hypertensive from normotensive patients is derivable – as three of the included studies attempted – but has limited clinical utility, since the hypertensive condition is already known from blood pressure measurement at the time of the exam.

Even if this more modest target were accepted, the data do not support a single unified threshold. The 2.23-mm span between control-group means and the 4.14- to 7.79-mm range of study-specific optimal cutoffs indicate that the same numerical ONSD value carries different meanings depending on the study. The most plausible explanation is technical: whether the measurement is referenced to the inner or outer dural border, the acquisition axis, and the imaging plane all produce systematic differences in the literature on the order of 0.5 to 1 mm – a magnitude comparable to the very effect one seeks to detect. Pooling thresholds obtained under non-standardized techniques and against different diagnostic targets would amount to combining quantities known to differ from one another, a practice against which the methodological literature on metaanalysis explicitly warns.

A direct practical implication follows from this: the 5.8-mm threshold, currently the most widely used in obstetric studies, was transposed from neurocritical populations without validation in the hypertensive setting, and its performance here ranged from perfect to useless depending on the study – from no control participant reaching the value in four studies to 44% of controls reaching it in another.

Until technical standardization and validation against an objective reference standard are available, thresholds should be derived and reported by technique and by population, rather than transferred across contexts. Obtaining a defensible pooled cutoff would require individual participant data or multi-threshold modeling, approaches that the available aggregated data do not permit.

Reference standard: why fundoscopic examination is not an appropriate comparator

None of the fourteen studies performed fundoscopic examination or documented papilledema, which prevents any direct comparison between the two techniques. This absence, however, is not the main gap in the body of evidence. Because papilledema is itself an indirect sign of intracranial hypertension, funduscopy does not qualify as a reference standard: estimates of sensitivity and specificity require that each individual be classified according to a standard considered definitive, and validating a test against an imperfect reference penalizes it precisely in situations where it would be earlier or more sensitive than that reference.

It follows that agreement with fundoscopic findings is not the appropriate criterion for judging ONSD, and that the relevant reference standard remains measured ICP – which, as already noted, none of the included studies assessed. An indirect piece of evidence from the dataset itself illustrates the issue. Brzan Simenc et al.¹⁸ measured, in the same 30 patients with severe preeclampsia and during the same examination session, two ultrasonographic markers: optic disc height, which reflects papilledema, and ONSD.¹⁸ Optic disc height was abnormal in 23 participants (76.7%; 95% CI 59.1 to 88.2), whereas ONSD exceeded 5.8 mm in 13 participants (43.3%; 95% CI 27.4 to 60.8), with no positive cases among the 30 controls for either marker. The 33-percentage-point difference between markers obtained at the same moment and in the same individuals is consistent with the hypothesis that the 5.8-mm threshold, imported from neurocritical populations, is insensitive in this setting – an interpretation that aligns with the threshold analysis presented in the results.

This observation should be interpreted with caution. It comes from a single study with thirty participants; the proportions are paired, but the article does not publish the cross-tabulation, meaning that a formal paired-data test cannot be calculated and only marginal distributions can be compared. Both markers are ultrasonographic, and optic disc height measured by ultrasound is not equivalent to papilledema identified on funduscopy; moreover, the 1-mm threshold for disc height has likewise not been validated against objective ICP measurement. The finding therefore raises a hypothesis regarding the adequacy of the ONSD threshold, but does not allow one to conclude that ONSD is superior, equivalent, or inferior to funduscopy – a comparison that the available data simply do not permit.

The convergence of the paired-design studies adds an independent argument. ONSD decreased after magnesium sulfate administration and after delivery in four distinct studies, with magnitudes consistent across them. This temporal reversibility, although not poolable with the primary outcome, is difficult to explain by selection bias and supports the interpretation that ONSD tracks a dynamic pathophysiological phenomenon.

Limitations

This work has several important limitations. The first is the complete absence of comparison with an objective

ICP reference standard among the included studies, which restricts inference to mean differences and prevents any statement about true diagnostic accuracy. The second arises from how the primary data were reported: three studies required dispersion conversion – two from medians and one from standard error – and in the latter, the main table of the article was internally inconsistent with another table from the same study, an ambiguity that could only be addressed through sensitivity analysis. Although these conversions follow established methods and the effect remained stable when converted studies were excluded, they introduce uncertainty and rely on assumptions of symmetry.

The third limitation is the high heterogeneity, only partially explained by the discordant study and by variability in control groups. The fourth is the impossibility of deriving or validating a diagnostic threshold, both because of the absence of a reference standard and because of the variability in absolute values across studies, which restricts the immediate bedside applicability of the method. The fifth is the predominance of studies on preeclampsia, with only one study involving non-pregnant hypertensive patients, which prevented formal subgroup comparison and limits generalization to other hypertensive etiologies. Additional limitations include the risk of bias in the source studies, the small sample size in most of them, and the inability to formally assess publication bias with fewer than ten studies.

It is therefore reinforced that future studies should report the mean and standard deviation of ONSD for each group – clearly distinguishing them from the standard error – so as to allow direct and reproducible pooling.

Implications

For clinical practice, the findings support that ONSD is a bedside-measurable marker, reproducible and sensitive to clinical variation, whose behavior is consistent with the pathophysiology of intracranial involvement in acute hypertensive states. They do not, however, support its adoption as a substitute for fundoscopy or as a diagnostic test for intracranial hypertension: the reference standard needed to quantify its performance is lacking, and no threshold is transferable across populations and techniques. As long as these two gaps persist, the method may inform clinical decision-making alongside neurological assessment and neuroimaging, but cannot replace them.

For research, the findings allow precise specification of the study that is missing. It consists of a design in which the same participants undergo ONSD measurement and an objective ICP reference standard – either invasive measurement or opening pressure on lumbar puncture – preferably conducted in a population with non-obstetric hypertensive emergencies, currently represented by only one study among the nine poolable ones. Fundoscopy may be incorporated into this design as a clinically relevant comparator, but not as a reference standard, for the reasons discussed. Prior standardization of the acquisition technique – definition of the measurement border, axis, and plane – and availability of individual participant data

are prerequisites for population-specific thresholds to be finally estimated and validated.

Conclusion

In acute hypertensive states, the ONSD measured by transorbital ultrasonography was consistently greater than in controls, with a large effect size ($g = 1.55$; 95% CI 1.06 to 2.04) and robustness to sensitivity analyses, supporting its potential as a non-invasive bedside marker of intracranial involvement when fundoscopy is impractical. However, heterogeneity was high; one study yielded a discordant result; part of the data depended on dispersion conversions; no study compared the method with an objective ICP reference standard; and the data do not support adoption of a single cutoff value, given the incompatibility of absolute measurements across studies. These findings should be interpreted with caution and reinforce the need for standardization of both technique and threshold, for reporting of group-specific means and standard deviations, and for studies pairing ONSD with objective reference standards in the hypertensive setting.

Author Contributions

Conception and design of the research, acquisition of data, analysis and interpretation of the data, statistical analysis, writing of the manuscript and critical revision of the manuscript for intellectual content: Ramos JVO, Melo MDT.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

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Study Association

This study is not associated with any thesis or dissertation work.

Ethics Approval and Consent to Participate

This article does not contain any studies with human participants or animals performed by any of the authors.

Use of Artificial Intelligence

During the preparation of this work, the authors used **Claude (Anthropic)** to assist in the preparation of the text and in performing and verifying the resulting calculations. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

Availability of Research Data

The underlying content of the research text is contained within the manuscript.

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*Supplemental Materials

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Increased Blood Pressure and Increased Optic Nerve Sheath Diameter: Intracranial Involvement or a Nonspecific Marker?

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Short Editorial related to the article: Ultrasound Measurement of Optic Nerve Sheath Diameter in Acute Hypertensive States For Detection of Intracranial Involvement: A Meta-Analysis

Effects of increased blood pressure extend beyond the systemic arteries

A hypertensive emergency is defined by presence of acute target-organ damage, not merely by an increased blood pressure reading. In brain, however, identifying such involvement at bedside remains challenging. Headache, nausea, visual disturbances, seizures, and altered consciousness are clinically important but nonspecific manifestations. Although fundoscopy has traditionally played an important role in clinical assessment, its reliability depends on adequate training, appropriate technical conditions, and patient cooperation. Moreover, papilledema may be absent during initial hours of increased intracranial pressure (ICP).¹ Within this diagnostic window, ultrasonographic measurement of optic nerve sheath diameter (ONSD) represents an appealing option: it is rapid, portable, and repeatable and capitalizes on anatomical continuity between intracranial subarachnoid space and perioptic compartment.^{2,3}

Article accompanying this short editorial provides most focused synthesis to date of ONSD findings in acute hypertensive states. Its results are consistent with those of previous studies involving acute hypertension, severe preeclampsia, and eclampsia.⁴⁻⁶ Review included 14 studies comprising 995 participants, predominantly patients with preeclampsia or eclampsia, together with a considerably smaller group of nonpregnant patients with hypertension. Across nine studies with continuous data suitable for pooling comprising 426 hypertensive patients and 283 controls, ONSD was significantly greater in hypertensive group, with a large standardized mean difference (Hedges'g: 1.55; 95% CI: 1.06-2.04; $p < 0.001$). This is not a trivial finding: it suggests that association between acute hypertension and optic nerve sheath distension is sufficiently consistent that it cannot readily be dismissed as an isolated artifact.

Palavras-chave

Arterial Pressure; Optic Nerve; Intracranial Pressure; Ultrasonography

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A robust effect does not establish a validated diagnosis

Large effect size, however, coexisted with substantial heterogeneity ($I^2 = 87\%$). Eight of nine studies reported large and directionally consistent effects, whereas one yielded a discordant result, with numerically greater ONSD values among controls. Excluding this study increased the pooled effect estimate to 1.77 (95% CI: 1.50-2.04) and reduced I^2 to 51.8%, which suggests that much of inconsistency was attributable to a single study. Nevertheless, remaining heterogeneity should not be overlooked: study populations, control groups, acquisition techniques, measurement boundaries, insonation planes, and ultrasound equipment varied across studies.

Dichotomous findings pointed in same direction but warrant similar caution. In five studies reporting observed event counts, hypertensive patients had greater odds of an ONSD exceeding the threshold adopted in each study (odds ratio [OR]: 11.58; 95% CI: 1.45-92.85; $I^2 = 73.7\%$). Because of the extremely wide confidence interval, frequent zero-event cells, and reliance on a continuity correction, this estimate is more informative about the direction of the association than about its precise magnitude. After exclusion of discordant study, OR increased to 29.54 and heterogeneity fell to zero. This apparent improvement in precision, however, does not overcome the limitations of the underlying studies.

The principal evidence gap is more fundamental: none of 14 studies compared ONSD with invasive ICP measurements or cerebrospinal fluid opening pressure. Meta-analysis therefore demonstrates that on average acutely hypertensive patients have a larger ONSD than controls. It does not demonstrate that all such patients have intracranial hypertension nor does it establish the diagnostic accuracy of ONSD for detecting this condition. Receiver operating characteristic curves reported in individual studies assessed the ability of ONSD to distinguish preeclampsia from normotension, a distinction already identifiable from blood pressure measurements and the obstetric context, rather than its ability to detect increased ICP. Conflating these diagnostic targets would transform a phenotypic association into an unwarranted claim of pathophysiological equivalence.

These limitations do not negate the diagnostic performance of ONSD measurement in other populations. In neurocritically ill patients without traumatic brain injury, a systematic review of 18 studies comprising 1,484

participants reported a pooled sensitivity of 92%, specificity of 90%, and area under the curve of 0.925 for detecting increased ICP.⁷ These findings support use of ONSD as a screening tool and reinforce its biological plausibility. However, they cannot be extrapolated automatically to acute hypertensive states, which differ in their underlying etiologies, measurement techniques, and reference standards.

Autoregulation and Monro-Kellie 4.0: the mechanism matters

Cerebral autoregulation provides the principal mechanistic link among mean arterial pressure (MAP), ONSD, and ICP. When autoregulation is intact, an increase in MAP triggers arteriolar vasoconstriction, thereby limiting the transmission of systemic pressure to the cerebral microvasculature. When the upper limit of autoregulation is exceeded or cerebrovascular reactivity is impaired, pressure is transmitted more passively, promoting hyperperfusion, increased cerebral blood volume, and vasogenic edema.^{8,9}

The Monro-Kellie 4.0 model further posits that this response is governed by intracranial compliance and compensatory reserve, both of which vary dynamically across intracranial regions. Interactions among the blood, cerebrospinal fluid, and interstitial compartments, compounded by venous congestion or focal lesions, may create pressure gradients and exhaust regional compensatory reserve before overt global deterioration becomes apparent.⁹

Within this framework, ONSD should be viewed as a marker of pressure within the perioptic compartment rather than as a standalone measure of global intracranial dynamics. When measured bilaterally approximately 3 mm behind the globe using a standardized technique,^{1-3,7} ONSD may reflect rapid changes in pressure, although measurements remain susceptible to individual anatomical variation and technical factors. This sensitivity is both its principal strength and a major source of interpretive uncertainty.

A single cutoff may provide false reassurance

Accompanying article shows that available evidence does not support the use of a universal ONSD threshold. Reported cutoffs varied widely across studies and were derived for different clinical conditions. The 5.8-mm threshold frequently cited in obstetric research was extrapolated from neurocritical care populations and has not been specifically validated in this clinical setting. Even seemingly minor methodological differences (including the choice of the inner or outer dural border, measurement axis, and imaging plane) can alter ONSD values by approximately 0.5-1.0 mm. Such variation is clinically meaningful when proposed thresholds fall within the narrow range of 5-6 mm.

Moreover, the available evidence is overwhelmingly derived from patients with hypertensive disorders of pregnancy. Only one of the nine studies included in the

continuous-data meta-analysis evaluated nonpregnant patients with hypertension. Although that study also reported a large effect, its findings alone are insufficient to justify extrapolation to nonobstetric hypertensive emergencies. Studies using paired measurements found reductions in ONSD after magnesium sulfate administration or delivery, suggesting that ONSD reflects a dynamic and potentially reversible process. However, without a concurrent reference standard, these changes cannot be attributed solely to changes in ICP.

Positioning statement: context, trends, and multimodal concordance

Available evidence suggests that increased ONSD in acute hypertensive states should be regarded as a marker of possible intracranial involvement — modulated by cerebral autoregulation and compensatory reserve — rather than as a stand-alone diagnosis of intracranial hypertension. In isolation, an increased ONSD should not prompt aggressive blood pressure reduction or ICP-directed therapy. Conversely, a normal ONSD does not exclude severe cerebral disease, a focal intracranial lesion, or evolving intracranial hypertension. An excessively rapid reduction in MAP, particularly in patients with chronic hypertension and a rightward shift of the autoregulatory curve, may convert suspected cerebral hyperperfusion into iatrogenic cerebral hypoperfusion.

We therefore advocate a four-layered approach to interpretation. First, establish the clinical syndrome and confirm the presence of acute target-organ damage. Second, interpret MAP in the context of the patient's usual blood pressure, the rate of blood pressure increase, and the probable rightward shift of the autoregulatory curve associated with chronic hypertension. Third, integrate ONSD findings with the neurological examination, fundoscopy when feasible, and computed tomography or magnetic resonance imaging. Fourth, whenever possible, obtain an early baseline ONSD measurement and prioritize serial assessments performed using a standardized technique, ideally by the same operator. In the absence of a validated universal cutoff, intraindividual changes — interpreted alongside the clinical course, other neuromonitoring modalities, and controlled changes in MAP — may be more informative than a single measurement and may help identify improvement or deterioration over time.

The B-ICONIC consensus was developed for patients with traumatic brain injury, the population in which its supporting evidence is concentrated. Extrapolation to other populations, including patients with acute hypertensive states, is therefore based on low-certainty evidence and should not be presented as a validated protocol.¹⁰ Nevertheless, the underlying physiological principle of multimodal concordance remains relevant: when invasive ICP monitoring is unavailable, no noninvasive modality should be interpreted in isolation. Concordant findings across at least two modalities, such as ONSD measurement, transcranial Doppler or duplex ultrasonography, automated pupillometry, and noninvasive ICP waveform analysis,

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when integrated with clinical and neuroimaging findings, may provide a prudent approach to diagnostic triangulation in these patients.

Accordingly, an increased ONSD should prompt further corroboration rather than be regarded as a diagnostic endpoint. Its clinical relevance increases when it is concordant with abnormal transcranial Doppler findings, altered pupillometry, impaired noninvasive ICP waveform morphology, neurological deterioration, or radiological abnormalities. When findings are discordant, the acquisition technique should be reviewed, the measurement repeated, the possibility of intracranial compartmentalization considered, and the diagnostic evaluation expanded. Brzan Simenc et al., for example, identified discrepancies among ocular ultrasonographic markers in patients with severe preeclampsia, underscoring that indirect markers may respond differently to the same pathophysiological process and should not be regarded as interchangeable.⁵

The next step in this field should not be merely to identify another cutoff. Prospective studies should simultaneously assess MAP, ONSD, invasive ICP when monitoring is clinically indicated or cerebrospinal fluid opening pressure

when available, PaCO₂, patient position, neuroimaging findings, and markers of cerebral autoregulation. They should also standardize the ultrasound equipment, acquisition plane, and measurement boundaries and evaluate preeclampsia/eclampsia, hypertensive encephalopathy, posterior reversible encephalopathy syndrome, intracranial hemorrhage, and nonobstetric acute hypertension as distinct clinical entities. Individual participant data and serial measurements will be necessary to establish technique- and population-specific thresholds and to determine whether ONSD provides incremental prognostic information or meaningfully guides treatment.

The article accompanying this short editorial strengthens the evidence for an association between acute hypertension and increased ONSD while clearly delineating the boundaries of current knowledge. Figure 1 displays the proposed relationship among MAP, autoregulatory integrity, and the response of the perioptic compartment. Measurement is valuable; interpretation is indispensable. Clinical utility of ONSD lies not in treating it as an absolute manometer, but in using it as a dynamic window into a complex intracranial system as part of a concordant, multimodal, physiologically informed assessment.

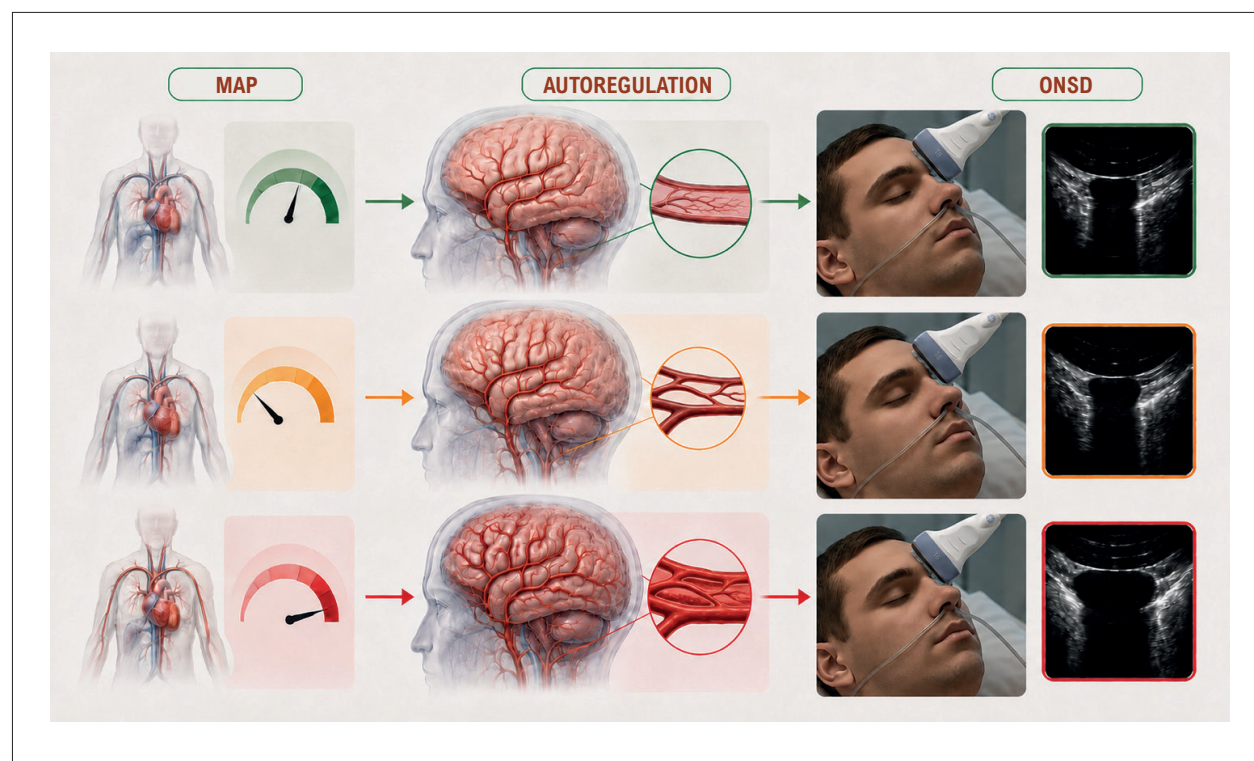


Figure 1 – Proposed physiological model of the relationship among MAP, cerebral autoregulation, and ONSD. In upper panel, preserved autoregulation induces arteriolar vasoconstriction, limiting the transmission of increased systemic pressure to the intracranial circulation and preventing a clinically relevant increase in ONSD. In middle panel, impaired autoregulation allows passive vasodilation and an increase in cerebral blood volume, potentially resulting in ONSD enlargement. In lower panel, more severe autoregulatory failure is associated with cerebral hyperemia, greater intracranial involvement, and more pronounced optic nerve sheath distension. This figure presents a conceptual model and should not be interpreted as a stand-alone diagnostic test. MAP: mean arterial pressure; ONSD: optic nerve sheath diameter.

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Left Atrial Strain Assessment in Hereditary Amyloidosis: A Systematic Review

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Abstract

Background: Hereditary transthyretin amyloidosis (ATTRv) is a genetic disorder caused by extracellular deposition of amyloid fibrils derived from plasma transthyretin in tissues following loss of its tetrameric structure, affecting the heart and nervous system.

Objective: This study aimed to assess left atrial function in ATTRv and to discuss its relevance as a tool for early detection of cardiac involvement, as well as its prognostic value.

Methods: This systematic literature review was conducted in accordance with PRISMA guidelines and registered in PROSPERO (CRD42051116316). The following databases were searched: Embase, PubMed, Scopus, and LILACS, including studies published between January 2010 and August 2025. MeSH terms used included “cardiac amyloidosis,” “transthyretin amyloidosis,” “ATTR,” “echocardiography,” “strain,” and “left atrium.”

Results: Nine studies were included, comprising a total of 1,290 patients with amyloidosis. Assessment of left atrial function demonstrated a progressive reduction in left atrial strain, particularly reservoir strain, measured by peak atrial longitudinal strain (PALS), across the clinical spectrum of ATTRv, as follows: unaffected carriers (PALS 23%–30%), neuropathic phenotype (PALS 20%–25%), and amyloid cardiomyopathy (PALS 8%–15%).

Conclusion: This systematic review demonstrates that left atrial strain dysfunction is a consistent finding in patients with ATTRv, including carriers and individuals with isolated polyneuropathy. Reduced PALS and increased atrial stiffness emerge as promising parameters for early detection of cardiac involvement, with potential prognostic value. These findings should be interpreted with caution due to the observational design of the included studies. Further studies with larger sample sizes are needed.

Keywords: Amyloidosis; Left Atrial Function; Familial Amyloid Neuropathies.

Introduction

Amyloidosis is a disease characterized by abnormal deposition of amyloid fibrils, mainly affecting the heart and nervous system. It may result from immunoglobulin light chains, variant transthyretin, or wild-type transthyretin.¹⁻⁴ In hereditary transthyretin amyloidosis (ATTRv), the mutant transthyretin protein, which has a tetrameric structure, loses its stability and misfolds, forming fibrillar aggregates that deposit in several organs, particularly in the peripheral and autonomic nervous systems (polyneuropathy phenotype), cardiac chambers (cardiomyopathy phenotype), or presenting a mixed phenotype.^{3,5,6} The diagnosis and treatment of this potentially severe and underdiagnosed disease have significantly advanced in recent years, highlighting the need for early identification of cardiac involvement in individuals carrying pathogenic variants.^{2,7,8}

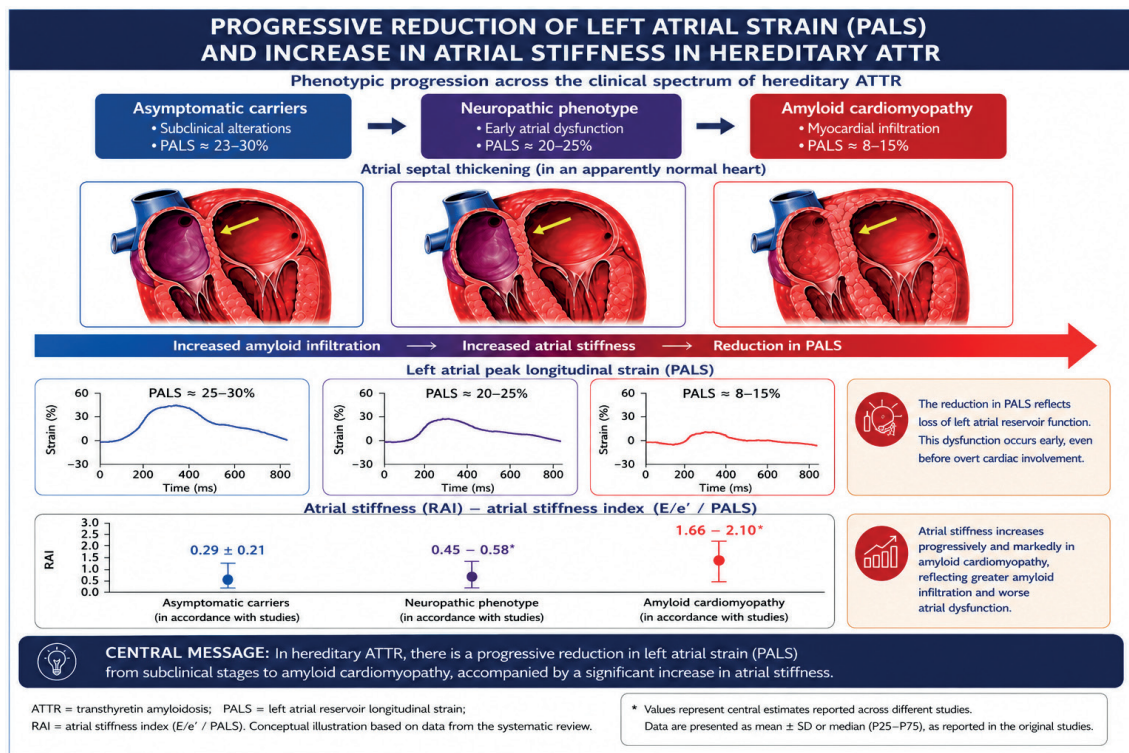
Speckle-tracking echocardiography has demonstrated an important role in the diagnosis of cardiac amyloidosis through the assessment of myocardial deformation (strain), particularly by identifying the apical sparing pattern, characterized by preserved contractility of the apical segment and greater impairment of basal segments of the left ventricle.⁹⁻¹¹ The assessment of atrial function using speckle-tracking has emerged as an early diagnostic tool in hereditary amyloidosis.¹²

The left atrium performs three fundamental functions: it acts as a reservoir, serves as a conduit, and has a contractile (pump) role.¹² Bandera et al. defined reservoir strain, or peak atrial longitudinal strain (PALS), as the ability of the atrium to expand during ventricular systole, with its peak value occurring at the beginning of left ventricular filling. Contraction strain (pump function) represents atrial shortening, with peak value at the onset of atrial contraction (in individuals in sinus rhythm), whereas conduit strain reflects early diastolic emptying and is calculated as the difference between reservoir and contraction strain.^{13,14} Left atrial stiffness is calculated as the ratio between E/e' and reservoir strain.^{13,15,16} According to Pathan et al. (2016), normal reference values for reservoir, conduit, and contraction strain are 39.4% (95% confidence interval [CI]: 38.0%–40.8%), 23.0% (95% CI: 20.7%–25.2%),

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Central Illustration: Left Atrial Strain Assessment in Hereditary Amyloidosis: A Systematic Review



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Progressive reduction in left atrial strain (PALS) and increase in atrial stiffness across the clinical spectrum of hereditary ATTR. Conceptual illustration based on findings from the systematic review. ATTR: transthyretin amyloidosis; PALS: peak atrial longitudinal strain; RAI: atrial stiffness index (E/e' divided by PALS).

and 17.4% (95% CI: 16.0%–19.0%), respectively.¹² Normal atrial stiffness values have a mean of 0.21 ± 0.1 .¹⁷

This review aimed to identify alterations in left atrial strain assessed by speckle-tracking echocardiography in patients with ATTRv and to discuss its relevance for early detection of cardiac involvement and prognostic value (Central Illustration).

Methods

A systematic review was conducted according to a prespecified protocol registered in PROSPERO and reported in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (Figure 1).

Selection criteria

Inclusion criteria

We included original observational studies (cross-sectional, case-control, and cohort) evaluating left atrial function in individuals with ATTRv. The search was restricted to studies published in Portuguese and English.

Exclusion criteria

We excluded duplicate studies, case reports, and case series with fewer than 10 patients. Additionally, studies published in other languages, those focusing on immunoglobulin light-chain amyloidosis, and those evaluating left atrial strain in cardiopathies unrelated to ATTRv were excluded.

Search strategy

A comprehensive and systematic search was conducted in the electronic databases Embase, PubMed, Scopus, and LILACS, covering the period from January 2010 to August 2025. The search strategies (i.e., specific keywords and MeSH terms used) are detailed in the Supplementary Material.

Study analysis

Two authors independently reviewed titles and abstracts of articles and selected the studies compatible with the inclusion criteria. Afterwards, final eligibility was determined through full-text review. Any disagreement was resolved by consulting a third author.

Data from the included articles were extracted using a data collection form, including study design, year of publication,

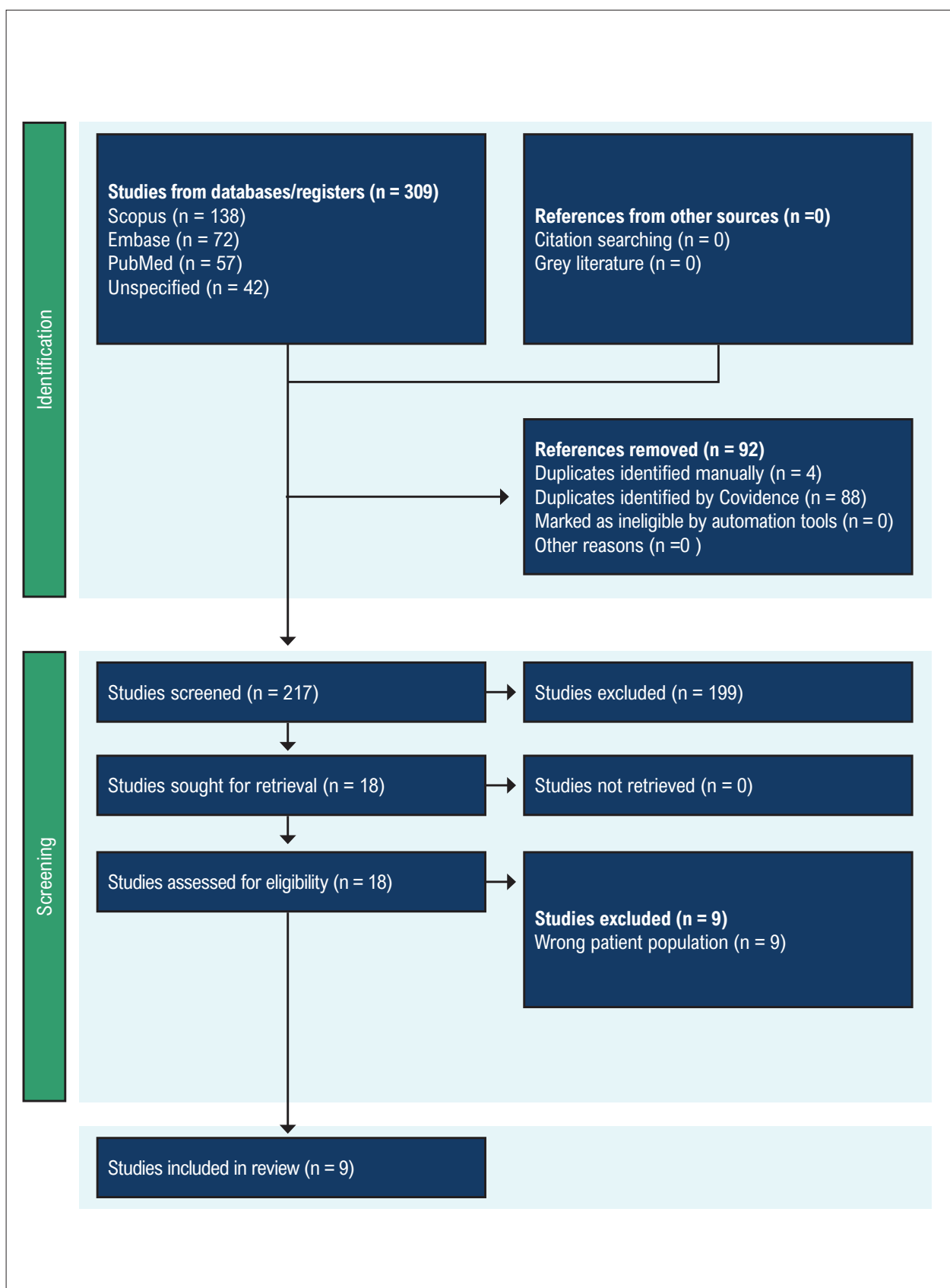


Figure 1 – Systematic literature review flowchart.

methodology, demographic characteristics, sample size, and clinical outcomes. In studies with heterogeneous populations, only data related to patients with ATTRv were extracted. PALS, also referred to as reservoir strain, was analyzed in all studies. Conduit strain, contraction strain, and left atrial stiffness were also assessed when available.

Assessment of risk of bias and statistical analysis

The methodological quality of the included studies was independently assessed by two reviewers using the Newcastle–Ottawa Scale (NOS), adapted for application to observational studies with different designs, including cohort, case-control, and cross-sectional studies. Although widely used, it is recognized that the NOS has limitations when evaluating studies without a control group.

The scale is structured into three main domains: selection of participants, comparability of groups, and assessment of outcomes. A total score was calculated for each study, allowing classification of methodological quality (risk of bias) as low, moderate, or high. Disagreements between reviewers were resolved by consensus.

Results

The search strategy identified 309 potentially relevant studies. After removal of duplicates, 217 studies remained and were screened by title and abstract; subsequently, relevant articles were selected for full-text review. A total of 18 articles were assessed in full, of which 9 were excluded based on the predefined criteria. Consequently, 9 studies were included in the systematic review.

A total of 1,290 individuals with amyloidosis were included in the analysis. The search was completed in August 2025. The included studies were conducted in Italy (n = 5), England (n = 1), Mexico (n = 1), the United States (n = 1), and Sweden (n = 1) and were published between 2016 and 2024. The analyzed studies included patients with hereditary amyloidosis categorized into three groups: unaffected carriers, patients with polyneuropathy, and patients with cardiac amyloidosis. Sample sizes ranged from 21 to 241 individuals with the genetic mutation.

All studies used ultrasound equipment (GE; Esaote; Philips Medical) with dedicated software for left atrial assessment using speckle-tracking echocardiography. Most studies reported data collection for at least one of the three functional phases of the left atrium (PALS, conduit, and contraction), as well as atrial stiffness when available (Table 1).

Outcomes were reported as mean and standard deviation or median and interquartile range for strain parameters (PALS, conduit, contraction, atrial stiffness), rather than as proportions of individuals classified as having abnormal values based on validated cutoff points.

Across all included studies, a reduction in left atrial strain was observed, with varying magnitudes according to clinical phenotype (Figure 2). This alteration was present not only in patients with cardiac amyloidosis but also in carriers and in patients with polyneuropathy without overt cardiac involvement. Although the high frequency of this finding

suggests that atrial dysfunction is common in ATTRv, it was not possible to estimate its prevalence, as the included studies primarily reported mean values or between-group differences rather than proportions of affected individuals.

Unaffected carriers

The results showed that unaffected carriers had mildly reduced PALS values,^{18–20} consistent with the findings of Aceves Velazquez et al.,²¹ who studied 30 individuals (PALS 30%, $p = 0.03$). In 2023, Di Lisi et al.¹⁵ published a study to identify early signs of cardiac involvement across different groups of hereditary amyloidosis. In group C of Di Lisi et al.¹⁵ (carriers), PALS values were reduced in 11 individuals ($23.64\% \pm 10.06\%$), while mean atrial stiffness was above the normal range (0.29 ± 0.21).

Patients with isolated polyneuropathy

In patients with polyneuropathy, the results showed a significant reduction in left atrial function even in the absence of overt cardiac involvement. Group B of Di Lisi et al.¹⁵ (only polyneuropathy) demonstrated reduced PALS values ($23.63\% \pm 11.2\%$, $p = 0.005$; group A vs. group B) and increased atrial stiffness (0.58 ± 0.2). In 2024, Di Lisi et al.¹⁶ published a study evaluating the effects of patisiran on cardiac function. At baseline (T0), the neuropathy group (n = 14) showed reduced PALS ($24.65\% \pm 11.35\%$) and elevated atrial stiffness (0.45 ± 0.43).²² In the study by Di Bella et al.,²³ 28 patients were evaluated using both echocardiography and cardiac magnetic resonance imaging (MRI). Late gadolinium enhancement (LGE) on MRI was used to assess atrial amyloid deposition, while echocardiographic strain was used to quantify left atrial deformation. PALS values were significantly lower in the group with atrial LGE (n = 14) compared with the group without LGE (n = 14) ($22.8\% \pm 13\%$ vs. $59.6\% \pm 33.1\%$; $p = 0.002$ and $p = 0.001$, respectively).

The other phases of atrial function were also more impaired in the LGE group than in the non-LGE group. Conduit strain was significantly lower in the LGE group compared with the non-LGE group ($10.2\% \pm 6.2\%$ vs. $30.2\% \pm 22.4\%$; $p = 0.01$ and $p < 0.0001$, respectively). Similarly, contraction strain (global pre-A strain) was reduced in the LGE group compared with the non-LGE group ($12.6\% \pm 7.8\%$ vs. $26.2\% \pm 15\%$; $p = 0.001$ and $p = 0.01$, respectively). Overall, left atrial function was significantly lower in patients with atrial LGE than in those without LGE.

Cardiac amyloidosis

Patients with overt cardiac amyloidosis exhibited the most pronounced reductions in PALS. In the study by Bandera et al.,¹³ individuals with the V122I mutation had lower PALS values (8.0% [5.3% – 10.9%]) compared with those carrying the T60A mutation (11.4% [7.0% – 15.7%]; $p < 0.05$). Other parameters of atrial function were also consistently reduced. Conduit strain was 7.0% (4.7% – 10.0%) in T60A and 6.1% (4.2% – 8.2%) in V122I ($p = \text{NS}$), while contraction strain was 5.0% (2.8% – 8.4%) in T60A and 3.1% (1.6% – 5.0%) in V122I ($p < 0.05$). In addition, atrial stiffness was significantly higher (2.12 vs. 1.67 ; $p < 0.001$).

Original Article

Table 1 – Summary of study design, results, and conclusions

Study	Method	Outcome	Results	Conclusions
Aceves Velazquez et al., 2020 ²¹	Cross-sectional within a cohort. Objective: To determine whether strain is a good predictor of cardiac involvement suggestive of amyloid deposition in the heart. Population: 30 participants with ATTRv without known cardiac involvement.	PALS	PALS decreased from 34% to 30% ($p = 0.03$).	Echocardiographic strain may detect early abnormalities in patients with cardiac involvement due to ATTRv, suggesting potential prognostic value.
Bandera et al., 2022 ¹³	Cross-sectional. Objective: To assess LA stiffness and mechanics using speckle-tracking echocardiography and to analyze the association between atrial functional parameters and clinical outcomes. Population: Patients with ATTR-CA. N = 906 participants (551 ATTRwt; 355 ATTRv – 241 V122I; 93 T60A and 21 others).	PALS, conduit strain, contraction strain, atrial stiffness	PALS (%): T60A 11.4% (7.0%–15.7%); V122I 8.0% (5.3%–10.9%), $p < 0.05$ (T60A vs. V122I). Conduit strain (%): T60A 7.0% (4.7%–10.0%); V122I 6.1% (4.2%–8.2%), $p = \text{NS}$. Contraction strain (%): T60A 5.0% (2.8%–8.4%); V122I 3.1% (1.6%–5.0%), $p < 0.05$. Atrial stiffness: T60A 1.67 (0.87–2.70); V122I 2.12 (1.34–3.29), $p < 0.001$.	Lower PALS in V122I compared to ATTRwt and T60A; higher LA stiffness in V122I; both associated with worse prognosis.
de Gregorio et al., 2016 ²²	Cross-sectional. Objective: To evaluate and compare distinctive characteristics of LA size and function in patients with ATTR-CA and HCM. Population: 32 patients (16 with ATTR-CA and 16 with HCM) and 15 healthy controls.	PALS and contraction strain	PALS (%): 14.1 ± 4.7 , $p < 0.001$ (comparison between ATTR-CA, HCM, and controls). Contraction strain (%): 10.92 ± 0.56 , $p < 0.01$.	PALS significantly impaired in ATTR-CA vs. HCM and controls; also lower in HCM vs. controls. PALS $< 19\%$ in 94% of ATTR-CA vs. 31% of HCM and none of controls ($p < 0.001$). ROC suggested cutoff PALS $\leq 19\%$ and contraction $\leq 11.1\%$.
Di Bella et al., 2016 ²³	Case-control study. Objective: To analyze atrial function in patients with and without atrial amyloid deposition. Population: Patients with familial amyloid polyneuropathy (TTR-related) without cardiac disease. 50 participants: 28 patients and 22 controls.	PALS, conduit strain, contraction strain	PALS: LGE-atrial group ($n = 14$) $22.8\% \pm 13\%$, $p = 0.002$; non-LGE ($n = 14$) $59.6\% \pm 33.1\%$, $p = 0.001$; controls $47.4\% \pm 16.4\%$. Conduit strain: LGE $10.2\% \pm 6.2\%$, $p = 0.01$; non-LGE $30.2\% \pm 22.4\%$, $p < 0.0001$; controls $26.3\% \pm 11.9\%$. Contraction strain: LGE $12.6\% \pm 7.8\%$, $p = 0.001$; non-LGE $26.2\% \pm 15\%$, $p = 0.01$.	Cutoff PALS $\leq 40.9\%$: sensitivity 100%, specificity 71.6% (AUC 0.91). LA remodeling and dysfunction present; useful for clinical and prognostic stratification.
Di Lisi et al., 2023 ¹⁵	Cross-sectional. Objective: To analyze echocardiographic and speckle-tracking differences among carriers, neuropathic patients, and CA patients. Population: 31 patients with TTR mutation.	PALS and atrial stiffness	PALS: group A $9.8\% \pm 3$; group B $23.63\% \pm 11.2$ ($p = 0.005$); group C $23.64\% \pm 10.06$. Atrial stiffness: group A 1.6 ± 0.30 ; group B 0.58 ± 0.2 ; group C 0.29 ± 0.21 .	Monitoring PALS and stiffness may help identify disease progression.

Di Lisi et al., 2024 ¹⁶	Non-randomized experimental study. Objective: To evaluate patisiran effects on cardiac function using speckle-tracking. Population: ATTRv patients (group A n = 7; group B n = 14).	PALS and atrial stiffness	PALS: group A 12% ± 6%; group B 24.65% ± 11.35%. Stiffness: group A 2 ± 1; group B 0.45 ± 0.43.	Speckle-tracking useful for early diagnosis and monitoring; larger studies needed.
Henein et al., 2018 ¹⁹	Cross-sectional. Objective: Evaluate LA function in ATTRv and compare with HCM and controls.	Reservoir, conduit, contraction strain	PALS: 24 ± 7 vs. 29 ± 10 (controls), p = 0.015. Conduit: 11.0 ± 0.6 vs. 11.4 ± 0.6, p = 0.005. Contraction: 11.4 ± 0.5 vs. 11.7 ± 0.6, p = 0.025.	LA function reduced regardless of left ventricular thickness; useful for early screening and arrhythmic risk prediction.
Nochioka et al., 2017 ¹⁸	Cross-sectional. Objective: Characterize LA function in CA and determine mechanisms.	PALS, conduit, contraction strain	PALS 20.1 ± 13.9; multiple strain parameters impaired; no significant p differences.	Reduced LA function associated with worse survival; ATTRwt worst prognosis.
Trimarchi et al., 2023 ²⁴	Cross-sectional. Objective: Compare ATTRwt-CA vs. ATTRv-CA.	PALS, conduit, contraction strain	PALS: 9.7 ± 3.7 vs. 17.6 ± 7.5 (p = 0.004). Conduit: 17.6 ± 2.3 vs. 18 ± 3.5 (p = 0.8). Contraction: 12.5 ± 3.1 vs. 110 ± 4.7 (p < 0.0001).	Advanced echocardiography differentiates atrial and ventricular involvement between subtypes.

ATTR-CA: transthyretin cardiac amyloidosis; ATTRv: hereditary transthyretin amyloidosis; ATTRwt: wild-type transthyretin amyloidosis; AUC: area under the receiver operating characteristic curve; CA: cardiac amyloidosis; HCM: hypertrophic cardiomyopathy; LA: left atrial; LGE: late gadolinium enhancement; NS: not significant; PALS: peak atrial longitudinal strain; ROC: receiver operating characteristic curve; TTR: transthyretin.

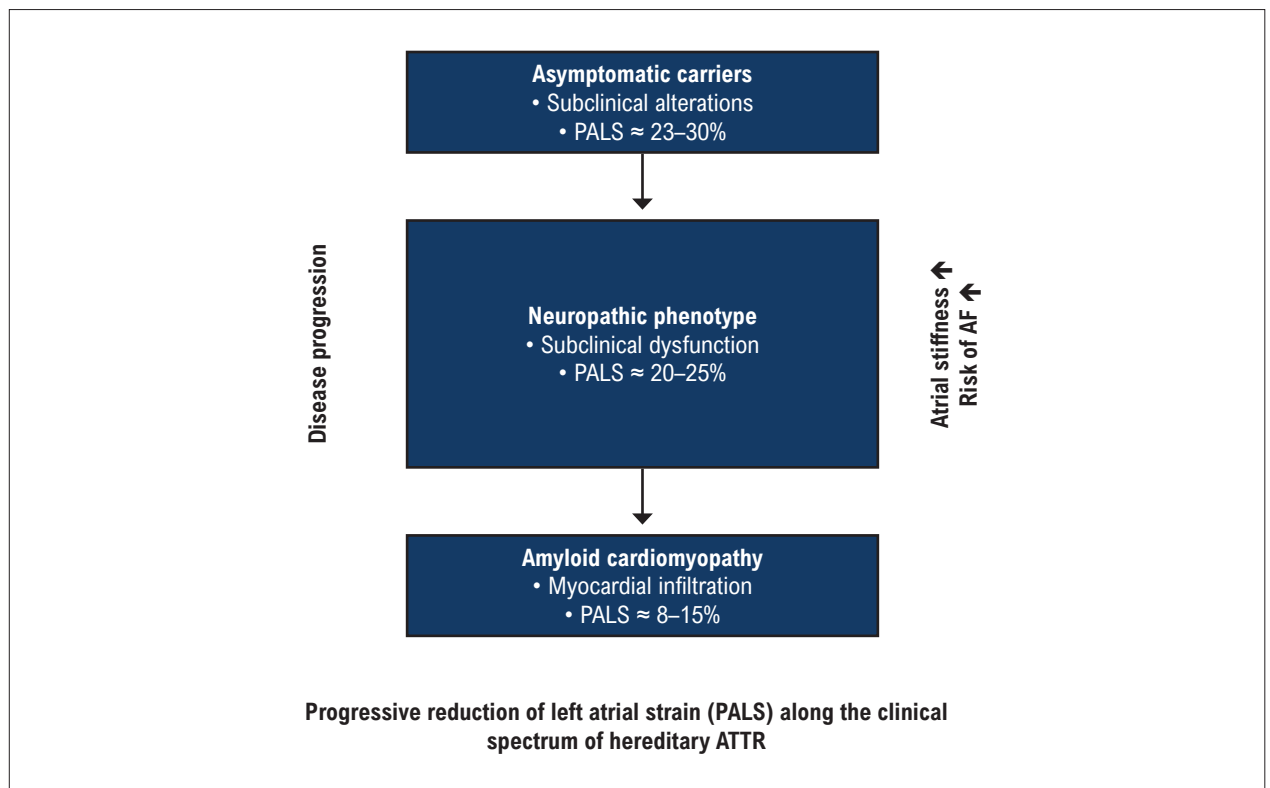


Figure 2 – Progression of atrial dysfunction in ATTRv. AF: atrial fibrillation; ATTR: transthyretin amyloidosis; PALS: peak atrial longitudinal strain.

Similarly, group A (cardiac involvement) in Di Lisi et al.¹⁵ showed reduced PALS ($9.8\% \pm 3\%$) and increased atrial stiffness (1.6 ± 0.30) in 7 individuals. Comparable findings were reported in the cardiac amyloidosis group at baseline (T0, $n = 7$) in Di Lisi et al.,¹⁶ with PALS of $12\% \pm 6\%$ and atrial stiffness of 2 ± 1 .

Henein et al.¹⁹ evaluated 46 patients with ATTRv confirmed by abdominal biopsy and genetic testing (predominantly V30M). Among them, 32 had left ventricular wall thickness > 12 mm (classified as “amyloid hypertrophy”) and 14 had wall thickness ≤ 12 mm. The mean PALS value was $24\% \pm 7\%$ ($p = 0.015$). Additionally, parameters derived from conduit and contraction strain were also reduced compared with healthy controls. Conduit strain (LASRe) was -1.0 ± 0.6 in the ATTR group versus -1.4 ± 0.6 in controls ($p = 0.005$), and contraction strain (LASRa) was -1.4 ± 0.5 versus -1.7 ± 0.6 ($p = 0.025$), respectively.

Nochioka et al.¹⁸ demonstrated that all parameters derived from speckle-tracking assessment of left atrial function were markedly impaired in 29 patients with cardiac amyloidosis. PALS was $20.1\% \pm 13.9\%$ ($p = 0.47$), peak longitudinal strain rate (LSR) was 0.88 ± 0.54 ($p = 0.12$), and total emptying fraction was $45.7\% \pm 16.8\%$ ($p = 0.73$). Conduit function parameters included early LSR of -0.81 ± 0.53 ($p = 0.13$) and passive emptying fraction of $23.6\% \pm 11.3\%$ ($p = 0.16$). Contraction function parameters included late LSR of -0.95 ± 0.91 ($p = 0.28$) and active emptying fraction of $31.8\% \pm 16.9\%$ ($p = 0.16$).

Trimarchi et al.²⁴ reported reductions across all three phases of atrial function in 20 patients with cardiac amyloidosis: PALS $17.6\% \pm 7.5\%$ ($p = 0.004$), conduit strain -8 ± 3.5 ($p = 0.8$), and contraction strain -10 ± 4.7 ($p < 0.0001$).

In the study by de Gregorio et al.,²² which evaluated left atrial size and function in 16 patients with transthyretin cardiac amyloidosis, 16 with hypertrophic cardiomyopathy (HCM), and 15 controls, mean PALS was significantly reduced in patients with transthyretin cardiac amyloidosis ($14.1\% \pm 4.7\%$) compared with HCM (19% – 20%) and controls (39% – 40%) ($p < 0.001$), demonstrating good diagnostic performance for differentiating these conditions (cutoff PALS $\leq 19\%$). Similarly, contraction strain was also reduced (-0.92 ± 0.56 ; $p < 0.01$).

Atrial stiffness emerged as an important prognostic marker. Bandera et al.¹³ identified it as an independent predictor of mortality (hazard ratio 1.23; 95% CI 1.03–1.49; $p = 0.029$). Other studies confirmed its association with the degree of atrial involvement and with impairment of reservoir, conduit, and contractile functions.

Lower PALS values and higher atrial stiffness were consistently associated with worse survival, greater atrial dilation, and increased risk of atrial arrhythmias. Furthermore, longitudinal data suggest that these alterations may precede clinical manifestations of heart failure, supporting their role as early screening tools.

Although multiple studies evaluating atrial strain in ATTRv were identified, a formal meta-analysis was not performed due to substantial clinical (different phenotypes), methodological (different software and acquisition protocols), and statistical heterogeneity ($I^2 > 90\%$ in exploratory analyses). In addition,

variability in data reporting (mean $\pm$ standard deviation vs. median and interquartile range or proportions based on cutoffs) limited direct comparability. Therefore, a narrative and tabular synthesis was performed, highlighting consistent trends, particularly the progressive reduction in PALS and increase in atrial stiffness across the disease spectrum.

Risk of bias analysis

According to the methodology described, the risk of bias was assessed using the NOS (Figure 3). Only two of the nine included studies were classified as having high methodological quality, characterized by larger sample sizes and robust multivariate analysis (Bandera et al.¹³ and Nochioka et al.¹⁸), while the remaining studies were classified as having moderate quality.

The main limitations were related to small sample sizes (Trimarchi et al.,²⁴ Henein et al.,¹⁹ de Gregorio et al.,²² Di Lisi et al.,¹⁵ and Di Bella et al.²³), lack of adjustment for potential confounding factors (Henein et al.,¹⁹ Di Bella et al.²³ and Trimarchi et al.²⁴), and methodological heterogeneity.

These findings highlight the need for prospective studies with greater methodological rigor to consolidate the prognostic role of atrial strain in ATTRv. A detailed description of the methodological quality assessment of the included studies, including individual NOS domain scores, is provided in the Supplementary Material.

Discussion

In this systematic review, left atrial dysfunction was consistently observed across different stages of ATTRv, including asymptomatic carriers, patients with isolated polyneuropathy, and those with overt cardiomyopathy. In all analyzed studies, PALS was reduced compared with reference values described in healthy individuals, and this alteration was associated with worse prognosis, increased atrial stiffness, and progressive left atrial dilation.

Amyloid fibril deposition in the atria and ventricles has been increasingly studied, and it is believed that deterioration of atrial function may occur early due to impairment of atrial mechanics secondary to fibril deposition, rather than solely as a consequence of ventricular dysfunction and diastolic impairment.

Cardiac amyloidosis is histologically characterized by extensive amyloid infiltration of the atria, leading to loss of normal architecture, vascular remodeling, and increased subendocardial collagen deposition, which translates into a significant increase in atrial stiffness. This abnormal stiffness is associated with reduced reservoir and contractile functions. Approximately one third of patients may present with absence of atrial contraction despite sinus rhythm on electrocardiography, a phenomenon known as atrial electromechanical dissociation. This finding, described by Bandera et al.,¹³ is associated with a thromboembolic risk similar to that observed in patients with atrial fibrillation, suggesting that atrial strain assessment may play a key role in cardioembolic risk stratification and may even support the indication for anticoagulation in patients without sustained atrial fibrillation.

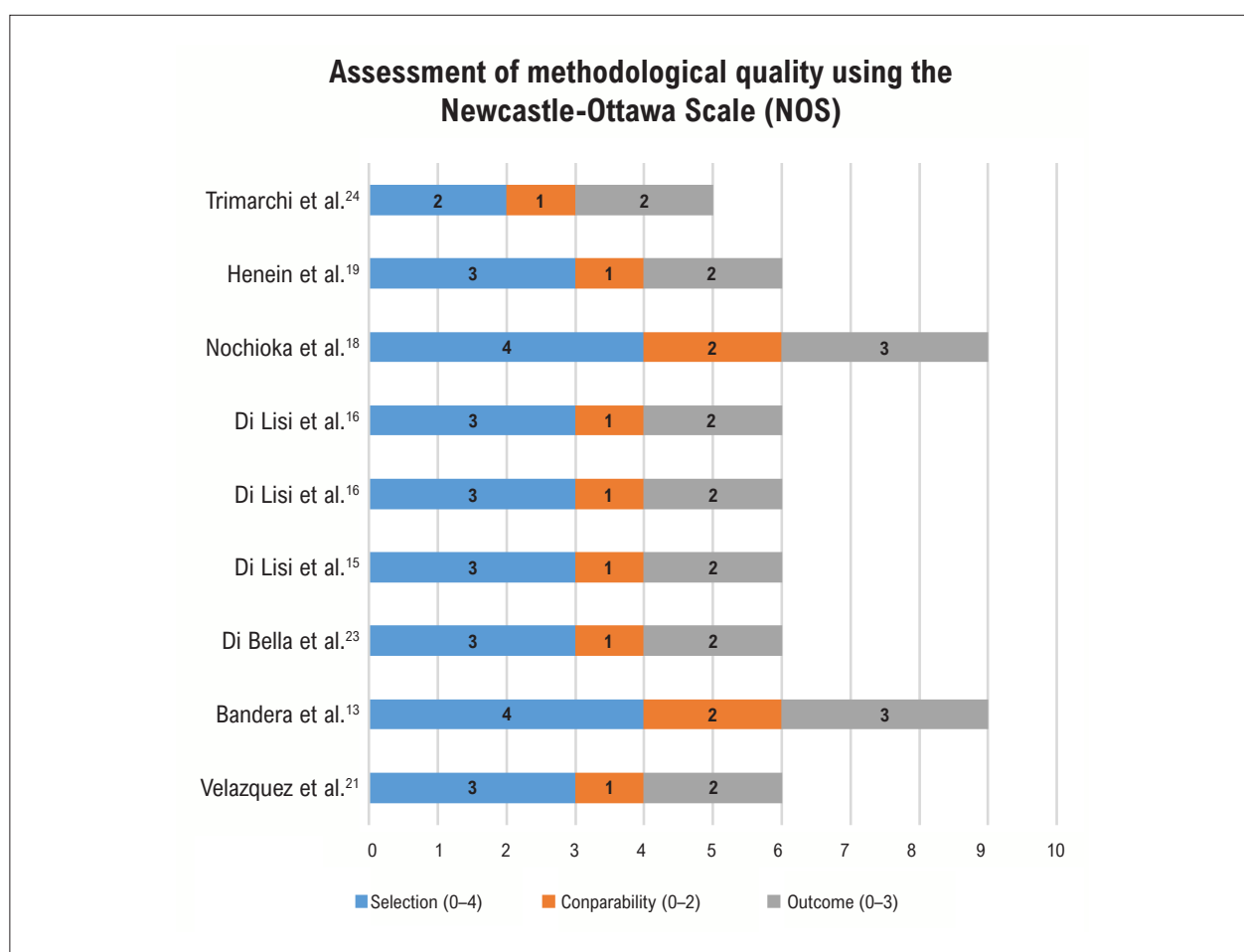


Figure 3 – Assessment of the methodological quality of the included studies using the Newcastle–Ottawa Scale (NOS), considering the domains of selection, comparability, and outcome. Most studies demonstrated moderate methodological quality, with two studies classified as high quality.

Another important finding of this review is the prognostic role of atrial strain. Akintoye et al.²⁰ demonstrated that progressive reductions in PALS and atrial contraction function are associated with a higher risk of mortality and heart failure hospitalization. Consistently, Bandera et al.¹³ identified atrial stiffness as an independent predictor of mortality, even after adjustment for biomarkers and clinical variables, reinforcing the role of atrial strain as a robust prognostic tool.

The complexity of cardiac amyloidosis remains a challenge in cardiology. It is a genetic condition that leads to restrictive cardiomyopathy, involving mutations in the transthyretin gene located on chromosome 18q12.1, with multiple variants, different degrees of penetrance, variable expressivity, and environmental factors that interact in disease expression. Some mutations are predominantly associated with polyneuropathy, such as V30M, whereas others, such as V122I, are more frequently associated with cardiomyopathy or mixed phenotypes.

With the increasing availability of genetic testing, the natural history of asymptomatic TTR mutation carriers has changed, with

greater emphasis on detecting subclinical cardiac involvement using imaging modalities such as cardiac MRI, bone scintigraphy with pyrophosphate, and speckle-tracking echocardiography. The study by Aceves Velázquez et al.²¹ demonstrated that even asymptomatic carriers may show reduced PALS and progressive increases in atrial stiffness over time, even in the absence of ventricular dysfunction, supporting the role of atrial strain as an early marker of amyloid infiltration.

De Gregorio et al.²² reported reduced PALS and contraction strain in patients with cardiac amyloidosis compared with controls and individuals with HCM, independent of left atrial volume and ventricular ejection fraction. These findings are consistent with those of Nochioka et al.,¹⁸ who demonstrated impairment of conduit and contraction components across different etiologies of cardiac amyloidosis. Thus, atrial dysfunction in ATTRv reflects not only increased filling pressures and restrictive ventricular physiology but also intrinsic atrial failure related to amyloid infiltration.

In the study by Di Lisi et al.,¹⁵ a progressive worsening of atrial dysfunction (PALS and stiffness) was observed from

asymptomatic carriers to patients with polyneuropathy and cardiomyopathy, reinforcing the importance of early assessment in these groups. The authors suggest that carriers should be monitored by echocardiography up to 10 years before the expected age of clinical manifestation in order to detect early changes. Notably, Di Bella et al.²³ proposed a PALS cutoff $\leq 40.9\%$ for the diagnosis of atrial amyloidosis, with 100% sensitivity and 71.6% specificity (AUC 0.91), suggesting additional diagnostic value for this parameter.

More recently, beyond its diagnostic role, atrial strain has also been investigated as a parameter for therapeutic monitoring. Di Lisi et al.¹⁶ reported significant improvement in atrial deformation parameters in patients treated with patisiran, supporting its role in assessing response to disease-modifying therapies.

Finally, the study by Henein et al.¹⁹ showed that patients with ATTRv, increased septal thickness, and fragmented fibrils have a higher risk of arrhythmias, suggesting that atrial function assessment may contribute not only to early detection and prognosis but also to arrhythmic risk stratification and to defining the optimal timing for initiation of antiarrhythmic therapy.

Limitations

Some limitations inherent to this systematic review should be considered. First, the predominance of observational studies, often single-center and with small sample sizes, limits the generalizability of the findings.

Second, significant methodological heterogeneity was identified among the included studies, including differences in echocardiographic acquisition protocols, frame rates, speckle-tracking software, and definitions of atrial strain parameters.

Additionally, the inclusion of populations across different stages of the disease spectrum — from asymptomatic carriers and predominantly neuropathic phenotypes to patients with established cardiac amyloidosis — provided a comprehensive overview but precluded the performance of a formal quantitative meta-analysis.

Conclusion

This systematic review demonstrates that left atrial dysfunction, as assessed by speckle-tracking echocardiography, is a consistent finding in patients with ATTRv. The available evidence suggests that left atrial strain is useful not only in patients with established cardiac amyloidosis but also in carriers and individuals with isolated amyloid polyneuropathy, enabling early detection of subclinical cardiac involvement.

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Atrial stiffness, associated with impairment of reservoir, conduit, and contractile functions, emerges as an independent prognostic marker in this population. Therefore, the integration of left atrial strain into routine clinical follow-up may facilitate timely diagnosis of cardiac involvement and allow earlier implementation of therapeutic strategies that have significantly improved clinical outcomes and prognosis in hereditary amyloidosis.

Author Contributions

Conception and design of the research: Cardoso LAA, Hatem MAB, Aras R; acquisition of data: Cardoso LAA, Silva RO; analysis and interpretation of the data: Cardoso LAA, Hatem MAB, Cardoso RO, Silva RO; statistical analysis: Cardoso LAA, Cardoso RO, Silva RO; writing of the manuscript: Cardoso LAA, Hatem MAB, Cardoso RO, Aras R; critical revision of the manuscript for intellectual content: Hatem MAB, Aras R.

Potential Conflict of Interest

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Study Association

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Ethics Approval and Consent to Participate

This article does not contain any studies with human participants or animals performed by any of the authors.

Use of Artificial Intelligence

During the preparation of this work, the author(s) used ChatGPT to assist with translation, figure creation, and grammar correction. After using this tool/service, the author(s) reviewed and edited the content as needed and take full responsibility for the content of the published article.

Availability of Research Data

The underlying content of the research text is contained within the manuscript.

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*Supplemental Materials

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The Extracellular Matrix Speaks. But Are We Truly Listening? Left Atrial Strain, Hereditary Transthyretin Amyloidosis, and Some Reflections

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Short Editorial related to the article: Left Atrial Strain Assessment in Hereditary Amyloidosis: A Systematic Review

Left atrial strain, especially left atrial reservoir strain (LASr), is an important tool in the assessment of atrial function and diastology. It changes before remodeling becomes detectable on echocardiography and contributes to a better understanding and characterization of diastolic dysfunction and left atrial–left ventricle (LA–LV) uncoupling.^{1–3} In patients with preserved ejection fraction, LASr values <18% strongly suggest elevated filling pressures.^{4,5}

In amyloid cardiomyopathy, the mean values of the atrial strain components are characteristically very reduced compared with individuals without the disease, and may serve as relevant clinical clues for diagnosis.^{6,7} Atrial dysfunction in amyloid cardiomyopathy results from two main mechanisms: direct infiltration of amyloid fibrils into the atrial wall, and chronic elevation of left ventricular filling pressures.⁷ Characteristically, the atrial wall is thin and highly dependent on the integrity of the extracellular matrix; therefore, even small deposits of amyloid fibrils can reduce reservoir strain, before increases in atrial volume or diameter occur.⁷

The diseased extracellular matrix progresses to fibrosis, impairing atrial relaxation, reducing its compliance, increasing its stiffness, and promoting remodeling — a process known as amyloid atrial myopathy.⁷ In this context, the atrium is not only a victim of ventricular dysfunction and elevated filling pressures, but also suffers directly from the deposition of amyloid fibrils within its walls. This progressively compromises its reservoir, conduit, and booster pump functions, increasing the likelihood of thromboembolic events, even in the absence of atrial fibrillation.⁸

The most prominent phenotypic expression of the degree of amyloid infiltration in the atrial wall is atrial electromechanical dissociation. This dissociation occurs when there is electrical activity in the sinus node, that is,

the presence of P waves on the resting electrocardiogram, despite the absence of A waves on mitral Doppler or a very low or even absent booster pump strain value.⁷ Bandera et al.⁷ evaluated approximately 900 patients with heart failure due to transthyretin amyloidosis — both ATTRv (variant/hereditary transthyretin amyloidosis) and ATTRwt (wild-type transthyretin amyloidosis) — and observed this intriguing electromechanical dissociation in 22% of cases, identifying it as an independent risk factor associated with worse prognosis, similar to that seen in patients with clinical atrial fibrillation.⁷ From this perspective, amyloid atrial myopathy represents a continuous remodeling process, characterized by impairment of atrial function (deformation and stiffness index), structure (volume), and electrophysiology. Atrial cardiomyopathy may present dramatically reduced strain values, reflecting extensive involvement and an advanced degree of chamber dysfunction.

In the study by Akintoye et al.,⁸ cutoff values of LASr <6.4% and LASct <2.4% demonstrated good discriminatory ability to predict thromboembolic events in a mixed population of patients (50.2% AL and 49.8% ATTR).⁸

In transthyretin amyloid cardiomyopathy, particularly in patients with ventricular dysfunction and heart failure, the atrial stiffness index, calculated as the E/e' to LASr ratio, has already shown important prognostic value.⁷ This index was independently associated with mortality, reflecting functional atrial impairment and providing incremental prognostic information beyond conventional echocardiographic variables.^{3,7} However, its potential role in identifying subclinical cardiac involvement and in stratifying patients at earlier stages of the disease remains under investigation.

In a study titled “Assessment of Left Atrial Strain in Hereditary Amyloidosis: A Systematic Review”, alterations in reservoir strain were observed in amyloid cardiomyopathy (LASr 8–15%), but also in individuals with the neurological phenotype (LASr 20–25%) and, interestingly, in asymptomatic carriers of pathogenic variants in the transthyretin (TTR) gene (LASr 23–30%). These findings raise the hypothesis that this tool may function as a marker of subclinical dysfunction. However, this still appears to lack more robust evidence, as the studies with the largest sample sizes in this particular review did not include asymptomatic carriers and evaluated mixed populations, including ATTRh, ATTRwt, and AL amyloidosis.^{7,9} On the other hand, when the analysis was performed specifically for hereditary ATTR and in individuals with a positive genotype and negative

Keywords

Extracellular Matrix; Heart Atria; Amyloidosis

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phenotype, LASr was reduced and the atrial stiffness index was increased. It is worth emphasizing, once again, that this evidence derived from small, observational studies.^{10,11}

In another recent systematic review evaluating the prognostic value of strain in patients with transthyretin amyloidosis (ATTRwt and ATTRv), the atrial stiffness index emerged as the main predictor of mortality. Here, similarly, the results should be viewed with reservations, considering the significant methodological limitations of the included studies.¹²

Evaluating atrial deformation in cohorts composed exclusively of patients with hereditary ATTR remains a challenge. Most available studies predominantly include patients with wild-type ATTR or mixed populations, combining individuals with both the hereditary and wild-type forms of the disease. In addition, the assessment of strain has inherent methodological limitations, including the need for high-quality echocardiographic image acquisition, variability among different manufacturers and speckle-tracking software, and the lack of universal standardization of reference values for this specific population. These factors hinder both the routine incorporation of the technique into clinical practice and the direct comparison of available studies. Consequently, fundamental questions remain unanswered: What is the best cutoff value to define subclinical cardiac involvement? Does the alteration in atrial mechanics precede, accompany, or follow ventricular impairment?

Identifying which diagnostic test changes earliest in amyloidosis still lacks a definitive answer. The available evidence is based on multimodal comparative assessments (brain natriuretic peptide [BNP], pyrophosphate scintigraphy, and cardiac magnetic resonance imaging) and on indirect comparisons, suggesting that native T1 mapping and extracellular volume on cardiac MRI may change earlier.¹³ When left atrial strain is incorporated into this scenario of subclinical diagnosis, an equally promising

and physiopathologically compelling rationale emerges. It is important to emphasize that this hypothesis is also based, thus far, on indirect comparisons between studies, as no prospective investigations have simultaneously evaluated the temporal evolution of atrial strain and tissue-characterization parameters on MRI in patients with hereditary ATTR.

In the context of arrhythmias, atrial fibrillation goes beyond the concept of a simple rhythm disturbance and represents, in many cases, the clinical expression of atrial myopathy. This disease of the atrium leads patients undergoing electrical cardioversion or catheter ablation to present, classically, greater management complexity and high rates of recurrence.¹⁴⁻¹⁶ Although robust evidence is still lacking, the study of atrial deformation and atrial stiffness emerges as an interesting strategy to refine the stratification of these patients, helping identify those most likely to benefit from rhythm-control interventions.

It is well established that reservoir strain and atrial stiffness are markedly altered in patients with clinically manifest amyloid cardiomyopathy and, possibly – albeit to a lesser extent – also in asymptomatic carriers of pathogenic TTR variants. However, several questions still need to be addressed by larger studies focused exclusively on hereditary amyloidosis. The interstitial space holds many secrets that may perhaps be revealed through a more accurate assessment of the integrity of the extracellular matrix, its remodeling, and its behavior over time.

In the era of disease-modifying therapies for amyloidosis, early detection of cardiac involvement has become highly relevant clinically. In this context, left atrial strain and the atrial stiffness index emerge as important functional biomarkers in the early investigation of hereditary ATTR. Confirming their true diagnostic value in the natural history of the disease will ideally depend on prospective studies specifically designed for this purpose.

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Serial Echocardiographic Assessment of Right Ventricular Function and Its Association With Functional Capacity, Dyspnea, and Pulmonary Diffusion in Post-COVID-19 Survivors

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Abstract

Background: Survivors of post-COVID-19 may experience persistent functional impairment and late cardiopulmonary sequelae. The right ventricle (RV) is particularly susceptible to injury, and RV free wall longitudinal strain (RVFWLS), measured by 2D speckle-tracking echocardiography (2D-STE), can detect subclinical RV systolic dysfunction.

Objective: To evaluate longitudinal changes in RV systolic function, assessed by RVFWLS, tricuspid annular plane systolic excursion (TAPSE), fractional area change (FAC), and tricuspid annular systolic velocity (S'), and to investigate their associations with functional capacity (30-second sit-to-stand test [30STS]), functional status (Post-COVID-19 Functional Status Scale [PCFS]), dyspnea (modified Medical Research Council [mMRC] scale), and carbon monoxide transfer coefficient (KCO) in post-COVID-19 survivors.

Methods: This observational analysis included participants from a prospective post-COVID-19 cohort evaluated at two follow-up visits (AV1 and AV2), approximately 4 and 13 months after the acute infection. Adults with confirmed SARS-CoV-2 infection and analyzable transthoracic echocardiography using 2D-STE were included. Statistical significance was defined as a two-sided $p < 0.05$.

Results: A total of 49 patients were included; 55.1% were women, the mean age was 50.7 ± 10.3 years, 63.3% had obesity, 77.6% required intensive care unit admission, and 67.3% underwent invasive mechanical ventilation. Performance on the 30STS improved (10.1 ± 3.3 vs 11.6 ± 3.1 repetitions; $p = 0.004$), and KCO increased (4.1 ± 0.7 vs 4.3 ± 0.8 mL/min/mmHg/L; $p = 0.002$), whereas mMRC scores ($p = 0.43$) and median PCFS scores ($p = 0.11$) remained unchanged. TAPSE decreased modestly but remained within the normal reference range (2.2 ± 0.3 vs 2.1 ± 0.2 cm; $p = 0.03$), while RVFWLS, FAC, and S' showed no significant changes over time. Cross-sectional correlations between RV systolic indices and clinical outcomes were weak and nonsignificant at both AV1 and AV2 ($|r| < 0.30$; $p > 0.05$). Longitudinally, changes in RVFWLS were positively correlated with changes in KCO ($r = 0.33$; $p = 0.05$), whereas changes in FAC were inversely correlated with changes in PCFS scores ($r = -0.35$; $p = 0.02$).

Conclusion: In this cohort of post-COVID-19 survivors, functional capacity and pulmonary diffusing capacity improved over time, whereas RVFWLS remained persistently reduced without significant longitudinal change. These exploratory findings suggest that RV systolic indices should not be interpreted in isolation as markers of functional limitation during the late post-COVID-19 period and support the use of an integrated, multiparametric approach to patient assessment.

Keywords: Post-Acute COVID-19 Syndrome; Right Ventricular Dysfunction; Echocardiography; Global Longitudinal Strain.

Introduction

Post-COVID-19 is characterized by new or persistent symptoms that typically develop within 3 months after acute SARS-CoV-2 infection, persist for at least 2 months, and substantially affect daily functioning.¹ Dyspnea, reduced

exercise tolerance, and fatigue are among the most common manifestations, suggesting that persistent cardiopulmonary abnormalities may contribute to long-term functional impairment.^{1,2} However, these symptoms are multifactorial and are often inadequately explained by abnormalities within a single organ system, which underscores the need for integrated phenotyping encompassing cardiac, pulmonary, and functional domains.^{2,3}

Cardiac involvement in COVID-19 ranges from overt myocardial injury to subclinical myocardial dysfunction. The right ventricle (RV) is particularly vulnerable because of its sensitivity to acute increases in pulmonary vascular load resulting from hypoxic pulmonary vasoconstriction,

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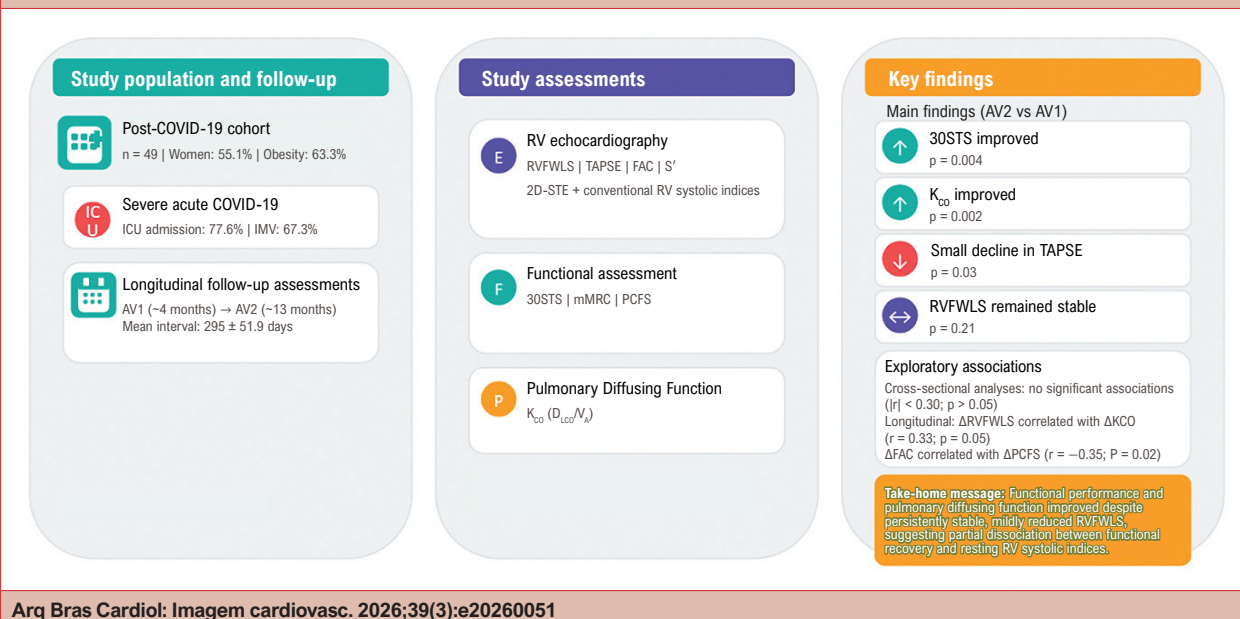
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Central Illustration: Serial Echocardiographic Assessment of Right Ventricular Function and Its Association With Functional Capacity, Dyspnea, and Pulmonary Diffusion in Post-COVID-19 Survivors



Serial Echocardiographic Assessment of Right Ventricular Function and Its Association With Functional Capacity, Dyspnea, and Pulmonary Diffusion in Post-COVID-19 Survivors. 2D-STE: 2D speckle-tracking echocardiography; 30STS: 30-second sit-to-stand test; AV1: first post-acute evaluation; AV2: second post-acute evaluation; DLCO: diffusing capacity of the lung for carbon monoxide; FAC: fractional area change; ICU: intensive care unit; IMV: invasive mechanical ventilation; KCO: carbon monoxide transfer coefficient; mMRC: modified Medical Research Council; PCFS: Post-COVID-19 Functional Status; RV: right ventricle; RVFWLS: RV free wall longitudinal strain; S': tricuspid annular systolic velocity; TAPSE: tricuspid annular plane systolic excursion; VA: alveolar volume.

thromboinflammation, microvascular dysfunction, the effects of invasive mechanical ventilation (IMV), and acute respiratory distress syndrome. During the acute phase of COVID-19, RV dysfunction — including abnormalities identified by 2D speckle-tracking echocardiography (2D-STE)-derived RV longitudinal strain — has consistently been associated with adverse clinical outcomes and mortality.^{4,5} A Brazilian systematic review with meta-analysis of hospitalized patients with COVID-19 reported a high prevalence of echocardiographic abnormalities, with pooled estimates of left ventricular and RV systolic dysfunction of 25% and 17%, respectively, highlighting the clinical value of cardiac imaging during the acute phase.⁶ 2D-STE provides a sensitive, reproducible assessment of RV mechanics, and RV free wall longitudinal strain (RVFWLS) can identify subtle systolic dysfunction even when conventional indices, such as tricuspid annular plane systolic excursion (TAPSE), fractional area change (FAC), and tricuspid annular systolic velocity (S'), remain within normal reference ranges.⁷ Furthermore, normative data demonstrate clinically meaningful variation in RVFWLS according to age and sex, emphasizing the importance of contextual interpretation and longitudinal assessment.⁸

Despite accumulating evidence of RV abnormalities during the acute phase of COVID-19, longitudinal data

on RVFWLS in patients with post-COVID-19 and its relationship with functional capacity, patient-reported functional status, dyspnea severity, and pulmonary diffusing capacity remain limited. Follow-up studies have yielded heterogeneous results and have generally focused on imaging outcomes alone, with limited integration of functional testing and pulmonary physiological measures, particularly in cohorts characterized by severe acute illness and a high burden of cardiometabolic comorbidities.^{9,10} Consequently, it remains unclear whether longitudinal changes in RV mechanics parallel, or diverge from, recovery in functional performance and pulmonary diffusing capacity.

Accordingly, the primary aim of this study was to characterize the longitudinal trajectory of RVFWLS and conventional RV systolic indices (TAPSE, FAC, and S') between approximately 4 and 13 months after acute COVID-19. Secondary aims were to investigate the cross-sectional and longitudinal associations of RV systolic function with functional capacity assessed by the 30-second sit-to-stand test (30STS), functional status measured by the Post-COVID-19 Functional Status (PCFS) Scale, dyspnea severity assessed using the modified Medical Research Council (mMRC) scale, and pulmonary diffusing capacity measured by the carbon monoxide transfer coefficient (K_{CO}). We

also explored whether baseline functional and pulmonary measures independently predicted follow-up RVFWLS after adjustment for baseline RVFWLS.

Methods

Study design and setting

This observational study represents an analysis of a prospective cohort of post-COVID-19 survivors followed at a dedicated post-COVID outpatient research clinic within a tertiary university hospital in southern Brazil. For the present analysis, participants underwent two standardized follow-up evaluations: AV1 (first post-acute evaluation), performed approximately 4 months after the acute phase of COVID-19, and AV2 (second post-acute evaluation), performed approximately 13 months after the acute illness. Medical records from the index hospitalization were reviewed to obtain clinical characteristics and markers of disease severity during the acute phase.

Participants

Eligible participants were adults (≥ 18 years) with SARS-CoV-2 infection confirmed by reverse transcription polymerase chain reaction using nasopharyngeal and/or oropharyngeal swab specimens, who received care during the acute phase and subsequently attended outpatient follow-up. The parent prospective cohort comprised 124 post-COVID-19 survivors. For the present paired longitudinal analysis, participants were eligible if they completed both follow-up assessments and had analyzable transthoracic echocardiography (TTE), including RVFWLS, at both AV1 and AV2. Accordingly, no formal prospective sample size calculation was performed for this secondary analysis.

Exclusion criteria were cognitive or psychiatric impairment precluding the provision of informed consent or completion of study questionnaires; missing required measurements or non-analyzable echocardiographic examinations at AV1 and/or AV2; terminal illness or receipt of palliative care; pregnancy; and age < 18 years.

Study procedures and data collection

At both AV1 and AV2, participants underwent the following assessments, according to their availability at each visit: i) TTE; ii) pulmonary function testing, including spirometry and pulmonary diffusing capacity testing, when applicable; iii) assessment of dyspnea and functional status using the mMRC and the PCFS; iv) anthropometric measurements; and v) evaluation of functional capacity using the 30STS. Vital signs, including systolic and diastolic blood pressure, heart rate, and SpO_2 , were recorded at each visit.

Demographic and clinical variables

Age and sex were recorded for all participants. Body mass index was calculated as weight in kilograms divided by height in meters squared (kg/m^2) and classified according to World Health Organization criteria.¹¹ Pre-existing comorbidities, including hypertension, diabetes mellitus, chronic lung

disease (asthma or chronic obstructive pulmonary disease [COPD]), heart failure, and coronary artery disease, were collected for descriptive purposes and were not considered primary analytical variables.

Severity of acute COVID-19

The severity of acute COVID-19 was classified according to the highest level of care required during hospitalization: mild (no hospitalization), moderate (hospital ward admission), or severe (intensive care unit [ICU] admission, with or without IMV). Indicators of respiratory support and other markers of disease severity, including oxygen therapy, IMV, and SpO_2 , were extracted from medical records when available.

Assessment of functional capacity

Functional capacity was assessed using the 30STS according to the Senior Fitness Test protocol.¹² Age- and sex-specific normative values were used solely to provide clinical context and were not applied as diagnostic cutoffs.

Assessment of dyspnea and functional status

Dyspnea severity was assessed using the mMRC (score range, 0-4).¹³ Functional status was evaluated using the PCFS (grades 0-4), based on the validated Brazilian Portuguese version.¹⁴

Acquisition of echocardiographic images

TTE was performed using a Vivid S6 ultrasound system (GE HealthCare, Tirat Carmel, Israel) equipped with an M4S phased-array transducer, allowing acquisition of 2D, M-mode, Doppler, and myocardial strain images. Image acquisition and quantitative measurements were performed in accordance with contemporary international recommendations for echocardiographic assessment of the right heart.⁸

Echocardiographic measurements

Right ventricular free wall longitudinal strain

RVFWLS was measured using 2D-STE from an RV-focused apical four-chamber view. Images were optimized for myocardial tracking, with a target frame rate of 50-80 frames/s. Analyses were performed using three consecutive cardiac cycles. RVFWLS was calculated as the arithmetic mean of the peak systolic longitudinal strain values obtained from the basal, midventricular, and apical segments of the RV free wall.⁸

Definition of right ventricular systolic dysfunction

For categorical analyses, RV systolic dysfunction was defined according to prespecified thresholds consistent with contemporary international recommendations: TAPSE < 1.7 cm, FAC $< 35\%$, $S' < 9.5$ cm/s, and RVFWLS $> -20\%$ (ie, less negative than -20%).⁸

Pulmonary function testing

Pulmonary function testing was performed at the study clinic and included spirometry and measurement of diffusing capacity using the single-breath technique. All tests were conducted by trained personnel in accordance with current American Thoracic Society/European Respiratory Society standards for acceptability and reproducibility.¹⁵

Pulmonary diffusing capacity was measured as the diffusing capacity of the lung for carbon monoxide (D_{LCO}) using the single-breath method. Alveolar volume (V_A) was measured concurrently, and the carbon monoxide transfer coefficient (K_{CO}) was calculated as D_{LCO}/V_A . For the purposes of this study, pulmonary diffusing function was primarily represented by K_{CO} (mL/min/mmHg/L).¹⁶

Study variables and analytical strategy

The primary echocardiographic outcomes were RVFWLS, TAPSE, FAC, and S' measured at AV1 and AV2. Functional and pulmonary outcomes included performance on the 30STS, PCFS scale grade, mMRC dyspnea score, and K_{CO} .

Analyses were conducted using three complementary approaches. First, cross-sectional analyses examined the associations between RV echocardiographic parameters and functional or pulmonary outcomes separately at AV1 and AV2. Second, longitudinal analyses evaluated within-participant changes over time, with change scores (Δ) calculated as the value at AV2 minus the value at AV1. These analyses were restricted to participants with complete paired measurements for the variable of interest. Third, categorical analyses classified participants as improved, stable, or worsened according to prespecified criteria. For RV systolic indices, the predefined thresholds for RV systolic dysfunction were used to facilitate clinically meaningful categorization.

Statistical analysis

Data were entered into Microsoft Excel and analyzed using IBM SPSS Statistics for Windows, version 22 (IBM Corp., Armonk, N.Y., USA). Figures were generated using R, version 4.5.2 (R Foundation for Statistical Computing), with the “tidyverse” package. Selected stratified analyses, including comparisons according to ICU admission and sex, as well as adjusted models when applicable, were performed in R.

The distribution of continuous variables was assessed using the Shapiro-Wilk test. Continuous variables are presented as mean $\pm$ SD or median (IQR) as appropriate, whereas categorical variables are presented as absolute and relative frequencies. Comparisons between AV1 and AV2 were performed using paired t tests or Wilcoxon signed-rank tests according to data distribution. Between-group comparisons in stratified analyses were conducted using Student's t tests or Mann-Whitney U tests, as appropriate. Categorical variables were compared using Fisher's exact test.

Associations between echocardiographic parameters and functional or pulmonary outcomes were assessed using Pearson or Spearman correlation coefficients according to

the distributional characteristics of data. Correlation strength was interpreted using prespecified thresholds based on the absolute correlation coefficient: weak (< 0.30), moderate (0.30 - 0.49), and strong (≥ 0.50).¹⁷

A sensitivity power analysis for correlation coefficients was performed to contextualize the absence of a prospective sample size calculation. Assuming a two-sided significance level of $\alpha = 0.05$ ($p < 0.05$) and 80% statistical power, the minimum detectable correlation coefficients were approximately $|r| = 0.39$ for $n = 49$, $|r| = 0.40$ for $n = 46$, $|r| = 0.42$ for $n = 43$, and $|r| = 0.46$ for $n = 35$.

Accordingly, weaker associations may not have been detected. Because no formal adjustment for multiple comparisons was applied, analyses involving multiple correlations and subgroup comparisons should be considered exploratory. 95% CIs are reported where appropriate, and effect sizes are presented as Cohen's d or rank-biserial correlation coefficients, as applicable.

Ethical considerations

The study was approved by the institutional Human Research Ethics Committee in accordance with Brazilian National Health Council Resolution 466/2012 (protocol no. 4.290.578). Written informed consent was obtained from all participants before study enrollment.

Results

Participants and follow-up

Among the 124 participants enrolled in the parent prospective cohort, 49 completed both follow-up visits and had analyzable paired echocardiographic examinations. Women comprised 55.1% (27/49) of the cohort, and obesity was present in 63.3% (31/49). Pre-existing comorbidities included hypertension in 33 participants (67.3%), diabetes mellitus in 15 (30.6%), chronic lung disease (asthma or COPD) in two (4.1%), and heart failure with reduced ejection fraction in one (2.0%).

Most participants required hospitalization during the acute phase of COVID-19, with 38 (77.6%) admitted to the ICU and 33 (67.3%) requiring IMV (Table 1).

The AV1 was performed a mean of 122.6 ± 52.8 days (4.0 ± 1.7 months) after the acute illness, whereas the AV2 occurred after a mean of 417.4 ± 24.5 days (13.7 ± 0.8 months). The mean interval between assessments was 295.0 ± 51.9 days. The study design and principal findings are summarized in Central Illustration.

Functional capacity, dyspnea, functional status, and pulmonary diffusion

Between AV1 and AV2, functional capacity as assessed by the 30STS and K_{CO} improved significantly. In contrast, dyspnea severity (mMRC) and functional status (PCFS) remained unchanged (Table 2).

Longitudinal changes in right ventricular function

Among the RV systolic indices, TAPSE showed a modest decline between AV1 and AV2, although values remained within the normal reference range. No significant longitudinal changes were observed in RVFWLS, FAC, or S' (Table 3).

Cross-sectional associations between right ventricular function and clinical outcomes

Cross-sectional analyses performed separately at AV1 and AV2 revealed no significant associations between RV systolic indices and functional or pulmonary outcomes (all $p > 0.05$) (Table S1; Table S2).

Table 1 – Baseline characteristics and acute-phase severity of the study participants (n = 49)

Variable	Overall
Age, years	50.7 ± 10.3
Sex	
Male	22 (44.9)
Female	27 (55.1)
BMI, kg/m ²	32.1 ± 5.8
BMI category	
Normal weight (18.5–24.9 kg/m ²)	1 (2.0)
Overweight (25.0–29.9 kg/m ²)	17 (34.7)
Obesity (≥ 30.0 kg/m ²)	31 (63.3)
Hospitalization during acute COVID-19	
No	5 (10.2)
Yes	44 (89.8)
Severity of acute COVID-19	
Mild	5 (10.2)
Moderate	6 (12.2)
Severe	38 (77.6)
ICU admission	
No	11 (22.4)
Yes	38 (77.6)
IMV	
No	16 (32.7)
Yes	33 (67.3)

Data are presented as mean ± SD or n (%) as appropriate. BMI: body mass index; ICU: intensive care unit; IMV: invasive mechanical ventilation.

Longitudinal associations

In analyses based on within-participant changes ($\Delta = \text{AV2} - \text{AV1}$), changes in RVFWLS were positively correlated with changes in K_{CO} ($r = 0.33$; $p = 0.05$), whereas changes in FAC were inversely correlated with changes in PCFS scores ($r = -0.35$; $p = 0.02$). No other longitudinal correlations reached statistical significance (Table 4).

In analyses based on categorical trajectories (improved, stable, or worsened), changes in TAPSE were inversely correlated with the trajectory of 30STS performance ($\rho = -0.37$; $p = 0.01$), whereas all other associations were nonsignificant (Table S3).

Stratified analyses by acute-phase severity and sex

When participants were stratified according to ICU admission during the acute phase, RVFWLS at AV1 showed a nonsignificant trend toward less favorable values among patients requiring ICU care than among those who did not ($-16.8 \pm 4.7\%$ vs $-19.3 \pm 3.4\%$; $p = 0.07$). No significant between-group differences were observed for the remaining RV systolic indices or for functional and pulmonary measures (Table 5). At AV2, RV echocardiographic parameters, functional outcomes, and K_{CO} were comparable between the ICU and non-ICU groups (Table 6).

Sex-stratified analyses demonstrated no significant differences in RV echocardiographic parameters or functional and pulmonary outcomes at AV1. At AV2, men exhibited lower TAPSE and FAC values than women, whereas RVFWLS and S' remained comparable between sexes. PCFS scores showed a borderline difference between men and women (Table 7).

Table 2 – Functional status, dyspnea, functional capacity, and pulmonary diffusion at AV1 and AV2

Variable	AV1	AV2	p-value
mMRC	1.0 (0.0–2.0)	1.0 (0.0–2.0)	0.430
PCFS	2.0 (1.0–3.0)	2.0 (1.0–3.0)	0.110
30STS	10.1 ± 3.3	11.6 ± 3.1	0.004
K_{CO} , mL/min/mmHg/L	4.1 ± 0.7	4.3 ± 0.8	0.002

p-values were calculated using the Wilcoxon signed-rank test for ordinal variables (mMRC and PCFS) and the paired t test for continuous variables (30STS and K_{CO}). Data are presented as mean ± SD or median (IQR) as appropriate. 30STS: 30-second sit-to-stand test; AV1: first post-acute evaluation; AV2: second post-acute evaluation; K_{CO} : carbon monoxide transfer coefficient; mMRC: modified Medical Research Council; PCFS: Post-COVID-19 Functional Status.

Table 3 – Longitudinal changes in right ventricular echocardiographic measures between AV1 and AV2

Variable	AV1	AV2	MD*	95% CI	p-value
TAPSE, cm	2.2 ± 0.3	2.1 ± 0.2	−0.09	−0.17 to −0.01	0.03
RVFWLS, %	−17.4 ± 4.5	−18.4 ± 3.5	−0.99	−2.53 to 0.56	0.21
FAC, %	46.8 ± 7.4	44.6 ± 11.2	−2.26	−5.75 to 1.23	0.20
S', cm/s	12.6 ± 2.4	12.2 ± 2.0	−0.45	−1.02 to 0.12	0.12

*MD was calculated as AV2 − AV1. Data are presented as mean ± SD. AV1: first post-acute evaluation; AV2: second post-acute evaluation; FAC: fractional area change; MD: mean difference; RVFWLS: right ventricular free wall longitudinal strain; S': tricuspid annular systolic velocity; TAPSE: tricuspid annular plane systolic excursion.

Table 4 – Correlations between longitudinal changes in RV echocardiographic measures and clinical outcomes

RV parameter ΔRV*	mMRC	PCFS	30STS	KCO
RVFWLS	−0.16 (p = 0.28)	−0.06 (p = 0.71)	0.007 (p = 0.96)	0.33 (p = 0.05)
TAPSE	−0.12 (p = 0.43)	−0.01 (p = 0.92)	−0.19 (p = 0.21)	0.003 (p = 0.99)
FAC	−0.17 (p = 0.25)	−0.35 (p = 0.02)	0.07 (p = 0.67)	−0.06 (p = 0.73)
S'	0.02 (p = 0.89)	0.02 (p = 0.89)	−0.21 (p = 0.17)	−0.28 (p = 0.11)

Values are correlation coefficients (r or p) with corresponding p-values. Pearson or Spearman correlation coefficients were used as appropriate. *ΔRV was calculated as AV2 − AV1. 30STS: 30-second sit-to-stand test; AV1: first post-acute evaluation; AV2: second post-acute evaluation; FAC: fractional area change; K_{co}: carbon monoxide transfer coefficient; mMRC: modified Medical Research Council; PCFS: Post-COVID-19 Functional Status; RV: right ventricle; RVFWLS: RV free-wall longitudinal strain; S': tricuspid annular systolic velocity; TAPSE: tricuspid annular plane systolic excursion.

Table 5 – Right ventricular echocardiographic measures and clinical outcomes at AV1 according to ICU admission

Variable	Non-ICU (n = 11)	ICU (n = 38)	p-value	Effect size*
RVFWLS, %	−19.3 ± 3.4	−16.8 ± 4.7	0.07	0.55
TAPSE, cm	2.2 ± 0.3	2.2 ± 0.3	0.81	0.08
FAC, %	49.2 ± 7.4	46.1 ± 7.3	0.25	0.40
S', cm/s	12.4 ± 2.3	12.7 ± 2.4	0.71	−0.12
30STS, repetitions	11.3 ± 1.6	10.0 ± 3.6	0.36	0.38
K _{co} , mL/min/mmHg/L	4.0 ± 0.5	4.2 ± 0.8	0.32	−0.30
mMRC, median (IQR)	1.0 (0.0-3.0)	1.0 (0.0-2.0)	0.09	−0.06
PCFS, median (IQR)	2.0 (0.5-2.5)	2.0 (2.0-3.0)	0.65	0.27

p-values were calculated using the Student's t test for normally distributed continuous variables and the Mann-Whitney U test for non-normally distributed or ordinal variables. Data are presented as mean ± SD or median (IQR) as appropriate. *Effect size is presented as Cohen's d for independent-samples t tests and rank-biserial correlation for Mann-Whitney U tests. 30STS: 30-second sit-to-stand test; AV1: first post-acute evaluation; FAC: fractional area change; ICU: intensive care unit; K_{co}: carbon monoxide transfer coefficient; mMRC: modified Medical Research Council; PCFS: Post-COVID-19 Functional Status; RVFWLS: right ventricular free wall longitudinal strain; S': tricuspid annular systolic velocity; TAPSE: tricuspid annular plane systolic excursion.

In analysis of covariance models with RVFWLS at AV2 as the dependent variable, baseline RVFWLS as a covariate, and each baseline functional or pulmonary measure entered individually as the predictor of interest, none of the baseline functional or pulmonary measures independently predicted follow-up RVFWLS after adjustment for baseline RVFWLS (Table 8).

Discussion

This study provides a longitudinal assessment of post-COVID-19 survivors from a cohort characterized by severe acute illness and a high burden of cardiometabolic comorbidities. Over a mean follow-up interval of approximately 10 months, objective measures of functional performance, assessed by the 30STS, and pulmonary

Table 6 – Right ventricular echocardiographic measures and clinical outcomes at AV2 according to ICU admission

Variable	Non-ICU (n = 11)	ICU (n = 38)	p-value	Effect size*
RVFWLS, %	−18.1 ± 2.7	−18.5 ± 3.7	0.69	0.12
TAPSE, cm	2.2 ± 0.2	2.1 ± 0.3	0.38	0.29
FAC, %	43.4 ± 15.7	45.4 ± 9.9	0.97	−0.18
S ₁ , cm/s	12.3 ± 1.6	12.2 ± 2.1	0.89	0.04
30STS, repetitions	11.9 ± 2.4	11.5 ± 3.1	0.89	0.13
K _{co} , mL/min/mmHg/L	4.1 ± 0.7	4.3 ± 0.8	0.51	−0.23
mMRC, median (IQR)	1.0 (0.2-1.0)	1.0 (0.0-2.0)	0.40	0.05
PCFS, median (IQR)	2.0 (1.0-2.0)	2.0 (1.0-3.0)	0.50	0.22

*p-values were calculated using the Student's t test for normally distributed continuous variables and the Mann-Whitney U test for non-normally distributed or ordinal variables. Data are presented as mean ± SD or median (IQR) as appropriate. *Effect size is presented as Cohen's d for independent-samples t tests and rank-biserial correlation for Mann-Whitney U tests. 30STS: 30-second sit-to-stand test; AV2: second post-acute evaluation; FAC: fractional area change; ICU: intensive care unit; K_{co}: carbon monoxide transfer coefficient; mMRC: modified Medical Research Council; PCFS: Post-COVID-19 Functional Status; RVFWLS: right ventricular free wall longitudinal strain; S₁: tricuspid annular systolic velocity; TAPSE: tricuspid annular plane systolic excursion.*

Table 7 – Right ventricular echocardiographic measures and clinical outcomes at AV2 according to sex

Variable	Male (n = 22)	Female (n = 27)	p-value	Effect size*
RVFWLS, %	−18.0 ± 3.3	−18.7 ± 3.7	0.47	−0.20
TAPSE, cm	2.0 ± 0.2	2.2 ± 0.3	0.01	−0.71
FAC, %	43.5 ± 5.8	46.1 ± 14.3	0.04	0.34
S ₁ , cm/s	12.0 ± 2.1	12.4 ± 2.0	0.46	−0.21
30STS, repetitions	12.3 ± 3.2	11.1 ± 2.8	0.19	−0.23
K _{co} , mL/min/mmHg/L	4.4 ± 0.9	4.1 ± 0.7	0.36	0.30
mMRC, median (IQR)	0.5 (0.0-1.2)	1.0 (0.0-2.0)	0.66	0.18
PCFS, median (IQR)	1.5 (0.0-2.2)	2.0 (2.0-3.0)	0.05	0.22

*p-values were calculated using the Student's t test for normally distributed continuous variables and the Mann-Whitney U test for non-normally distributed or ordinal variables. Data are presented as mean ± SD or median (IQR) as appropriate. *Effect size is presented as Cohen's d for independent-samples t tests and rank-biserial correlation for Mann-Whitney U tests. 30STS: 30-second sit-to-stand test; AV2: second post-acute evaluation; FAC: fractional area change; K_{co}: carbon monoxide transfer coefficient; mMRC: modified Medical Research Council; PCFS: Post-COVID-19 Functional Status; RVFWLS: right ventricular free wall longitudinal strain; S₁: tricuspid annular systolic velocity; TAPSE: tricuspid annular plane systolic excursion.*

Table 8 – ANCOVA models evaluating baseline functional and pulmonary measures as predictors of RVFWLS at AV2 after adjustment for baseline RVFWLS

Model (predictor at AV1)	F (df1, df2)	p-value	Partial η^2
mMRC	1.930 (1. 47)	0.17	0.039
PCFS	0.180 (1. 47)	0.67	0.004
30STS	1.345 (1. 45)	0.25	0.029
K_{CO}	0.225 (1. 39)	0.64	0.006

The dependent variable was RVFWLS at AV2. Baseline RVFWLS (AV1) was included as a covariate. Each model included a single baseline functional or pulmonary measure as the predictor of interest. 30STS: 30-second sit-to-stand test; ANCOVA: analysis of covariance; AV1: first post-acute evaluation; AV2: second post-acute evaluation; df: degrees of freedom; K_{CO} : carbon monoxide transfer coefficient; mMRC: modified Medical Research Council; PCFS: Post-COVID-19 Functional Status; RVFWLS: right ventricular free wall longitudinal strain.

diffusing function, indexed by the K_{CO} , improved significantly. In contrast, dyspnea severity and self-reported functional status, assessed using the mMRC and the PCFS, respectively, remained unchanged despite a favorable descriptive trend. From a cardiovascular perspective, conventional RV systolic indices remained largely preserved, with the exception of a modest but statistically significant decline in TAPSE, which nevertheless remained within the normal reference range. Likewise, RVFWLS remained mildly reduced without significant longitudinal change, consistent with persistent subclinical RV systolic involvement.⁸

The susceptibility of the RV to injury during acute COVID-19 is well established. Pulmonary vascular abnormalities and thrombo-inflammatory processes increase RV afterload and may precipitate RV systolic dysfunction.⁵ In 2022, investigators at the Mayo Clinic compared pre-COVID-19 echocardiograms with the first outpatient post-COVID-19 examination using blinded core laboratory strain analysis and a stringent definition of clinically meaningful deterioration. Overall, they found no clinically meaningful change in mean RV free wall strain, although a subset of patients experienced significant worsening, particularly those with new cardiopulmonary symptoms and pre-existing cardiovascular disease.⁷ Longitudinal studies from other cohorts have likewise suggested that RV remodeling and dysfunction improve in most survivors but persist in clinically important subgroups, potentially attenuating linear associations when analyses are performed across the entire cohort.¹⁸ Consistent with this heterogeneity, studies focusing on ICU survivors have reported more persistent impairment in RV strain and conventional RV systolic indices than in control populations,¹⁹ whereas other longitudinal cohorts have demonstrated statistically significant improvements in RV strain over approximately 1 year despite minimal absolute

changes.²⁰ Conversely, large cohorts with longer follow-up have reported RV strain values comparable to those of control participants in some settings,¹⁰ supporting the concept that post-COVID-19 RV mechanical abnormalities are generally subtle, heterogeneous across clinical phenotypes, and not consistently reflected by symptom burden.^{19,21} The present findings, which are characterized by preserved conventional RV systolic indices together with persistently but mildly reduced RVFWLS, fit within this heterogeneous body of evidence and underscore the importance of considering both clinical phenotype and methodological differences when interpreting results across studies.

The substantial cardiometabolic burden of our cohort also warrants consideration when interpreting the persistently reduced RVFWLS values. Although guideline-recommended thresholds are useful for categorical classification, they were not developed specifically for post-COVID-19 populations with a high prevalence of obesity, hypertension, and diabetes mellitus. Accordingly, in the absence of a non-COVID control group and pre-infection echocardiographic data, residual abnormalities in RVFWLS should be interpreted with caution and should not be attributed solely to prior SARS-CoV-2 infection.

Cross-sectional analyses performed at both follow-up visits demonstrated weak and nonsignificant correlations ($|r| < 0.30$; $p > 0.05$) between RV systolic indices (RVFWLS, TAPSE, FAC, and S') and clinical outcomes, including dyspnea (mMRC), functional status (PCFS), functional capacity (30STS), and pulmonary diffusing function (K_{CO}). These findings suggest that, at a single time point during the late post-COVID-19 period, resting RV systolic performance, whether assessed by conventional echocardiographic parameters or myocardial deformation imaging, does not exhibit a linear relationship with dyspnea severity, self-reported functional limitation, objective functional performance, or pulmonary diffusing capacity.^{22,23} This observation is consistent with the multifactorial pathophysiology of post-COVID-19, in which persistent symptoms and perceived functional limitation likely reflect the combined effects of residual pulmonary disease, cardiovascular abnormalities, peripheral deconditioning, autonomic dysfunction, and psychosocial factors. These interacting mechanisms may contribute to the frequently observed dissociation between objective cardiopulmonary measurements and patient-reported outcomes.³

When longitudinal changes (Δ) were analyzed, two modest but biologically plausible associations emerged. Changes in RVFWLS were positively correlated with changes in K_{CO} ($r = 0.33$; $p = 0.05$), whereas changes in FAC were inversely correlated with changes in PCFS scores ($r = -0.35$; $p = 0.02$). The association between improvements in pulmonary gas transfer and RV mechanics is physiologically plausible given the sensitivity of RV performance to changes in pulmonary vascular afterload.²³ However, the association between Δ RVFWLS and ΔK_{CO} reached only the conventional threshold for statistical significance and should therefore be considered hypothesis-generating, particularly because no adjustment for multiple comparisons was performed. Partial recovery of the alveolar-capillary interface may be accompanied by parallel, albeit modest, improvement in RV mechanical function.^{24,25} Similarly, FAC — which is

generally considered a more global measure of RV systolic performance than annular indices alone — may capture clinically meaningful changes associated with patients' perceived functional trajectory in selected individuals.^{8,26,27}

Using the categorical trajectory approach, the inverse correlation between changes in TAPSE and the trajectory of 30STS performance ($p = -0.37$; $p = 0.01$) indicates that greater longitudinal reductions in TAPSE were associated with greater improvement in 30STS performance categories. TAPSE is highly load dependent, reflects only the longitudinal excursion of the tricuspid annulus, and is susceptible to measurement variability. Consequently, current guidelines recommend a multiparametric assessment of RV systolic function rather than reliance on TAPSE as a standalone measure.⁸ Although reduced TAPSE during acute COVID-19 hospitalization has consistently been associated with adverse outcomes, including mortality, in meta-analyses,²⁸ a small isolated decline during the late post-COVID-19 period, in the absence of concordant changes in FAC, S' , or RVFWLS, is more likely to reflect hemodynamic variation, measurement variability, or selective changes in longitudinal annular motion than a true deterioration in global RV systolic function.^{8,19} The stability of FAC and S' observed in our cohort further supports this interpretation.

The significant improvement in 30STS performance together with the increase in K_{CO} suggests objective recovery in both functional performance and pulmonary diffusing capacity, which may not be proportionately reflected by symptom-based or patient-reported functional measures. One plausible explanation is that improvements in 30STS performance partly reflect peripheral reconditioning, including gains in lower-extremity strength and endurance, enhanced tolerance to submaximal exercise, and/or participation in rehabilitation programs, all of which may improve functional performance despite stable echocardiographic findings.^{29,30} Systematic reviews and meta-analyses of rehabilitation interventions in post-COVID-19 populations have consistently demonstrated improvements in functional outcomes, including sit-to-stand performance.³¹ Likewise, longitudinal studies of survivors of COVID-19 hospitalization have frequently reported progressive improvement in pulmonary diffusing capacity (D_{LCO} and K_{CO}) over time, although residual impairment may persist in some individuals and recovery may eventually plateau, providing context for the modest increase in K_{CO} observed in our cohort.³² Despite these objective improvements, the stability of median mMRC and PCFS scores is consistent with evidence from cardiopulmonary exercise testing (CPET) studies and systematic reviews indicating that exertional intolerance and persistent dyspnea in post-COVID-19 arise from multiple interacting mechanisms (eg, ventilatory, perfusion-related, circulatory, peripheral, and autonomic abnormalities) making it unlikely that any single resting physiological marker adequately explains symptom severity or functional limitation.^{33,34}

Stratified analyses yielded additional findings that should be regarded as hypothesis-generating. When participants were stratified according to acute-phase severity, RVFWLS showed a nonsignificant trend toward more impaired values

among patients requiring ICU admission at AV1, whereas values converged by AV2, a pattern consistent with greater early RV vulnerability in severe COVID-19 followed by partial recovery or physiological adaptation over time.^{5,18} Sex-stratified analyses showed that men had lower TAPSE and FAC values at AV2 and experienced greater longitudinal reductions in TAPSE and S' , whereas women tended to report greater functional limitation on the PCFS. These observations should be interpreted cautiously because RV systolic indices are influenced by loading conditions and are subject to both biological and technical variability.⁸ Nevertheless, the greater symptom burden reported by women is consistent with previous studies of post-COVID-19 populations using functional status instruments and rehabilitation cohorts.³⁵⁻³⁷ Finally, analysis of covariance demonstrated that baseline mMRC, PCFS, 30STS, and K_{CO} were not independently associated with RVFWLS at follow-up after adjustment for baseline RVFWLS, suggesting that the initial severity of symptoms, functional impairment, or pulmonary dysfunction did not robustly predict subsequent RV myocardial deformation in this cohort.

Clinical implications

Our findings have three main clinical implications. First, neither RVFWLS nor conventional RV systolic indices emerged as robust standalone markers of late functional impairment or its longitudinal trajectory, supporting the use of an integrated assessment that combines echocardiography with functional testing and pulmonary evaluation, as advocated by recent post-COVID-19 phenotyping studies.²¹

Second, the modest associations observed in longitudinal (Δ -based) analyses suggest that temporal changes may be more informative than isolated measurements obtained at a single time point. However, the observed effect sizes were small and lacked consistent replication across analyses, indicating that noncardiac factors (eg, peripheral deconditioning, residual pulmonary disease, autonomic dysfunction, and psychosocial influences) are likely to play a predominant role in determining functional recovery in many patients.^{38,39}

Third, the optimal timing of cardiopulmonary assessment after COVID-19 remains uncertain. Earlier evaluations, including those performed during the acute phase of illness, may provide greater prognostic value than later assessments and warrant further investigation.

Study limitations

This study has several limitations. First, the relatively small sample size limited statistical power for correlation analyses, particularly after stratification and categorical trajectory classification, increasing the risk of type II error and reducing the precision of effect estimates. Sensitivity power analysis indicated that the available sample size was sufficient to detect correlations of at least moderate magnitude; therefore, weaker associations may have gone undetected. Consequently, nonsignificant findings should not be interpreted as definitive evidence of the absence of an association, and the results should be regarded as exploratory and hypothesis-generating.

Second, the limited sample size precluded meaningful subgroup analyses according to important cardiometabolic conditions, such as obesity and hypertension, because these would have resulted in small subgroup sizes and unstable estimates.

Third, no formal adjustment for multiple comparisons was performed; therefore, isolated findings with borderline statistical significance should be interpreted cautiously. Fourth, the absence of both a non-COVID control group and pre-infection echocardiographic data limits attribution of the observed abnormalities specifically to post-COVID-19 sequelae in this cohort with a high burden of pre-existing comorbidities.

Fifth, the availability of only two follow-up assessments precluded characterization of intermediate recovery trajectories, including the possibility of early improvement followed by a later plateau. Moreover, because the first follow-up assessment occurred approximately 4 months after the acute illness, RV abnormalities present during hospitalization or in the early post-discharge period may already have partially resolved, limiting characterization of the complete course of RV recovery.

Sixth, mechanistic interpretation is limited by the absence of invasive hemodynamic assessment by right heart catheterization and CPET, both of which could have better distinguished the relative contributions of ventilatory, circulatory, peripheral, and autonomic mechanisms to persistent exercise intolerance. In addition, potentially important confounding factors (eg, pre-COVID-19 physical activity, participation in rehabilitation programs, medical therapies, infecting viral variants, and socioeconomic characteristics) could not be comprehensively accounted for.

Finally, intraobserver and interobserver reproducibility of RVFWLS measurements was not formally assessed. Therefore, the contribution of measurement variability to the small longitudinal changes observed cannot be excluded. Moreover, 2D-STE-derived RV strain is intrinsically influenced by image quality, frame rate, tracking performance, observer variability, and vendor- or software-specific algorithms, while standardization of RV strain cutoff values remains incomplete.⁸

Conclusions

Among post-COVID-19 survivors with severe acute illness and a high burden of cardiometabolic comorbidities, functional capacity and pulmonary diffusing function improved during follow-up, whereas RVFWLS remained mildly reduced without significant longitudinal change. Conventional RV systolic indices remained largely preserved, with the exception of a modest decline in TAPSE that remained within the normal reference range. These

exploratory findings suggest a partial dissociation between recovery of functional and pulmonary performance and resting echocardiographic markers of RV systolic function during the late post-COVID-19 period, reinforcing the importance of an integrated, multiparametric, and individualized approach to patient assessment.

Author Contributions

Conception and design of the research: Rogelin M, Fonseca FR, Silva RM, Fialho GL; acquisition of data: Rogelin M, Aranha AFMG, Fonseca FR, Silva RM, Fialho GL; analysis and interpretation of the data, statistical analysis and writing of the manuscript: Rogelin M; obtaining financing: Silva RM; critical revision of the manuscript for intellectual content: Aranha AFMG, Fialho GL.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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Ethics Approval and Consent to Participate

This study was approved by the Research Ethics Committee for Human Subjects under approval number 4,290,578, dated 09/21/2020. All procedures involved in this study were in accordance with the 1975 Declaration of Helsinki and its subsequent amendments. Informed consent was obtained from all participants included in the study.

Use of Artificial Intelligence

The authors did not use any artificial intelligence tools in the development of this work.

Availability of Research Data

The data supporting the results of this study are available from the corresponding author upon reasonable request.

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*Supplemental Materials

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Position Statement on the Use of Point-of-Care Ultrasound in Cardiovascular Medicine – 2026: Executive Summary

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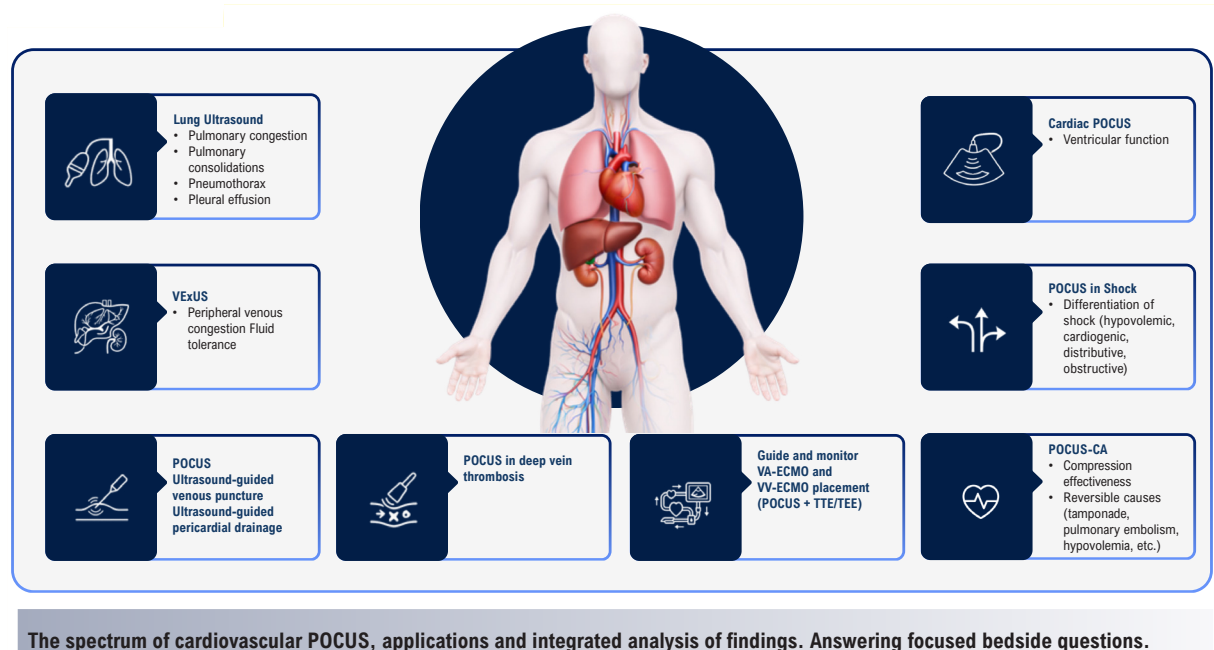
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Central Illustration: Position Statement on the Use of Point-of-Care Ultrasound in Cardiovascular Medicine – 2026: Executive Summary



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PE: Pulmonary embolism; POCUS: Point-of-care ultrasound; TEE: Transesophageal echocardiography; TTE: Transthoracic echocardiography; US: Ultrasound; VA-ECMO: Venoarterial extracorporeal membrane oxygenation; VExUS: Venous Excess Ultrasound Score; VV-ECMO: Venovenous extracorporeal membrane oxygenation.

Abstract

Point-of-care ultrasound (POCUS) is one of the most significant innovations in contemporary cardiovascular clinical practice, serving as an extension of the bedside physical examination. This executive summary outlines the Position Statement from the Department of Cardiovascular Imaging of the Brazilian Society of Cardiology (DIC-SBC), published in 2026, covering the key domains of cardiovascular POCUS application: cardiac assessment, lung ultrasound, assessment of systemic venous congestion (VExUS), screening for deep vein thrombosis, management of circulatory shock, short-term mechanical circulatory support, emergency medicine applications, cardiorespiratory arrest, and ultrasound-guided procedures. Fundamental concepts regarding training, certification,

and ethical and legal aspects relevant to the Brazilian context are discussed. This document emphasizes that POCUS does not replace a comprehensive diagnostic echocardiogram, but rather adds substantial clinical value when performed by properly trained professionals within structured protocols.

1. Introduction and Concept

Point-of-care ultrasound (POCUS) is defined as the use of ultrasound as an adjunct to the clinical examination, focused on answering an urgent clinical question at the bedside. In the cardiovascular context, it encompasses anatomical and functional assessment of the heart, lungs, and blood vessels in both inpatients and outpatients, from neonates to adults.¹⁻³

The main advantages of POCUS are portability, low cost, and accessibility. It can be used by properly trained cardiologists, critical care physicians, emergency physicians, and pediatricians in emergency departments, intensive care units (ICUs), operating rooms, and hard-to-reach settings. The miniaturization of equipment, with screens the size of a smartphone, and the advent of artificial intelligence (AI) to guide transducer positioning have progressively expanded its clinical application.

It is fundamental to distinguish POCUS from a comprehensive diagnostic echocardiogram. POCUS is used to answer specific, immediate clinical questions and does not replace a comprehensive echocardiographic assessment when the latter is indicated.⁴

2. Equipment, Training, and Certification

2.1. Equipment

The ideal equipment for POCUS should allow for image acquisition in one- and two-dimensional modes, spectral Doppler, and color flow mapping, using variable-frequency transducers and offering DICOM-format storage capabilities. Handheld devices perform adequately for most applications.

2.2. Structured Training

The Department of Cardiovascular Imaging of the Brazilian Society of Cardiology (DIC-SBC) has proposed the AcQUIRE protocol (AcQUIsition, Interpretation, and documentation of REsults), organized into three progressive levels of competence:

- **Level 1** (N = 30 exams; 2 weeks of training): Identification of key cardiac structures, acquisition of standard views, qualitative recognition of abnormalities, and documentation in the medical record.
- **Level 2** (N = 50 exams; 4 weeks of training): Understanding of POCUS protocols for differential diagnosis of shock and respiratory failure, in addition to assessment of fluid responsiveness and systemic congestion.
- **Level 3** (N = 70 exams; 12 weeks of training): Advanced assessment of valves, cardiac output (CO), filling pressures, and ultrasound-guided procedures.

This methodology includes an introductory theoretical-practical course (4 hours of online lectures and 8 hours of hands-on training with mannequins), practical training supervised by a qualified echocardiographer, assessment using a standardized checklist, and annual revalidation requiring a minimum score of 70% (Supplement 1). In order to maintain competence, professionals must perform at least 10 exams per month.⁵

2.3. Ethical and Legal Aspects in Brazil

Cardiovascular POCUS should be considered a bedside medical procedure, which does not replace a comprehensive diagnostic echocardiogram. Professionals who perform the

procedure assume civil liability for the actions taken, including the decision to perform, technical execution, interpretation, and documentation in the medical record.⁶

In Brazil, training in POCUS remains limited in undergraduate and medical residency curricula, resulting in inconsistent professional qualifications.⁷ There is a persistent lack of standardized procedure coding and clear reimbursement policies in both the Brazilian Unified Health System (SUS) and the supplementary health sector. Regulation by the Federal Council of Medicine, in coordination with medical specialty societies, is a priority to ensure legal protection for professionals and patient safety. Integration with telehealth strategies, specifically the *Programa Telessaúde Brasil Redes* (Brazil Telehealth Networks Program) and the *Ação Estratégica SUS Digital* (Digital SUS Strategic Action), strengthens the use of tele-POCUS as a tool to expand access to specialized cardiovascular assessment.

3. Cardiac POCUS

3.1. Main Echocardiographic Views

Cardiac POCUS utilizes five main echocardiographic views (Figure 1):

1. **Parasternal long-axis view:** assessment of global contractility, pericardial effusion, chamber dimensions, and regional wall motion.
2. **Parasternal short-axis view:** global contractility, regional wall motion, and pericardial effusion.
3. **Apical 4-chamber view:** global contractility, regional wall motion, and chamber dimensions.
4. **Subcostal view:** pericardial effusion, chamber dimensions, and global contractility.
5. **Subcostal inferior vena cava (IVC) view:** assessment of IVC and hepatic vein distensibility.

3.2. Assessment of Left Ventricular Systolic Function

Cardiac POCUS employs a qualitative approach to assess left ventricular (LV) systolic function; this method is more intuitive and clinically relevant than traditional quantitative methods (Simpson, Teichholz), which are more time-consuming and do not yield greater accuracy in emergency settings.⁸ The assessment considers endocardial excursion and myocardial thickening, classifying function into four categories (Table 1). Semiquantitative tools such as MAPSE (mitral annular plane systolic excursion) and EPSS (E-point septal separation) can serve as complementary measures. AI demonstrates good correlation with automated ejection fraction when image acquisition is adequate.⁹

3.3. Right Ventricular Assessment

Cardiac POCUS aids in the rapid diagnosis of conditions affecting the right ventricle (RV). RV enlargement is assessed by means of the RV/LV ratio: when the RV area exceeds two thirds of the LV area, it suggests enlargement and significant overload; when the RV/LV ratio is ≥ 1.0 , the finding suggests major overload.¹⁰ Lateral tricuspid annular

Ultrasound Views in Cardiac POCUS			
Window	Image	Transducer position	Best view for:
Parasternal long-axis Third intercostal space Left parasternal line Transducer marker toward the right shoulder			• Global contractility • Pericardial effusion • Chamber dimensions • Regional wall motion
Parasternal short-axis Third intercostal space Left parasternal line Transducer marker oriented toward the left shoulder			• Global contractility • Pericardial effusion • Segmental contractility • Chamber dimensions
Apical 4-chamber Left mid-clavicular line Apical impulse Transducer marker toward the left			• Global contractility • Chamber dimensions • Regional wall motion • Pericardial effusion
Subcostal Midline Below the xiphoid process Marker toward the left			• Pericardial effusion • Chamber dimensions • Global contractility
Subcostal IVC Midline Below xiphoid process Marker toward the left			• IVC distensibility • Hepatic vein distensibility

Figure 1 – Main views used in cardiac POCUS, with respective transducer positions and structures assessed. AO: aorta; IVC: inferior vena cava; POCUS: point-of-care ultrasound; LA: left atrium; LV: left ventricle RA: right atrium; RV: right ventricle.

plane systolic excursion (TAPSE < 1.7 cm) indicates RV systolic dysfunction and has prognostic value in patients with acute pulmonary embolism.¹¹ In the context of acute pulmonary embolism, RV dilation with septal flattening (D-shape) and McConnell's sign (present in only 12%–20% of cases) can assist in diagnosis.

3.4. Cardiac Tamponade

POCUS is a highly valuable tool for the early detection of cardiac tamponade, whose classic clinical signs (Beck's

triad) are not always present. Figure 2 provides an overview of the key findings. IVC distension with minimal respiratory variation and right atrial (RA) collapse during ventricular systole have high sensitivity; RV diastolic collapse is the most specific finding for filling restriction. Differentiation between pericardial and pleural effusion in the parasternal long-axis view is based on the relationship with the descending aorta; effusions anterior to the descending aorta are pericardial, whereas posterior effusions are pleural.¹²

Special Article

3.5. Advanced POCUS: LVOT VTI and E/e' ratio

Stroke volume is calculated as the product of the left ventricular outflow tract (LVOT) velocity–time integral (VTI)

Table 1 – Qualitative assessment of left ventricular systolic function

Normal	Thickening of most LV segments, with endocardial displacement toward the center of the LV.
Hyperdynamic	Increased endocardial excursion and myocardial thickening, leading to partial or total systolic obliteration of the LV
Reduced systolic function	Reduced endocardial excursion and myocardial thickening.
Severe dysfunction	Severely reduced endocardial excursion and myocardial thickening.

Videos 1 to 13 (Supplement 2) provide examples. LV: left ventricle.

and the LVOT area. In healthy individuals, the LVOT VTI ranges from 18 to 22 cm at heart rates between 55 and 95 bpm. Variations in LVOT VTI reflect changes in stroke volume and guide real-time therapeutic decisions.¹³ An average E/e' ratio > 14 has high specificity for elevated left atrial pressure (LAP) and a strong association with fluid intolerance; an E/e' ratio < 8 has good accuracy for predicting LAP < 18 mmHg.¹⁴

4. Lung Ultrasound

4.1. Basics and Artifacts

Lung ultrasound (LUS) relies on artifacts generated from the pleural line. Under normal conditions, aerated lungs produce **A-lines** (horizontal reverberation artifacts). Thickening of interalveolar spaces or filling of alveoli with fluid or inflammatory material generates **B-lines** (vertical artifacts propagating across the entire ultrasound field). Table 2 describes the main findings and their interpretation.

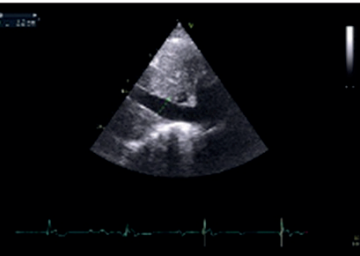
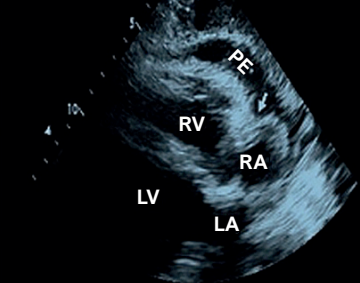
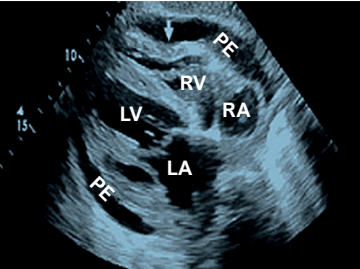
Inferior vena cava distension*		• High sensitivity • Low specificity • Easily identified • Good interobserver agreement
Right atrial collapse during ventricular systole		• High sensitivity • Low specificity • Good interobserver agreement
Right ventricular collapse during ventricular diastole		• Low sensitivity • High specificity • Better interobserver agreement in advanced stages⁵⁰

Figure 2 – Key findings of cardiac tamponade on POCUS. *IVC distension may be absent in cardiac tamponade associated with severe hypovolemia. Other findings may contribute to diagnosis, including leftward shift of the interventricular septum during inspiration (part of the physiology of pulsus paradoxus). 12 IVC: inferior vena cava; LA: left atrium; LV: left ventricle; PE: pericardial effusion; RA: right atrium; RV: right ventricle.

4.2. Examination Protocols

Three main protocols are recommended according to the clinical context (Figure 3):

- **BLUE protocol** (Bedside Lung Ultrasound in Emergency): divides each hemithorax into three quadrants (two anterior and one posterolateral basal [PLAPS point]). The **B-profile** (≥ 3 B-lines per quadrant with preserved pleural sliding) indicates pulmonary congestion, with a sensitivity of 97% and a specificity of 95%.¹⁵ Recommended in emergency settings.
- **8-quadrant protocol**: recommended for grading and longitudinal monitoring of congestion in patients with heart failure, without compromising time or accuracy.¹⁶
- **12-quadrant protocol**: includes the posterior chest region; indicated for interstitial syndromes such as pneumonia due to SARS-CoV-2 infection.

Table 2 – Description of the most frequent lung ultrasound findings and their interpretation

Finding	Descrição	Significado
Pleural line	Hyperechoic curvilinear line beneath the ribs.	Interface between the parietal and visceral pleurae.
Pleural sliding	Sliding of the visceral pleura over the parietal pleura during respiration.	Rules out pneumothorax and pleural adhesions.
A-lines	Horizontal reverberation artifacts originating from the pleural line.	Aerated lung (normal), COPD, or pneumothorax (with loss of pleural sliding).
B-lines	Vertical artifacts originating from the pleural line that extend across the entire ultrasound field.	Accumulation of hydrostatic and/or inflammatory fluid or fibrosis in the interlobular septa and alveoli.
Z-lines	Static vertical artifacts that do not extend to the bottom of the field.	No pathological significance. Should be differentiated from B-lines.
Lung point	Transition point between pleural sliding and the absence of movement.	Pathognomonic for pneumothorax. The more lateral the lung point, the larger the pneumothorax.
Lung pulse	Rhythmic movement of the pleura synchronized with the heartbeat.	Rules out pneumothorax in the absence of pleural sliding.
Barcode sign (stratosphere sign)	Horizontal lines across the entire M-mode ultrasound field.	Indicative of pneumothorax.
Plankton sign	Mobile punctate echoes within the fluid.	May indicate infection or hemothorax; may appear after aggressive diuretic therapy.
Septated (loculated) effusion	Debris, fibrin strands, and septations.	Complex effusion; suggestive of infection, abscess, empyema, or fibrosis, hindering pleural drainage.
Air bronchograms	Hyperechoic punctate echoes trapped within bronchi and surrounded by consolidation.	When mobile (dynamic), suggestive of pneumonic consolidation; when static, suggestive of atelectasis.
Shred sign	Irregular, deep subpleural hyperechoic line separating the consolidated zone from the partially aerated zone.	Present in non-translobar consolidations, most frequently associated with pneumonia.
Curtain sign	Overlapping of aerated lung during respiration, obscuring the image of the liver or spleen.	Aerated lung bases at the point of analysis.
Jellyfish sign	Segment of collapsed lung exhibiting undulating movement within a large pleural effusion.	Compressive atelectasis.
Subpleural consolidation	Small subpleural hypoechoic area (triangular, circular, or polygonal).	Pulmonary embolism, atelectasis, infection, hemorrhage, or neoplasm.
Translobar consolidation	Absence of air in the lung, presenting a solid-organ texture (hepatization).	Pneumonia or atelectasis.

COPD: chronic obstructive pulmonary disease.

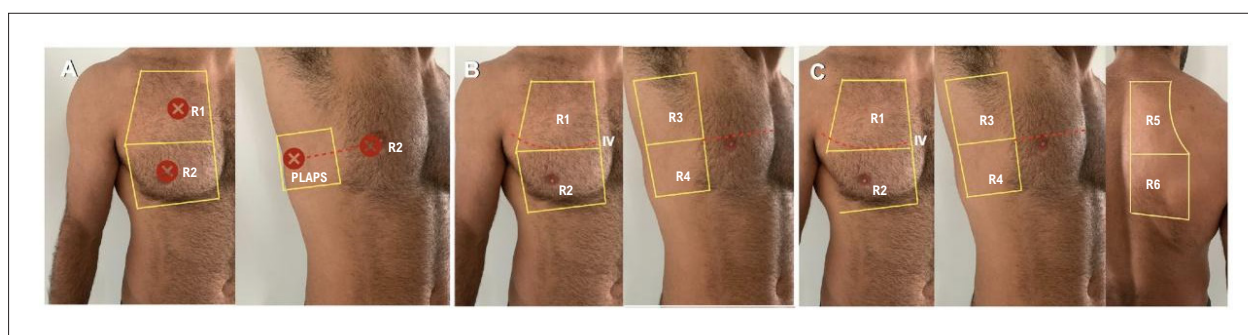


Figure 3 – Recommended lung ultrasound protocols. A – BLUE protocol¹⁵; B – 8-quadrant protocol¹⁷; C – 12-quadrant protocol.¹⁸
Note: See the references for further details. BLUE: Bedside Lung Ultrasound in Emergency; PLAPS: posterolateral alveolar and/or pleural syndrome.

4.3. Main Applications

- **Pulmonary congestion:** LUS detects extravascular lung fluid with diagnostic performance equivalent to that of BNP measurement and superior to that of chest radiography.¹⁹ The Brazilian Heart Failure Guideline recommends (class I, level C) the integrated use of LUS and echocardiography to assess congestion in patients with acute heart failure.²⁰
- **Pleural effusion:** LUS shows 93% accuracy for detecting pleural effusion, versus 47% for chest radiography.¹⁵ The Balik method estimates volume by multiplying the greatest distance between the parietal pleura and the lung tissue during expiration (in cm) by 200, resulting in an estimate in mL.
- **Pneumothorax:** Sensitivity of 90% and specificity of 98%.²¹ The absence of pleural sliding is the finding with the highest sensitivity; lung point is the only pathognomonic finding.
- **Pulmonary embolism:** A triangular subpleural consolidation in the posterobasal regions is a suggestive finding. Triple POCUS (cardiac + venous + pulmonary) demonstrated a sensitivity of 90% and a specificity of 86% for pulmonary embolism in a multicenter study involving 357 patients.²²

5. VExUS: Assessment of Systemic Venous Congestion

5.1. Introduction and Relevance

Patients with RV failure, pulmonary hypertension, or fluid overload frequently develop systemic venous congestion, leading to reduced arteriovenous gradient, elevated capillary hydrostatic pressure, and interstitial edema. This mechanism causes organ (especially kidney) dysfunction, perpetuating a vicious cycle of morbidity and mortality.²³ Venous excess ultrasound (VExUS) has emerged as a reliable, reproducible method with good interobserver agreement for quantifying this congestion.²⁴

5.2. Protocol and Grading

VExUS sequentially analyzes the following four components (Figure 4):

1. **IVC:** Measured 2 cm proximal to the IVC–RA junction, during end-expiratory apnea. IVC < 2 cm: VExUS grade 0 (no congestion). IVC ≥ 2 cm: proceed to analysis of the remaining components.
2. **Hepatic vein (pulsed-wave Doppler):** Three patterns:
 - Type 1 (normal): S wave > D wave
 - Type 2 (increased RA pressure): S wave < D wave
 - Type 3 (markedly increased RA pressure): reversed S wave
3. **Portal vein (pulsed-wave Doppler):** Classified by pulsatility fraction:
 - Type 1: oscillation < 30%
 - Type 2: oscillation 31%–50%
 - Type 3: oscillation > 50% or flow reversal
4. **Renal interlobar vein (pulsed-wave Doppler):**
 - Type 1: continuous flow
 - Type 2: biphasic flow
 - Type 3: monophasic flow

Final grading:

- Grade 0: IVC < 2 cm
- Grade 1: IVC ≥ 2 cm + type 1 or 2 patterns, in any combination
- Grade 2: IVC ≥ 2 cm + one type 3 waveform
- Grade 3: IVC ≥ 2 cm + two or more type 3 waveforms

5.3. Clinical Evidence and Applications

The original study by Beaubien-Souligny et al.²⁶ validated the score in 145 postoperative cardiac surgery patients, demonstrating a significant association with subsequent acute kidney injury (hazard ratio = 3.69; 95% confidence interval [CI]: 1.65–8.24; p = 0.001). Subsequent studies have demonstrated its applicability in cardiorenal syndrome, complex hyponatremia, acute coronary syndromes, non-

Quantification of systemic venous congestion – VExUS

Step 1:

IVC analysis



If IVC ≥ 2 cm,
proceed to step 2

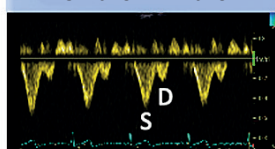


Step 2:

Hepatic vein
analysis

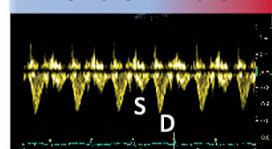
Type 1

S wave > D wave



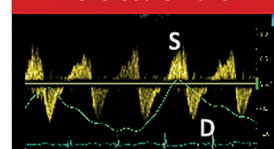
Type 2

S wave < D wave



Type 3

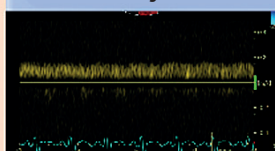
Reversed S wave



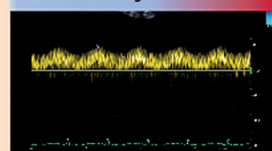
Step 3:

Portal vein
analysis

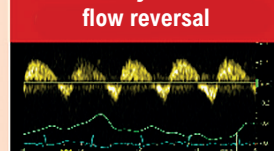
Pulsatility < 30%



Pulsatility 30%-50%



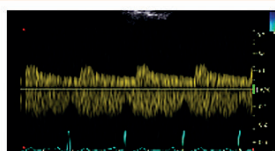
Pulsatility > 50% or
flow reversal



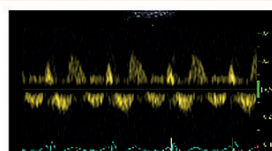
Step 4:

Interlobar renal
vein analysis

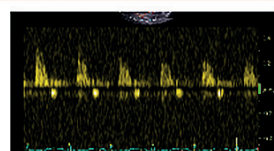
Continuous flow



Biphasic flow



Monophasic flow



Step 5: Integrate data and grade

GRADE 0

Absence of congestion
IVC < 2 cm

GRADE 1

Mild congestion
IVC ≥ 2 cm + any
combination of type 1
and type 2 waveforms

GRADE 2

Moderate congestion
IVC ≥ 2 cm +
one type 3 waveform

GRADE 3

Severe congestion
IVC ≥ 2 cm + two or
more type 3 waveforms

–

Right atrial pressure

+

Figure 4 – VExUS grading: when the IVC diameter is greater than 2 cm, three grades of venous congestion are defined based on the severity of changes observed in hepatic, portal, and renal interlobar vein flow; these should ideally be recorded during end-expiratory apnea. IVC: inferior vena cava; VExUS: venous excess ultrasound. Adapted from Koratala et al.²⁵

cardiac perioperative assessment, and pediatric patients in the ICU.²⁷⁻³⁰

VExUS does not assess the need for fluid replacement, but it is a key indicator of fluid tolerance, identifying cases where discontinuing fluid resuscitation or removing fluid would be beneficial. VExUS 0 or 1: fluid-tolerant; VExUS 2 or 3: fluid-intolerant.

6. POCUS in Deep Vein Thrombosis

POCUS for the assessment of proximal deep vein thrombosis (DVT), performed by appropriately trained professionals in urgent and emergency settings, currently has a **grade I recommendation and level B evidence**.

The extended compression protocol, also known as three-point compression ultrasound, is currently recommended (Figure 5), supported by the European Society of Intensive Care Medicine consensus and the American College of Emergency Physicians' emergency ultrasound guidelines.³¹ DVT diagnosis is established by visualizing a thrombus (intraluminal echogenic material) or identifying venous incompressibility. In acute thrombosis, incompressibility often precedes visualization of the thrombus (Figure 5).

A meta-analysis by Pomero et al.³³ demonstrated a sensitivity of 96.1% (95% CI: 90.6%–98.5%) and a specificity of 96.8% (95% CI: 94.6%–98.1%) for compression ultrasound performed by emergency physicians. The examination is performed in under 5 minutes, reducing diagnostic delays and the need for unnecessary comprehensive scans.

The technical sequence evaluates the saphenofemoral junction, the area 1–2 cm distal to the saphenofemoral junction, the proximal and mid-to-distal segments of the femoral vein in the thigh (at 2–3 cm intervals), and the popliteal vein. The linear transducer (5–10 MHz) is positioned transversely over the vein, with progressive compression to assess for complete collapse.⁵

7. POCUS in Patients with Circulatory Shock

7.1. Diagnostic Approach

POCUS is the method of choice for the initial hemodynamic assessment and monitoring of patients with circulatory shock, allowing for diagnosis of hemodynamic profile within 2 minutes, even when performed by non-specialists.³⁴ The proposed approach integrates the BLUE, cardiac POCUS, and adapted EGLS protocols, addressing five sequential key questions:

- Is there tamponade?** Investigate for moderate to severe pericardial effusion, dilated IVC with minimal respiratory variation, and diastolic collapse of the right heart chambers (swinging heart).
- Is the patient hypovolemic?** A hyperdynamic LV (kissing walls) or small-diameter IVC (≤ 10 mm) with collapse throughout the respiratory cycle. Lungs without B-lines (A-pattern).
- Is important LV systolic dysfunction the cause of shock?** Significant LV systolic dysfunction associated

with pulmonary congestion (B-profile on LUS) and/or systemic venous congestion (dilated IVC). Pure cardiogenic shock is unlikely to be the primary cause of instability in the presence of a normal lung pattern.

- Are there signs of RV distension (*cor pulmonale*)?** RV $> 60\%$ of the LV (mild *cor pulmonale*); RV = LV (moderate); or RV $> LV$ (severe), with septal flattening (D-shape) and dilated IVC.
- Is there pneumothorax?** Absence of pleural sliding and presence of a lung point.

Figure 6 shows the complete diagnostic algorithm.

7.2. Fluid Responsiveness and Fluid Tolerance

Fluid responsiveness (FR) is defined as an increase in CO $> 10\%$ – 15% induced by an increase in preload. The main parameter for estimating CO via POCUS is the LVOT VTI (normal: 18–22 cm at a heart rate of 55–95 bpm).

- Passive leg raising (PLR):** An increase in VTI of $\geq 10\%$ induced by PLR predicts an increase in CO following fluid infusion with 84% accuracy.³⁵ PLR can be performed in patients under spontaneous or mechanical ventilation. Intraobserver variability of VTI measurements ($\pm 11\%$) should be considered. Changes $> 20\%$ are more likely to represent true FR.
- Expiratory and inspiratory pause maneuvers (TOEF/TOIF):** The sum of the absolute variation ($\geq 13\%$) in LVOT VTI during combined TOEF and TOIF maneuvers has shown 93% accuracy in predicting FR; this approach is reserved for more experienced practitioners.³⁶
- Fluid tolerance:** Assessed via the presence of B-lines on LUS (pulmonary congestion) and the VExUS score (systemic venous congestion). VExUS 0 or 1: fluid-tolerant; VExUS 2 or 3: fluid-intolerant.

8. POCUS in Short-Term Mechanical Circulatory Support

POCUS plays a multifaceted role in short-term mechanical circulatory support, encompassing initial patient assessment, guidance of cannulation, continuous hemodynamic monitoring, and early detection of complications.

8.1. Intra-Aortic Balloon Pump

Transesophageal echocardiography (TEE) is preferable to fluoroscopy for guiding intra-aortic balloon pump insertion because it allows for real-time visualization, is portable, and does not utilize ionizing radiation. Correct positioning requires the tip of the intra-aortic balloon to be located approximately 2 cm distal to the origin of the left subclavian artery. TEE also allows for the exclusion of primary contraindications (significant aortic regurgitation, aortic dissection) prior to insertion.

8.2. Venoarterial Extracorporeal Membrane Oxygenation

Echocardiography is essential across the four phases of venoarterial extracorporeal membrane oxygenation (ECMO)

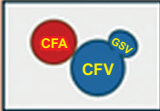
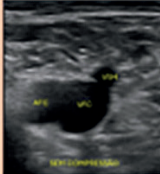
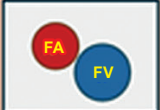
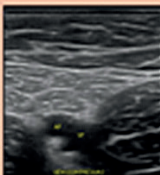
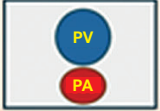
EXAMINATION SEQUENCE	DESCRIPTION	IMAGE/DIAGRAM
Patient positioning	Supine position with external rotation of the lower limb and slight knee flexion.	
View at the saphenofemoral junction	Position the transducer in the inguinal region at the level of the SFJ. Obtain images with and without compression, observing complete vein collapse.	   
View distal to the saphenofemoral junction	Position the transducer in the inguinal region, 1–2 cm distal to the SFJ. Obtain images with and without compression, observing complete vein collapse.	 
Femoral vein views	Position the transducer on the proximal and mid-to-distal thigh segments. Obtain images with and without compression, observing complete vein collapse every 2–3 cm.	   
Popliteal vein view	Position the transducer in the popliteal fossa. Obtain images with and without compression, observing complete vein collapse.	   

Figure 5 – Sequence of views for the extended three-point compression ultrasound protocol.³² CFA: common femoral artery; CFV: common femoral vein; FA: femoral artery; FV: femoral vein; GSV: great saphenous vein; PA: popliteal artery; PV: popliteal vein; SFJ: saphenofemoral junction.

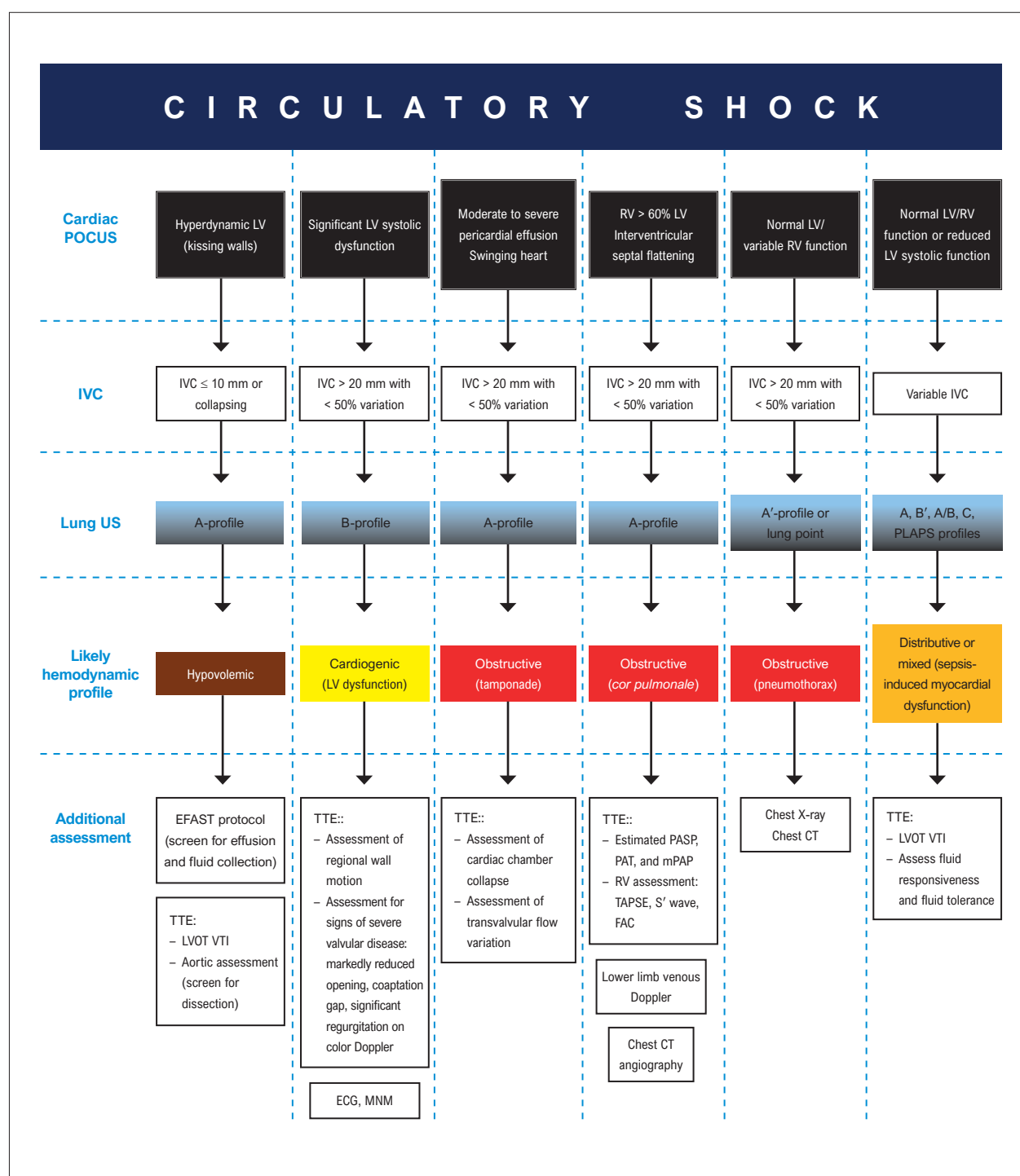


Figure 6 – Initial diagnostic algorithm for circulatory shock based on POCUS. CT: computed tomography; ECG: electrocardiogram; FAC: fractional area change; IVC: inferior vena cava; LV: left ventricle; LVOT: left ventricular outflow tract; MNM: myocardial necrosis markers; mPAP: mean pulmonary artery pressure; PASP: pulmonary artery systolic pressure; PAT: pulmonary acceleration time; PLAPS: posterolateral alveolar and/or pleural syndrome; POCUS: point-of-care ultrasound; RV: right ventricle; TAPSE: tricuspid annular plane systolic excursion; TTE: transthoracic echocardiogram; VTI: velocity-time integral. Adapted from the ECLS, BLUE, and EFAST protocols.

support: pre-cannulation, cannulation and initiation, monitoring for malfunction, and weaning. Special attention must be paid to the absence of aortic valve opening during peripheral support; this finding indicates blood stasis, risk of thrombosis, and the need for LV decompression strategies. All patients on acute mechanical circulatory support should undergo daily echocardiography, with additional focused exams in the event of acute hemodynamic deterioration.³⁷

Beside cardiovascular echocardiography for venovenous and venoarterial ECMO across the pre-cannulation, cannulation and initiation, malfunction, and weaning phases requires a highly specialized approach with well-defined protocols, extending beyond the scope of basic POCUS.

9. POCUS in Emergency Settings

9.1. Chest Pain

POCUS aids in the differential diagnosis of life-threatening conditions in patients with chest pain, including pulmonary embolism, pneumothorax, and pericardial diseases. The identification of pericardial effusion has an accuracy of over 95%, even when performed by emergency physicians with adequate training.³⁸ Assessment of the aorta in suspected dissection and analysis of regional LV wall motion to identify acute coronary syndrome require advanced training and should be performed by cardiovascular imaging specialists.

Regarding diagnosis of pulmonary embolism, the combination of cardiac findings (RV dilation, McConnell's sign, D-shaped septum), pulmonary findings (triangular subpleural consolidation), and vascular findings (noncompressible proximal DVT) has shown a specificity of over 95% (Table 3). In patients with hemodynamic instability, cardiac POCUS should be the first tool employed, given that the absence of signs of RV overload can rule out massive pulmonary embolism as a possible cause.

9.2. Dyspnea and Hemodynamic Instability

LUS is a key tool for rapid assessment of patients with dyspnea. The presence of ≥ 3 B-lines in a single intercostal space suggests significant pulmonary congestion, with distribution and severity correlating with the clinical presentation. Integrated use of the VExUS protocol to assess systemic venous congestion complements the management of patients with hemodynamic instability and/or organ dysfunction, particularly regarding risk stratification for acute kidney injury.

9.3. Peripheral Edema

POCUS is useful for investigating specific causes of peripheral edema, especially DVT, complementing LUS (pulmonary congestion) and VExUS (systemic venous congestion) in differential diagnosis.

Table 3 – POCUS as an aid to diagnosis of pulmonary embolism³²

Finding	Interpretation	Observations
Deep vein thrombosis	Visualization of a thrombus in a noncompressible deep vein (femoral, popliteal, etc.)	Highly suggestive of pulmonary embolism if associated with respiratory symptoms
RV dilation	RV diameter > LV diameter (RV/LV > 1) in parasternal or apical views	Suggestive of RV pressure overload (sign of massive/submassive embolism).
McConnell's sign	Hypokinesis of the basal and mid-portions of the RV free wall with apical sparing	Highly suggestive of pulmonary embolism (specificity ~94%).
Interventricular septal flattening	Shift of the interventricular septum toward the LV during diastole	Indicates RV pressure overload.
Pulmonary hypertension	Estimated PASP	Can be calculated based on peak tricuspid regurgitation velocity.
Thrombus in transit	Direct visualization of thrombus in the right heart chambers	Specific, but low sensitivity. Differential diagnosis includes embolic masses, such as tumors and vegetations.
Pulmonary artery thrombus	Direct visualization of thrombus in the main pulmonary artery or its branches (rare)	Specific, but low sensitivity (more common in central pulmonary embolism).
Pleural effusion	Fluid in the pleural cavity (usually small to moderate)	Nonspecific, but common in pulmonary embolism
Triangular subpleural consolidations	Suggestive of pulmonary infarction	Patients with pulmonary embolism without pulmonary infarction may show a normal LUS pattern.

LUS: lung ultrasound; LV: left ventricle; PASP: pulmonary artery systolic pressure; RV: right ventricle.

10. POCUS during Cardiopulmonary Arrest

POCUS during cardiopulmonary arrest (POCUS-CPA), when performed by a trained operator, allows assessment of the quality of chest compressions, diagnosis of reversible causes of arrest (hypovolemia, tension pneumothorax, pulmonary embolism, and cardiac tamponade), monitoring of interventions, and assessment of the response to treatment.³⁹ The method also provides relevant prognostic data regarding the likelihood of return of spontaneous circulation (Figure 7).

The **CASA** (Cardiac Arrest Sonographic Assessment) protocol is the only one that has demonstrated a reduction in the duration of interruptions for rhythm checks, and it is recommended for routine implementation.⁴⁰

Technical aspects: A phased-array transducer (3.5–5 MHz) is recommended. Images should be acquired during the 10-second pause for rhythm assessment and analyzed throughout the resuscitation cycle. The subcostal view is the recommended initial approach. Subcostal images can be acquired during chest compressions to assess their effectiveness.

Reversible causes identified by POCUS-CPA:

- **Cardiac tamponade:** A dilated IVC prompts further assessment; differential diagnosis from pleural effusion is based on the relationship to the descending aorta.
- **Pulmonary embolism:** Sudden RV dilation (RV/LV ≥ 1:1), D-shaped septum.
- **Tension pneumothorax:** Absence of pleural sliding, stratosphere sign, lung point.
- **Hypovolemia:** Complete ventricular collapse and IVC collapse.

Important limitation: The use of POCUS-CPA remains subject to uncertainty, as it has not yet demonstrated a significant impact on patient prognosis, primarily due to the lack of a universal protocol definitively incorporated into advanced cardiovascular life support.

11. Ultrasound-Guided Procedures

11.1. Vascular Access

Ultrasound-guided catheter placement is safer than the “blind” (unguided) technique. The dynamic (real-time) technique is preferred, as it increases accuracy, reduces the number of attempts, and decreases complications. Two puncture planes can be used:

- **Short-axis:** Technically more accessible; the limitation is the inability to continuously visualize the needle tip.
- **Long-axis:** Allows direct visualization of the needle tip along its entire trajectory, offering greater control and safety, although it is technically more challenging.

The main sites for ultrasound-guided puncture are the internal jugular vein, femoral vein, and subclavian vein.

11.2. Ultrasound-Guided Pericardiocentesis

When performed by experienced professionals with appropriate training, ultrasound-guided pericardiocentesis presents major event rates of 0.3% to 3.9% and minor event rates of 0.4% to 20%, compared to a morbidity of ~20% and mortality of 6% with the traditional “blind” subxiphoid technique.⁴¹ The parasternal apical window is the most frequently used (66% of cases in the Mayo Clinic series). Correct catheter placement is confirmed by the injection of 5 mL of agitated saline.

11.3. Assessment of the Full Stomach

Gastric POCUS assesses the quantity and quality of gastric contents prior to procedures such as TEE, enhancing safety by identifying a full stomach containing liquid (anechoic appearance of the distended gastric antrum) or solid matter (heterogeneous appearance with hyperechoic areas). This assessment is particularly relevant in conditions associated with gastroparesis (diabetes, obesity, hemodynamic instability).

12. Final Considerations and Future Perspectives

Cardiovascular POCUS represents a natural extension of contemporary physical examination, with proven potential to positively impact clinical decision-making in emergency, intensive care, and outpatient settings. Responsible adoption of this technology requires clear legal regulation, standardized training with competency certification, adequate supervision, and continuous quality monitoring.

In Brazil, the incorporation of cardiovascular POCUS into the SUS faces significant structural barriers, including limited availability of equipment, irregular training, lack of standardized care flows, and logistical challenges; however, there are growing opportunities through telehealth programs, federal funding (SUS Digital, FINEP), and state funding (FAPERJ). Handheld devices priced at USD 4,000 to 6,000 represent a viable alternative for expanding access in regions with limited infrastructure.

It is likely that the advent of AI for image interpretation, automatic B-line counting, and the development of integrated algorithms will significantly expand the use of POCUS in emergency medicine, intensive care, and cardiology. The future of cardiovascular medicine will likely involve POCUS as an integral component of bedside clinical assessment, yet always interpreted in light of the clinical history, physical examination, and other patient data.

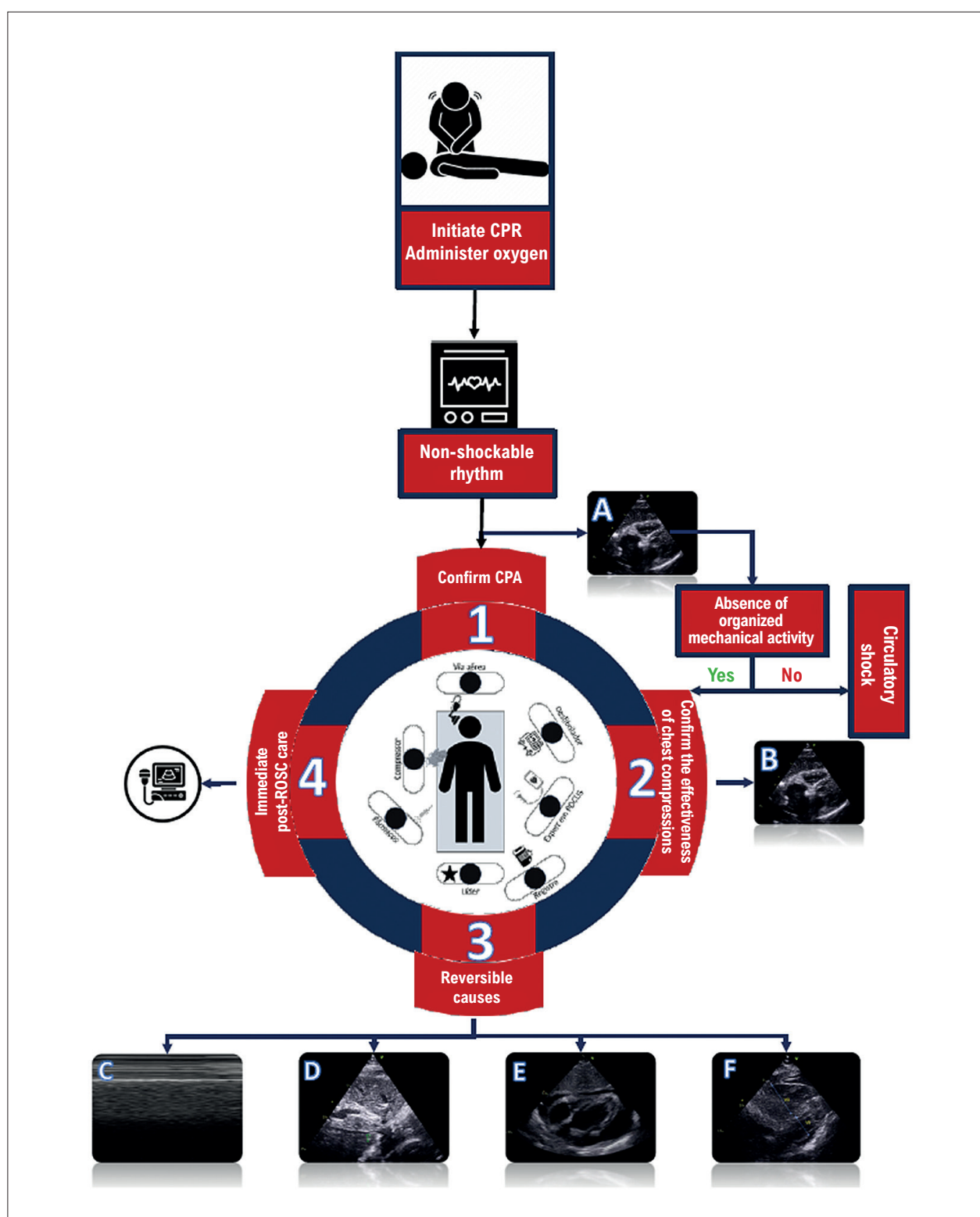


Figure 7 – Utility of POCUS-CPA. The illustration in the center depicts the team positioning suggested in this statement for performing POCUS-CPA. The subcostal view allows rapid confirmation of CPA versus cardiac mechanical activity and of shockable versus non-shockable rhythm (panel 1), as well as assessment of the effectiveness of chest compressions (panel 2B). It is possible to identify reversible causes, such as tension pneumothorax (panel 3C), hypovolemic shock (panel 3D), cardiac tamponade (panel 3E), and signs of pulmonary embolism (panel 3F). After ROSC, a targeted assessment can be performed to investigate other causes (panel 4). CPA: cardiopulmonary arrest; CPR: cardiopulmonary resuscitation; ROSC: return of spontaneous circulation.

Special Article

Position Statement on the Use of Point-of-Care Ultrasound in Cardiovascular Medicine – 2026: Executive Summary

The report below lists declarations of interest as reported to the SBC by the experts during the period of the development of these statement, 2025/2026.

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Artificial Intelligence in Carotid Ultrasonography: Current Status and Future Directions

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Abstract

To review the current applications of artificial intelligence (AI) in carotid ultrasonography and its future perspectives. This narrative review was based on recent studies addressing machine learning, deep learning, radiomics, and integration with advanced ultrasound modalities, including contrast-enhanced ultrasound (CEUS), elastography, three-dimensional ultrasound, microvascular flow imaging (MFI), and ultrafast ultrasound. Carotid assessment has evolved from an approach focused primarily on the degree of luminal stenosis to a more comprehensive evaluation encompassing plaque burden, morphology, composition, and vulnerability. AI algorithms have been applied to automated plaque detection, image segmentation, plaque stability classification, radiomic feature extraction, and prediction of ischemic events. When combined with advanced imaging techniques, these models may improve reproducibility, reduce operator dependence, and reveal quantitative patterns that conventional visual assessment may not detect. Despite promising results, important challenges remain regarding image standardization, external validation, model explainability, and prospective clinical impacts. AI has the potential to transform carotid ultrasonography into a multiparametric tool for personalized medicine. Its clinical implementation will depend on robust validation, integration into clinical workflows, and demonstration of incremental value over conventional ultrasonography.

Introduction

Carotid atherosclerosis is an important marker of cardiovascular and cerebrovascular risk and has traditionally been assessed using ultrasonography with a predominant

focus on the degree of luminal stenosis. This paradigm was established by landmark studies that supported therapeutic decision-making, particularly in symptomatic patients. However, advances in understanding of plaque biology have shown that stenosis alone does not fully account for the clinical risk, especially in asymptomatic individuals or those with non-obstructive lesions.^{1–4}

Over the past decades, increasing evidence has demonstrated that the presence of plaque, its atherosclerotic burden, and morphological and compositional characteristics provide relevant prognostic information beyond that offered by traditional clinical risk scores. In contemporary cohorts, even small carotid plaques (including those associated with stenosis of less than 50%) have been associated with a progressive increase in the risk of atherosclerotic events, mainly when bilateral or accompanied by femoral artery involvement, reinforcing the concept of systemic and multivascular subclinical atherosclerosis.² In primary prevention, the quantification of plaque burden has shown greater predictive value than carotid intima-media thickness alone and has influenced clinical decision-making, including intensification of statin therapy.⁵ These findings support the transition from a model focused exclusively on hemodynamics to a more comprehensive approach centered on plaque characterization and individualized risk stratification.^{1–3,6,7}

Carotid ultrasonography plays a central role in this context, as it is a widely available imaging modality, free of ionizing radiation, and capable of providing information on anatomical, hemodynamic, and tissue characterization. In addition to plaque detection, carotid ultrasonography can assess maximum plaque thickness, echogenicity, surface irregularity, ulceration, atherosclerotic burden, and, through more recent techniques, intraplaque neovascularization, biomechanical properties, and three-dimensional plaque volume.^{1,3} Clinical guidelines and consensus documents emphasize the role of carotid plaque as a biomarker of cardiovascular risk and the need to incorporate plaque characteristics beyond stenosis into clinical assessment.^{3,4,8,9} Consistent with this concept, standardized proposals (e.g., Carotid Plaque-RADS) reflect the shift toward a more integrated evaluation of plaque vulnerability and stroke risk.^{10,11}

Despite this potential, carotid ultrasonography remains partially limited by operator dependence, acquisition

Keywords

Carotid Arteries Ultrasonography; Artificial Intelligence; Atherosclerotic Plaque

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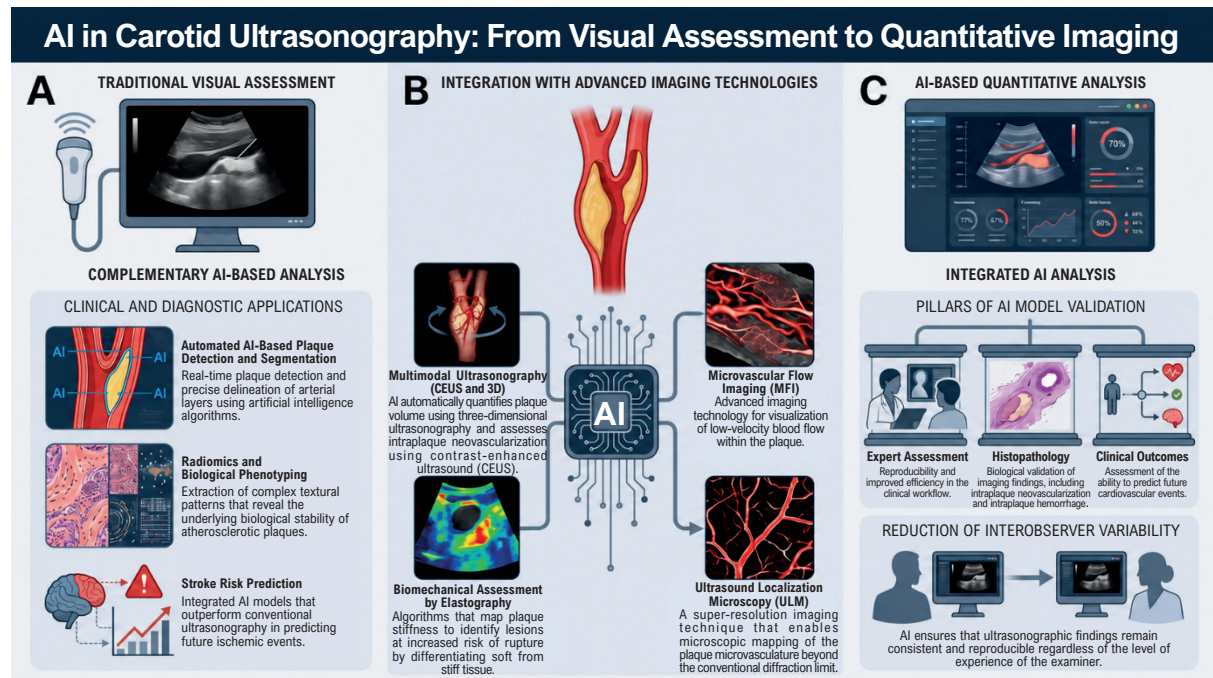
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Central Illustration: Artificial Intelligence in Carotid Ultrasonography: Current Status and Future Directions


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variability, heterogeneity across ultrasound systems, and subjectivity in the interpretation of complex plaque phenotypes. Relevant features, such as a lipid-rich necrotic core, intraplaque hemorrhage, neovascularization, inflammation, and fibrous cap fragility, may be inferred from ultrasound findings but are not always detected or quantified reproducibly.^{1,10,12} In this context, artificial intelligence (AI) has emerged as a promising tool.

The application of AI to carotid ultrasonography has expanded rapidly in recent years, encompassing automated plaque detection, lumen and vessel wall segmentation, plaque vulnerability classification, event prediction, and clinical workflow support. Models based on machine learning and deep learning have demonstrated the ability to extract textural and morphological patterns imperceptible to conventional visual inspection, with the potential to reduce interobserver variability, accelerate image analysis, and increase the prognostic value of carotid ultrasonography.^{13–16} In parallel, advanced modalities (e.g., contrast-enhanced ultrasound [CEUS], elastography, microvascular flow imaging [MFI], three-dimensional ultrasound, and super-resolution ultrasound) provide novel imaging biomarkers that can be integrated with AI using multiparametric approaches.^{17–21}

Therefore, this review discusses the current applications of AI in carotid ultrasonography and its future perspectives, with emphasis on plaque detection and quantification, vulnerability characterization, integration with advanced

imaging modalities, and the potential impact on risk stratification and clinical practice (Central Illustration). Radiomics-based image feature extraction, a fundamental process in carotid ultrasonography (Figure A). AI-based multimodal integration and assessment of carotid plaque (Figure B). Types of endpoints in contemporary investigations using AI (Figure C).

Fundamentals of AI Applied to Carotid Ultrasonography

The application of AI to carotid ultrasonography relies on converting images into information that algorithms can analyze. In practical terms, this involves transforming a two-dimensional, dynamic, and operator-dependent examination into a structured dataset that supports tasks, such as plaque detection, anatomical segmentation, tissue characterization, and risk stratification for clinical decision-making.^{13,14,22,23}

In general, AI applied to medical imaging can be understood at three main levels. The first is conventional machine learning, in which predefined features are extracted from the image and subsequently used by algorithms for classification or prediction. The second is deep learning, in which neural networks learn directly from image pixels and identify complex patterns without relying on manually selected variables. The third is the integration of both approaches, frequently combining automated segmentation, quantitative feature extraction, and composite clinical-imaging models.^{13,14,22,24}

In carotid ultrasonography, this process begins with image acquisition, which provides the foundation for extracting input data, and no model can overcome severe limitations in input image quality. Inappropriate gain settings, excessive imaging depth, poor acoustic windows, marked acoustic shadowing, motion artifacts, limited standardization across ultrasound systems, or differences in acquisition protocols may substantially affect algorithm performance. This dependence explains why technical standardization and image harmonization have become central issues in the development of robust AI models.^{23,25,26}

Following image acquisition, many AI processing workflows include segmentation, which is the automatic or semi-automatic identification of structures of interest, such as the lumen, intima-media complex, arterial wall, and atherosclerotic plaque. This step is critical because it defines the region from which quantitative information will be extracted. When segmentation is inaccurate, the model learns from noise, poorly defined borders, or nonrepresentative regions.^{22,23,25-27}

Once the region of interest has been defined, AI can be applied in different ways. In conventional models, the image is converted into a set of quantitative features, including simple measurements (e.g., plaque thickness, plaque area, or mean echogenicity) and sophisticated descriptors of texture, heterogeneity, border characteristics, and intensity distribution. This is where radiomics plays a central role: it represents the transformation of an image into a rich matrix of quantitative variables (many of which are imperceptible to the human eye) that can be used to develop and train classification or predictive models.^{22,23,26,28,29}

This approach is particularly relevant in carotid ultrasonography because plaque vulnerability depends not only on the degree of stenosis or overall visual appearance of the plaque but also on microstructural characteristics related to lipid composition, fibrosis, calcification, intraplaque hemorrhage, inflammation, and neovascularization. Radiomics can be understood as the bridge between conventional imaging and biological phenotyping of the lesion.^{22,23,26,28}

In deep learning models, particularly convolutional neural networks, the network learns internal image representations through successive processing layers. Rather than requiring the investigator to define which features are relevant, the model independently identifies hierarchical patterns ranging from basic edges and contrast to complex shapes, textures, and spatial arrangements associated with plaque stability or vulnerability.^{13,15,29-32}

The development of a reliable model also depends on rigorous methodological design. In simple terms, the available data must be divided into training, validation, and test sets. When a model excessively learns the specific characteristics of the training dataset and loses its ability to generalize, overfitting occurs, a problem that remains common in small, single-center, or highly homogeneous datasets.^{16,23,26}

Another fundamental concept is external validation. A model that performs well using images acquired at a single center, with a single ultrasound system, and within a single population, may fail when applied to a different setting.

Therefore, the true clinical value of AI is not determined solely by high areas under the receiver operating characteristic curve within the original dataset but by its ability to maintain performance across independent populations and real-world clinical environments.^{13,16,26}

Performance metrics other than accuracy are equally relevant, including sensitivity, specificity, area under the receiver operating characteristic curve, calibration, and clinical utility. Models may accurately discriminate vulnerable plaques and still have limited clinical value if poorly calibrated, generate excessive false-positive results, or fail to influence clinical decision-making. Consequently, more mature studies integrate AI with clinical, laboratory, and hemodynamic variables rather than treating it as a standalone tool (i.e., multimodal AI).^{29,31,33}

Model explainability represents another key challenge. In imaging exams that remain closely linked to expert visual interpretation, “black-box” models are likely to encounter resistance. Accordingly, interpretability strategies (e.g., attention maps and feature importance analysis) help identify which image regions or quantitative patterns contributed to a given classification.^{14,26}

Current Applications of AI in Carotid Ultrasonography

Current applications of AI in carotid ultrasonography primarily focus on enhancing the ability of the exam to detect, quantify, and interpret signs of atherosclerosis in a more objective, rapid, and reproducible manner.^{1,16,24}

One of the most intuitive applications of AI is the automated detection of atherosclerotic plaque. Recent deep learning models have demonstrated high performance in identifying plaques on B-mode ultrasound images, including in multicenter settings. For example, He et al.¹³ demonstrated a deep learning algorithm capable of identifying and classifying carotid plaques according to plaque stability. At the population level, Omarov et al.³¹ showed that automated plaque detection on carotid ultrasonography could support cardiovascular risk prediction and help identify genetic determinants of atherosclerosis. Moving closer to clinical implementation, real-time models based on architectures (e.g., You Only Look Once) have also been explored for instantaneous plaque recognition in ultrasound images and videos, suggesting potential applications in assisted screening and reduction of operator variability.³⁰

However, plaque detection alone is only the first step. For quantitative image analysis, AI must accurately define the location of the lesion and its boundaries. This stage is critical because measurements, such as maximum plaque thickness, plaque area, and plaque burden, depend on reliable segmentation, which is inherently influenced by the quality of the pipeline used for model training. Moreover, most classification and quantitative modeling workflows require well-defined regions of interest.^{22,25} Once the plaque has been identified and segmented, AI can be applied to quantify atherosclerotic burden. In this context, its main contribution is the automation of measurements that are more time-consuming or less reproducible when performed manually.

Following plaque identification, studies using AI pipelines have increasingly focused on distinguishing stable from vulnerable plaques, which is probably the area in which AI most directly attempts to translate pathophysiology into clinical decision-making. The objective is not simply to recognize the presence of a lesion but to infer whether it exhibits characteristics associated with increased risk of plaque rupture, embolization, and subsequent vascular events.^{13–15}

Within this context, radiomics has assumed an important role as a clinical application of AI. Rather than relying solely on visual assessment or conventional morphological descriptors, radiomics transforms imaging data into a quantitative signature of plaque texture, heterogeneity, and internal organization. Song et al.²² demonstrated that combining AI-assisted segmentation with ultrasound-based radiomics enabled an accurate discrimination between stable and vulnerable plaques. Jadoon et al.²⁸ extended this concept by extracting radiomic features from B-mode images and carotid wall radiofrequency signals. Complementarily, Zhao et al.³⁴ showed that radiomic approaches applied to the perivascular microenvironment may provide relevant information for identifying symptomatic plaques.

This application also extends to event prediction and risk stratification. Recent studies indicated that AI can integrate ultrasound variables with clinical data to predict the risk of cerebrovascular events, including ischemic stroke and clinical disease progression. Song et al.²² and Jin et al.³² demonstrated that ultrasound image-based models, particularly when integrated with CEUS, may improve the prediction of vulnerable plaques associated with increased risk of acute ischemic stroke. In patients with type 2 diabetes mellitus, a radiomics nomogram developed based on carotid ultrasonography to predict the risk of ischemic stroke achieved superior performance when the radiomics score was combined with clinical variables.²⁹ Chen et al.³⁵ also investigated predictive modeling based on ultrasound markers of intraplaque neovascularization, while Gao et al.³⁶ proposed an automated deep learning model for stroke risk stratification in patients with carotid plaques.

More recently, Jiang et al.³⁷ described the UltraBot system, a large-scale learning robotic platform that may represent the most emblematic example of the ongoing trend toward exam automation. This integrated system employs a robotic arm that reproduces probe movements, transducer pressure, and scanning angles, followed by fully autonomous image analysis and pattern recognition through an end-to-end model. In that study, the system achieved a plaque detection rate of 90%. On a smaller scale, real-time plaque recognition systems based on dynamic ultrasound videos also point toward future applications in remote assistance, telemedicine, and automated screening.³⁰

Taken together, these applications reveal a clear pattern. The most advanced areas currently include plaque detection, segmentation, and classification in B-mode ultrasound images, along with substantial advances in CEUS, three-dimensional ultrasound, radiomics, and risk stratification. Nevertheless, the field remains characterized more by proof of capability than by full integration into routine clinical practice. In many situations, AI has already demonstrated performance comparable to

or exceeding conventional visual assessments for specific tasks. The next step is to demonstrate that this superiority is consistent, generalizable, and clinically meaningful.^{16,23,26}

Advanced Imaging Modalities and Their Integration with AI

Recent advances in carotid ultrasonography have substantially expanded the spectrum of information that can be extracted from the exam. Although conventional two-dimensional ultrasonography remains the foundation of carotid assessment, advanced modalities (e.g., CEUS, elastography, three-dimensional ultrasonography, MFI, and super-resolution techniques) provide more detailed insights into plaque composition, biomechanics, and microcirculation.^{1,20,21,38}

Among these modalities, CEUS occupies a prominent position because it enables a more accurate characterization of the carotid plaque surface and facilitates the detection of biomarkers of plaque vulnerability, particularly intraplaque neovascularization, which has been associated with increased risk of cerebrovascular events. CEUS adds a functional dimension to conventional ultrasonography, and its findings have been associated with histopathological characteristics and the presence of vulnerable plaques.^{39–44} The integration of AI with CEUS is promising because contrast imaging generates a large volume of dynamic information. Deep learning models can perform multitask segmentation and automated vulnerability assessment using CEUS images and videos.¹⁷ The combination of features derived from B-mode ultrasonography and CEUS, analyzed using AI, improves prediction of vulnerable plaques associated with acute ischemic stroke.^{17,32}

MFI represents the evolution of conventional Doppler techniques, which were developed to detect low-velocity blood flow in small-caliber vessels without the need for intravenous ultrasound contrast agents. MFI employs adaptive algorithms that separate true blood flow signals from tissue motion artifacts (clutter); thus, preserving low-velocity flow signals. The software also analyzes the spatial and temporal characteristics of ultrasound echoes to distinguish tissue motion artifacts from true blood flow. In carotid ultrasonography, this technology enables visualization of intraplaque microvascularization, improves lumen and vessel wall delineation, refines stenosis assessment, and facilitates the identification of plaque ulceration.^{20,44} Studies have demonstrated excellent agreement between MFI and CEUS in detecting intraplaque neovascularization, as well as correlations with histopathological findings, reinforcing its potential as a noninvasive tool for assessing carotid plaque vulnerability.⁴⁵

The most sophisticated example of this technological evolution is ultrasound localization microscopy, which enables assessing microvascular flow within human carotid plaques with histopathological correlation and at a spatial resolution substantially higher than that of conventional ultrasonography.²¹

Elastography, in turn, introduces a biomechanical dimension to plaque assessment. Strain elastography and shear-wave elastography infer the mechanical properties of the vessel wall and plaque based on the principle that lesions with different compositions exhibit distinct stiffness

and deformation patterns.^{19,46,47} Recent studies suggested that elastography differentiates vulnerable from stable plaques and is associated with clinical outcomes.^{35,47,48} The application of AI in this field may be particularly valuable by integrating elasticity maps with morphological, textural, and clinical information.⁴⁶

Three-dimensional ultrasonography adds another important dimension to carotid imaging. Its primary contribution is to provide a more accurate assessment of atherosclerotic burden, particularly through volumetric measurements. Unlike two-dimensional imaging, which captures only selected cross-sections of the lesion, three-dimensional ultrasonography enables plaque volume reconstruction, improved surface characterization, and more robust longitudinal monitoring.^{18,49,50} Integrating three-dimensional ultrasonography with AI is particularly well-suited because manual volumetric analysis is labor-intensive and highly examiner-dependent.^{49–51}

The above-mentioned imaging modalities clearly indicate that the future of carotid ultrasonography is multiparametric. Two-dimensional ultrasonography provides basic morphological information, CEUS depicts neovascularization, elastography characterizes biomechanical properties, MFI evaluates blood flow in vessels with very low flow velocities, three-dimensional ultrasonography quantifies plaque burden and volume, and super-resolution techniques bring imaging closer to histological resolution.^{1,20,21}

Methodological Limitations and Challenges for Clinical Implementation

Although the literature on AI applied to carotid ultrasonography has expanded rapidly, its interpretation requires careful methodological consideration. Overall, studies differ not only in algorithm architecture, sample size, and imaging modality but, more importantly, in the type of reference standard (i.e., ground truth) used to train and validate AI models. In practice, these reference standards generally fall into three main categories: expert assessment, histopathology, and clinical outcomes.^{23,26}

Expert-based reference standards are currently the most commonly used. This strategy offers the advantages of feasibility, scalability, and close alignment with routine clinical practice; however, it inherits the very human variability that AI is intended to reduce. In other words, an algorithm may become highly effective at reproducing the interpretative pattern of a specific expert or institution without necessarily capturing the underlying biological characteristics of the lesion. This helps explain why many studies report excellent internal performance while still raising concerns regarding generalizability and external validity.^{23,25,26} Available methodological reviews reinforce this concern. Although many models, particularly radiomics-based models, achieve high area under the curve (AUC) values, their overall methodological quality remains limited, with a high global risk of bias and weaknesses related to feature selection, validation, and reproducibility.^{23,26}

Histopathology-based reference standards are more methodologically robust because they anchor imaging findings to objective biological outcomes. In carotid plaque

studies, histopathological analysis enables validating features, such as intraplaque neovascularization, lipid-rich necrotic core, intraplaque hemorrhage, inflammation, and tissue composition. Studies involving CEUS, elastography, three-dimensional ultrasonography, and ultrasound localization microscopy are strengthened when imaging findings are correlated with carotid endarterectomy specimens.^{21,43,50} Nevertheless, histopathology reference standards also have limitations: they are derived from highly selected populations, which generally comprise patients with more advanced disease and surgical indications; thus, limiting their representativeness across the broader spectrum of outpatient clinical practice.

The third category, and possibly the most important for real-world implementation, is the use of clinical outcomes as the reference standard. In this context, the value of AI is no longer measured solely by the agreement with imaging findings or histopathology but rather by its ability to predict cardiovascular events, disease progression, or the need for intervention. Although this approach is the most clinically relevant, it is also the most challenging because it requires larger cohorts, longer follow-up periods, careful control of bias, and more robust predictive models.

These different levels of reference standards illustrate that the clinical implementation of AI depends on algorithmic accuracy and the specific clinical question the model is designed to answer. An algorithm trained to reproduce manual plaque contours generated by an expert addresses a fundamentally different problem from one validated against histopathology, and both differ from a system that predicts future clinical events. For AI to advance consistently in carotid ultrasonography, these levels must be integrated into a translational hierarchy: first, accurate segmentation and technical robustness; next, biological validation; and last, demonstration of prognostic value and impact on routine clinical decision-making.^{2,5,23,26}

In summary, the current challenge is not the development of increasingly sophisticated algorithms but the design of studies based on reference standards that are clearly defined, clinically relevant, and methodologically defensible. Without this foundation, there is a risk of producing technically impressive algorithms that are trained to reproduce imperfect representations of the disease. The successful clinical implementation of AI in carotid ultrasonography will depend less on performance within isolated datasets and more on its ability to integrate imaging, biology, and clinical outcomes into validated, reproducible, and clinically useful models.^{21,23,26}

Future Perspectives

Future perspectives for AI in carotid ultrasonography point less toward replacing the specialist and more toward establishing a progressively quantitative, multiparametric, and risk-oriented imaging ecosystem. The field appears to be moving toward the convergence of automated image acquisition, robust segmentation, advanced plaque phenotyping, and integration with clinical outcomes.^{1,20,21}

One of the most promising directions is the evolution of AI from retrospective classification systems to multimodal

models. Rather than analyzing B-mode images alone, future algorithms are expected to integrate information on plaque texture, plaque volume, neovascularization assessed by CEUS, MFI, biomechanical properties derived from elastography, local hemodynamics, and clinical and laboratory variables. Recent studies suggested that predictive performance improves when multiple sources of information are combined, reinforcing the concept that plaque vulnerability is unlikely to be adequately captured by a single biomarker.^{21,32,33,48}

Another important area of development is the automation of the exam. The emergence of robotic systems and AI-assisted image acquisition suggests that operator variability may be reduced during image acquisition.³⁷ In the medium term, AI may support image interpretation and real-time guidance of the examiner, automatic standardization of imaging planes, and selection of the most informative frames for subsequent analysis.^{1,3}

Another advance is the progress toward super-resolution imaging and direct quantification of plaque microcirculation. Ultrasound localization microscopy currently represents the clearest example of this frontier, enabling visualization and quantification of plaque neovessels at a spatial resolution substantially higher than that of conventional ultrasonography.²¹ Similarly, contrast-free MFI techniques may evolve from promising but heterogeneous technologies to more standardized imaging biomarkers, particularly when combined with AI algorithms for automated quantification and classification.^{20,21}

Conclusion

AI is repositioning carotid ultrasonography from a predominantly anatomical and operator-dependent exam to an increasingly quantitative, integrated, and risk-oriented imaging modality.

The true contribution of AI lies within this context rather than in competition with clinical expertise. Far from diminishing the role of the specialist, AI strengthens it by providing tools that improve the precision, efficiency, and speed of image

interpretation while establishing carotid ultrasonography as a valuable modality for individualized risk assessment and a more personalized approach to vascular disease.

Author Contributions

Conception and design of the research, acquisition of data, analysis and interpretation of the data, statistical analysis, writing of the manuscript and critical revision of the manuscript for intellectual content: Dannenhauer G, Santos SN, Petisco ACGP, Freire CMV, Albricker ACL, Barros FS.

Potential Conflict of Interest

The author declares no relevant conflicts of interest.

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Ethics Approval and Consent to Participate

This article does not contain studies involving human participants or animals conducted by any of the authors.

Use of Artificial Intelligence

During the preparation of this work, the author(s) used ChatGPT for searching bibliographic references and assembling the study's central figure. After using this tool/service, the author(s) reviewed and edited the content as needed and take full responsibility for the content of the published article.

Availability of Research Data

The data underlying this study are contained within the manuscript.

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Mitral Regurgitation with Multiple Jets: An Integrated and Hierarchical Approach

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Abstract

Mitral regurgitation (MR) with multiple jets is a highly complex diagnostic scenario, frequently encountered in Barlow disease and functional phenotypes associated with ventricular remodeling. Conventional two-dimensional methods (e.g., vena contracta width, color jet area, and hemispheric proximal isovelocity surface area) have important limitations in the presence of multiple regurgitant orifices, eccentric jets, the Coanda effect, overlap of flow convergence zones, or noncircular annular geometry, which may lead to underestimation of volume overload. Three-dimensional echocardiography overcomes part of these limitations by enabling en face characterization of the mitral valve, planimetric measurement of the vena contracta area using multiplanar reconstruction, and the application of volumetric methods based on directly measured anatomical areas. The three-dimensional continuity equation (3D-CE), particularly in mitral valve prolapse and Barlow disease, has demonstrated promising agreement with the regurgitant volume measured using cardiac magnetic resonance (CMR); however, the available evidence should still be interpreted in the context of recent studies and patient populations. CMR remains the reference standard for volumetric assessment when echocardiographic findings discord with the clinical presentation, acoustic windows are suboptimal, or pre-interventional decision-making involves borderline parameters. This review proposes a hierarchical, multiparametric, and technically reproducible approach for assessing MR with multiple jets.

Introduction

Mitral regurgitation (MR) with multiple jets is one of the most challenging scenarios in valvular echocardiography. This condition is frequently observed in Barlow disease and in complex forms of functional MR, and its quantification challenges the fundamental assumptions underlying conventional two-dimensional methods, which were originally developed for single regurgitant orifices and

simpler geometries, representing an important source of diagnostic error that may mask substantial volume overload.^{1,2}

In the presence of multiple regurgitant orifices, eccentric jets, and noncircular mitral annuli, conventional parameters (e.g., vena contracta width and hemispheric proximal isovelocity surface area [PISA]) may substantially underestimate the severity of regurgitation and its volumetric consequences. In this context, three-dimensional echocardiography and advanced volumetric methods have emerged as tools capable of more directly assessing the true geometry of the regurgitant orifice and integrating complex anatomical phenotypes.^{3–5}

This review discusses the physical and geometric principles underlying the limitations of two-dimensional methods and the role of three-dimensional techniques and cardiac magnetic resonance (CMR) in a multiparametric approach. We also propose a practical, hierarchical strategy for systematically assessing MR with multiple jets (Central Illustration). The main limitations of two-dimensional methods are summarized in Table 1.

Fundamental Principles: Why Multiple Jets Compromise Quantification

MR quantification is primarily based on estimating the effective regurgitant orifice area (EROA) and regurgitant volume (RV). The vena contracta (i.e., region of highest flow acceleration and smallest cross-sectional flow area) represents the echocardiographic marker that most closely approximates the effective regurgitant orifice. However, in the presence of multiple regurgitant orifices, geometric assumptions underlying conventional two-dimensional methods frequently become invalid. These limitations arise primarily from three physical mechanisms:^{1,2}

Quadratic relationship between diameter and area: as area increases with the square of the radius ($A = \pi r^2$), the sum of the linear widths of multiple jets measured by two-dimensional Doppler does not correspond to the sum of their effective areas. Thus, two jets measuring 3 mm width correspond to a combined area of approximately 14 mm², whereas a single 6-mm jet has an area of approximately 28 mm². Consequently, simply summing linear measurements may substantially underestimate the global EROA and MR severity.^{1,3–5}

Coanda effect: eccentric jets that adhere to the atrial wall dissipate kinetic energy along the adjacent surface; thereby, artificially reducing the apparent jet area on color Doppler imaging. This phenomenon leads to a systematic qualitative underestimation of regurgitation severity, particularly for posterior jets and those originating from the commissural regions. Figure 1 illustrates distinct patterns of regurgitant jets on three-dimensional color Doppler imaging, including separate jets.^{1,2,5}

Keywords

Mitral Valve Insufficiency; Three-Dimensional Echocardiography; Multimodal Imaging

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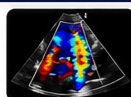
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Central Illustration: Mitral Regurgitation with Multiple Jets: An Integrated and Hierarchical Approach



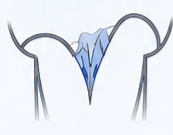
ECHOCARDIOGRAPHIC ASSESSMENT: STEP BY STEP

Multiple-Jet Mitral Regurgitation

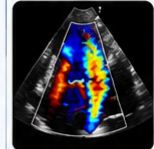
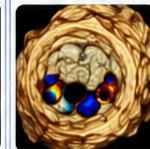


The assessment of MR with multiple jets should follow a systematic, reproducible, and mechanism-oriented sequence. The goal is to first define the anatomy and pathophysiology of regurgitation and then select the most appropriate quantitative method according to the valve phenotype.

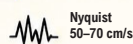
1 IDENTIFY THE MECHANISM BEFORE QUANTIFYING

CARPENTIER II
Prolapse / flail / Barlow

CARPENTIER IIb
Tethering / functional MR


- Analyze the parasternal long-axis view and the four-chamber view (A1-A2-A3 / P1-P2-P3).
- Assess prolapse, flail, systolic retraction, papillary muscles, mitral annulus, and leaflet coaptation.
- Apical color Doppler: number, direction, eccentricity, and systolic variation of the jets.
- 3D en face view (TEE or TTE with matrix-array transducer): number and location of orifices, extent of the involved segments, and commissural jets.

COLOR DOPPLER
APICAL 4-CHAMBER VIEW

3D EN FACE
(TEE/TTE)


2 CONFIGURE COLOR DOPPLER FOR 3D ACQUISITION



Nyquist
50-70 cm/s

Avoid very low values (blooming) or very high values (reduced sensitivity).



Color gain

Reduce until pixels disappear within structures without flow.



3D sector

Restrict to the minimum necessary to include all jets.



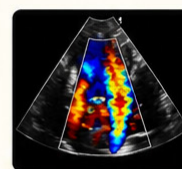
Volume rate

Aim for a volume rate ≥ 20 Hz.

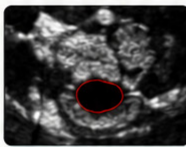
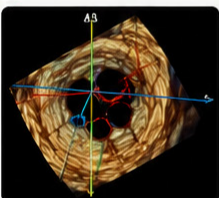


Acquisition

Prefer multibeam acquisition with stable sinus rhythm (attention to stitching artifacts).



3 PLANIMETRY OF VCA BY MPR: TECHNIQUE AND CAUTIONS



Measure at the smallest cross-sectional area of the jet, immediately distal to the regurgitant orifice.

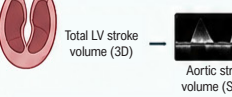
- Position the plane at the smallest cross-sectional area of the jet, before expansion into the left atrium.
- Measure each orifice separately.
- Distinguish true orifices from areas of flow convergence in the left atrium.
- ZVCA = sum of VCAs $\rightarrow$ estimated global EROA
- Measure ≥ 3 beats and use the average.
- High variability: technically unstable acquisition, low volume rate, arrhythmia, or beat-to-beat variation.
- In Barlow disease, integrate with 3D volumetry, preferably.

VCAS SEPARADAS



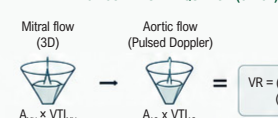
ZVCA = VCA₁ + VCA₂ + VCA₃
= estimated global EROA

4 VOLUMETRIC METHODS: QUANTIFICATION INDEPENDENT OF JET GEOMETRY

VOLUMETRIA 3D
(CONservation of Mass)


Less dependent on the number, direction, or geometry of the jets. Limitation: may underestimate LV volumes in relation to CMR.

3D CONTINUITY EQUATION (3D-CE)



Useful in Barlow disease: uses 3D areas, independent of jet geometry.

INDICATIONS

- VCA not visible or difficult to measure
- Eccentric multiple jets
- Discordance between qualitative parameters and remodeling

5 INTEGRATE SUPPORTING PARAMETERS



Pulmonary venous flow
Systolic reversal = strong sign of significant MR (absence does not exclude severity)



Continuous-wave Doppler of MR
Dense, triangular spectrum with early peak suggests significant regurgitation



Remodeling
LA and LV dilation, elevated PASP, and LVEF < 60% reinforce significant regurgitation



Global longitudinal strain
May help detect subclinical ventricular dysfunction, especially in Barlow disease.

Assessment should always be multiparametric and performed in the clinical context.

6 DECIDE WHEN TO REFER FOR CMR



- Discordance between echocardiographic findings and clinical status/remodeling
- Limited acoustic window
- Borderline parameters in the pre-intervention decision



CMR ADDS VALUE

- Quantification of regurgitant volume independent of jet geometry
- Tissue characterization with LGE, T1 mapping, and ECV (fibrosis and arrhythmic risk)



In prolapse with voluminous leaflets, incorporate the volume of prolapsed tissue into the calculation of regurgitant volume to avoid underestimation.

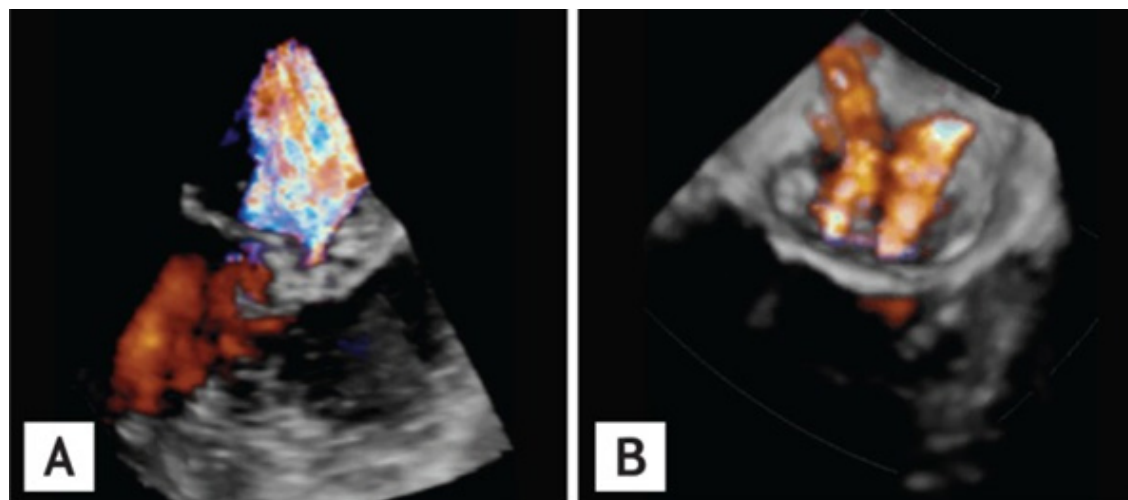


Figure 1 – Clinical examples of two patterns of functional mitral regurgitation evaluated by three-dimensional transesophageal color Doppler echocardiography: continuous jet (A) and two separate jets (B).

Limitations of the geometric assumptions underlying two-dimensional PISA: the PISA method assumes a single, central, hemispheric flow convergence zone, which is frequently absent when multiple regurgitant orifices are present. Adjacent, asymmetric, or partially overlapping flow convergence zones impair the estimation of total regurgitant flow and reduce the accuracy of the method. In Barlow disease, the presence of a large, noncircular mitral annulus amplifies these geometric distortions.¹⁻⁵

Three-dimensional Echocardiography: Tools and Role in the Multiparametric Approach

Three-dimensional echocardiography primarily provides a more direct and anatomical assessment of regurgitant orifice geometry; thus, reducing dependence on geometric assumptions inherent to conventional two-dimensional techniques. Despite these advantages, the method has several limitations, including lower spatial and temporal resolution, difficulty in defining color Doppler boundaries, the influence of regurgitant orifice nonplanarity, and dependence on acoustic window quality. Figure 2 demonstrates an example of a complex degenerative anatomy with a P2 flail leaflet evaluated using two-dimensional and three-dimensional imaging.³⁻⁶

Table 2 summarizes the main three-dimensional tools currently available, their potential roles, and respective limitations in assessing MR with multiple jets. In this context, incorporating the true three-dimensional mitral annular area into the three-dimensional continuity equation deserves particular attention. By avoiding the geometric assumption of annular circularity, which is inappropriate in Barlow disease because the mitral annulus is frequently dilated and noncircular, this approach has demonstrated excellent agreement with CMR and outperformed conventional two-dimensional methods. The application of multiplanar reconstruction for individual area measurements is illustrated in Figure 3.^{1,6-8,17}

CMR and Integrated Severity Criteria

CMR quantifies RV as the difference between total left ventricular stroke volume and antegrade aortic flow measured by phase-contrast imaging, an approach largely independent of the geometry or number of regurgitant jets. For this reason, CMR assumes a particularly important role in scenarios of greater anatomical complexity or when echocardiographic findings are discordant. Figure 4 illustrates this volumetric strategy using 3D echocardiography, while Figure 5 presents the indirect volumetric method using CMR, currently considered the reference standard when there is discordance between echocardiographic methods.

New 3D echocardiography software enables automated acquisition of ventricular volumes and left ventricular stroke volume, allowing regurgitant volume to be calculated as the difference between the ventricular stroke volume and the effective systolic volume ejected into the aorta. As with CMR, this is a volumetric method based on the principle of mass conservation, making it less influenced by the geometry of the regurgitant orifice, the presence of multiple jets, or the Coanda effect. Although it still depends on the quality of the three-dimensional acquisition and requires further clinical validation, this technology represents an important advance in the integrated assessment of complex MR.

CMR remains the reference volumetric method for quantifying MR. RVol is calculated as the difference between the left ventricular stroke volume obtained by cine-MRI and the antegrade aortic flow measured by phase-contrast imaging. Because it is practically independent of the number, direction, and geometry of the regurgitant jets, this approach maintains high accuracy in complex anatomies, making it an important complementary method when there is discordance between echocardiographic findings and the clinical context, or when therapeutic decision-making depends on more precise quantification.⁹⁻¹²

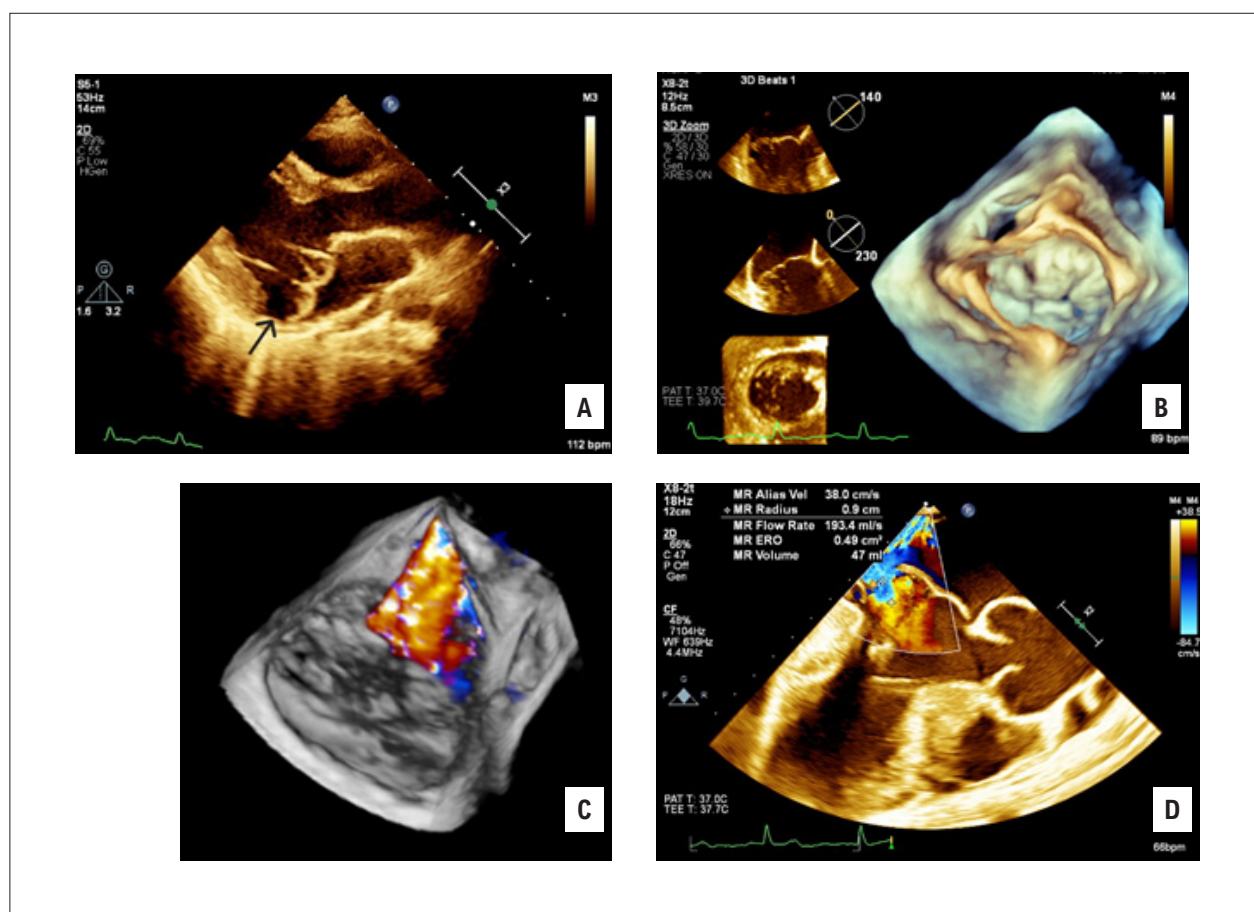


Figure 2 – Clinical example of degenerative mitral regurgitation with complex anatomy. A — Parasternal long-axis view, showing Barlow's disease, with prolapse of both leaflets and mitral annular disjunction (arrow). B — Three-dimensional zoomed image of the mitral valve, viewed from the left atrium (LA), with prolapse of multiple segments, characterizing Barlow's disease. C — Three-dimensional zoomed image with color Doppler. D — 110° cross-sectional view, showing jet eccentricity and hindering accurate measurement of PISA, EROA, and RVol, resulting in underestimation of MR severity. EROA of 0.49 cm², yet with an RVol of 47 mL: discordant parameters.

Table 1 – Limitations of two-dimensional methods for assessing mitral regurgitation with multiple jets

Method	Primary limitation	Clinical consequence
Two-dimensional vena contracta width	The sum of linear widths does not correspond to the sum of effective areas (quadratic relationship: $A = \pi r^2$).	Underestimation of global EROA; severe MR may be misclassified as moderate.
Two-dimensional hemispheric PISA	Assumes a single, central, hemispheric flow convergence zone; this assumption is frequently violated in the presence of multiple regurgitant orifices.	Reduced accuracy in multiple and eccentric jets; imprecise estimation of total EROA.
Color Doppler jet area	The Coanda effect artificially reduces the visible jet area.	Qualitative underestimation of severity; inadequate for quantitative assessment.
Volumetric method using two-dimensional measurements (ΔSV)	Propagation of geometric errors resulting from two-dimensional estimation of valvular areas and the left ventricular outflow tract.	Imprecise RV estimation using two-dimensional measurements; methods based on three-dimensional anatomical areas provide more reliable volumetric quantification.

PISA: proximal isovelocity surface area; EROA: effective regurgitant orifice area; RV: regurgitant volume; ΔSV : difference between stroke volumes.

Table 2 – Three-dimensional tools and their role in the assessment of mitral regurgitation with multiple jets

3D parameter	Role and limitations in mitral regurgitation with multiple jets
Three-dimensional VCA by multiplanar reconstruction (direct planimetry)	Enables more direct estimation of the area of each regurgitant orifice; the sum of individual VCAs provides an approximation of the global EROA. Demonstrates good correlation with CMR-derived RV. Limitations include temporal and spatial resolution, definition of color Doppler boundaries, and regurgitant orifice nonplanarity.
Three-dimensional PISA	Assesses the true flow-convergence surface, reducing the geometric assumptions of two-dimensional PISA. Limitations include reduced frame rate and overlap of flow convergence zones in adjacent jets. It has a complementary rather than primary role.
Three-dimensional volumetry: total LVSV – aortic SV (Simpson method)	RV is calculated as the difference between total LVSV, obtained by direct three-dimensional volumetry, and antegrade aortic SV. The method is less dependent on mitral annular geometry and largely independent of the number and eccentricity of regurgitant jets. The main limitation compared with CMR is the systematic underestimation of ventricular volumes.
Three-dimensional en face anatomy	Enables detailed anatomical assessment of the mitral valve apparatus, including the number and location of coaptation orifices, the extent of prolapse, flail, tethering, and annular dilatation. It is an indispensable tool for surgical and transcatheter procedural planning.
Three-dimensional continuity equation: annular area × velocity-time integral	RV is calculated using the true three-dimensional areas of the mitral annulus and the left ventricular outflow tract, reducing errors arising from the circularity assumption in the two-dimensional method. It is particularly useful in Barlow disease, in which the mitral annulus is frequently enlarged and noncircular, and largely independent of the number, eccentricity, and systolic duration of regurgitant jets. It has also demonstrated excellent agreement with CMR compared with conventional two-dimensional methods. The main limitation is the reduced applicability in the presence of other significant valvular heart diseases.

MR: mitral regurgitation; EROA, effective regurgitant orifice area; CMR, cardiac magnetic resonance; MAD, mitral annular disjunction.

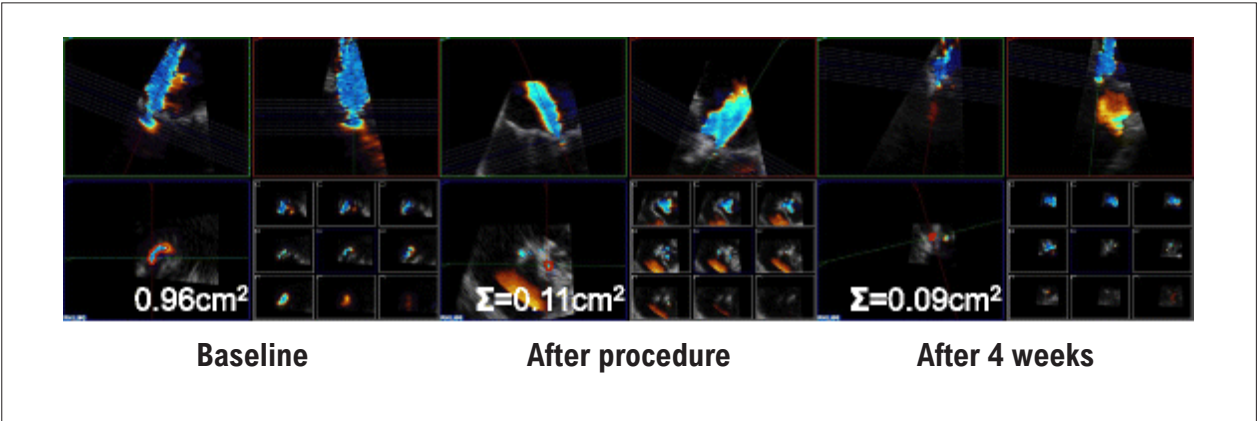


Figure 3 – Clinical example of vena contracta area measurement using three-dimensional transesophageal echocardiography and multiplanar reconstruction. Following transcatheter mitral valve repair, residual regurgitant jets are measured individually, and their areas are summed. Temporary reference image to be replaced with an anonymized exam. Source: Dietl et al. Cardiovascular Ultrasound. 2018;16:1. CC BY 4.0 license.

In patients with bileaflet mitral valve prolapse and bulky leaflets, the volume of prolapsed tissue must be incorporated into the RVol calculation to avoid underestimating the regurgitation.^{14,15} 4D Flow CMR further expands this capability by enabling three-dimensional assessment of regurgitant flow patterns. However, despite promising results, its routine clinical application remains limited.¹¹

No single parameter, including the summed three-dimensional vena contracta area, should be used as the sole determinant of MR severity. Contemporary guidelines consistently recommend a multiparametric approach integrating anatomical, quantitative, and hemodynamic data. In this context, the threshold values presented in Table 3 should be interpreted according to the underlying

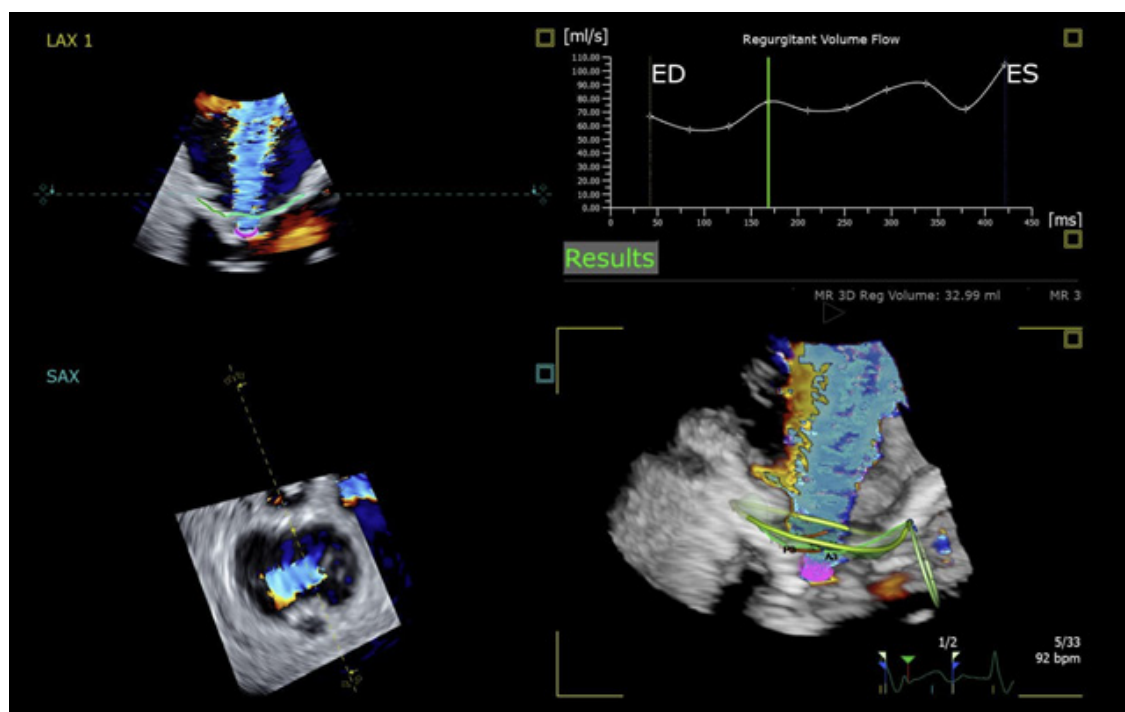


Figure 4 – Automated 3D color flow quantification using artificial intelligence to measure mitral regurgitant volume.

etiology, technical quality of the examination, and clinical context, particularly in complex phenotypes of MR with multiple jets.^{12,16,17}

Echocardiographic Assessment: A Stepwise Approach

The assessment of MR with multiple jets should follow a systematic, reproducible, and mechanism-oriented sequence. The primary objective is to define the anatomy and pathophysiology of regurgitation before selecting the quantitative method most appropriate for the specific valvular phenotype.^{1,–5,20}

The algorithm is summarized in the Central Illustration.

Step 1 — Identify the Mechanism Before Quantification

The first step is to define the mechanism of MR according to the Carpentier classification. In phenotypes with multiple jets, the most common findings are Type II, resulting from prolapse or flail in Barlow disease or multisegment fibroelastic degeneration, and Type IIIb, resulting from systolic leaflet restriction secondary to subvalvular tethering in ischemic or dilated functional MR.^{1,2,16,17}

The analysis should begin with the parasternal long-axis view, including frame-by-frame assessment of the A1-A2-A3 and P1-P2-P3 scallops, identification of prolapse, flail, systolic restriction, apical displacement of the papillary muscles, mitral annular dilatation and morphology, and presence of mitral annular disjunction. In the apical views, color Doppler imaging enables mapping of the number, direction, eccentricity, and systolic variation of regurgitant jets.^{1,2,6}

The three-dimensional en face view, obtained by transesophageal echocardiography or transthoracic echocardiography using a matrix-array transducer, complements the assessment by demonstrating the number and location of coaptation orifices, the extent of the involved scallops, and the presence of commissural jets, which are frequently difficult to characterize using two-dimensional imaging alone. This step establishes the hierarchy of the subsequent quantitative methods.⁶

Step 2 — Optimize Color Doppler Settings for Three-Dimensional Acquisition

Three-dimensional planimetry of the vena contracta area requires a carefully optimized color Doppler acquisition. Nyquist velocity should generally be maintained between 50 and 70 cm/s. Excessively low settings promote blooming artifacts and overestimate the color jet area, whereas excessively high settings reduce color Doppler sensitivity and may underestimate the vena contracta area.^{3–5}

Color gain should be progressively reduced until color pixels disappear from structures without flow while preserving the true regurgitant jet signal. Excessive gain artificially enlarges jet boundaries and represents the most common technical error in clinical practice. The three-dimensional sector should be restricted to the minimum volume required to include all regurgitant jets; thus, increasing the volume rate. Ideally, a volume rate of at least 20 Hz should be achieved. In patients with stable sinus rhythm, multibeam acquisitions may improve spatial resolution, although they increase the risk of stitching artifacts.^{1,3–6}

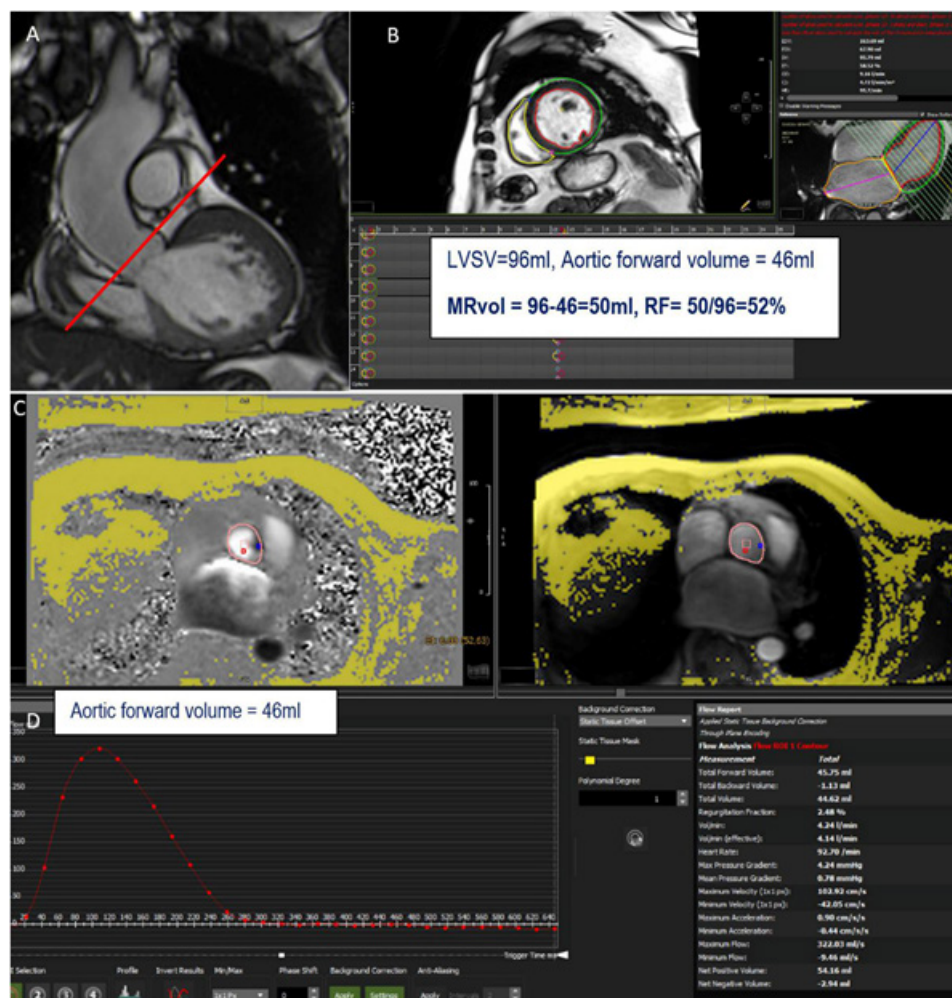


Figure 5 – Clinical example of mitral regurgitation assessment by cardiac magnetic resonance using the indirect method. The phase-contrast imaging plane is positioned above the aortic valve, and mitral regurgitant volume (MRvol) is calculated as the difference between left ventricular stroke volume (LVSV) and the antegrade aortic flow. LVSV: left ventricular stroke volume; MRvol: mitral regurgitant volume; RF: regurgitant fraction. Source: Vermes et al.¹³

Table 3 – Quantitative severity criteria and supportive parameters for primary mitral regurgitation

Parameter	Moderate MR	Severe MR
EROA (Σ VCA 3D)	0.20 – 0.39 cm ²	≥ 0.40 cm ² *
Regurgitant volume	30 – 59 mL	≥ 60 mL
Regurgitant fraction	30 – 49%	$\geq 50\%$
Pulmonary vein systolic flow reversal	Absent or blunted	Present (supportive finding)
Left atrial / left ventricular dilatation	Mild to moderate	Significant dilatation; possible subclinical ventricular consequences

EROA: effective regurgitant orifice area; MR: mitral regurgitation. *Threshold values are derived from literature predominantly on primary MR, but have not been specifically validated for all phenotypes of MR with multiple jets. These parameters should be interpreted within a multiparametric framework, considering the underlying etiology, technical quality of the examination, and clinical context. In secondary MR, the severity threshold for EROA is generally lower (≥ 0.20 cm²). Source: Zoghbi WA et al.; Vahanian A et al.^{1,2,16,17}

Step 3 — Planimetry of the Vena Contracta Area Using Multiplanar Reconstruction: Technique and Practical Considerations

Following acquisition of the three-dimensional color Doppler, the dataset should be analyzed using multiplanar reconstruction. The measurement plane should be positioned at the smallest cross-sectional area of the jet, immediately distal to the regurgitant orifice and before flow expansion into the left atrium.³⁻⁶

The most common technical error is measuring the area distally within the expanding jet, which results in overestimation of the vena contracta area. Each regurgitant orifice should be planimeted individually. In adjacent jets, true regurgitant orifices should be distinguished from zones of jet confluence within the left atrium. The sum of individual vena contracta areas provides a functional estimate of the global EROA.³⁻⁶

Measuring at least three cardiac cycles and using the mean value for analysis is recommended. A high variability suggests technical instability, low volume rate, arrhythmia, or significant respiratory variation. In Barlow disease, the vena contracta area should preferably be assessed using three-dimensional volumetric methods because of the complex and noncircular geometry of the mitral annulus.³⁻⁶

Step 4 — Volumetric Methods: Quantification Independent of Jet Geometry

Volumetric methods are useful when planimetry of the vena contracta area is not feasible, when multiple eccentric jets are present, or when qualitative parameters are discordant with the degree of cardiac remodeling.⁹⁻¹²

Three-dimensional volumetry based on the conservation of mass calculates RV as the difference between total left ventricular stroke volume (obtained by direct three-dimensional volumetry) and the antegrade aortic stroke volume. This approach is largely independent of the number, direction, or geometry of regurgitant jets, although it is subject to systematic underestimation of ventricular volumes compared with CMR.⁹⁻¹²

The three-dimensional continuity equation calculates RV as the difference between mitral and aortic stroke volumes using true three-dimensional anatomical areas. It is particularly useful in phenotypes, such as Barlow disease, in which the mitral annulus is enlarged, noncircular, and inadequately represented by two-dimensional linear measurements. In both methods, measurements should be obtained over multiple cardiac cycles, with particular attention to the correct positioning of pulsed-wave Doppler at the mitral annular plane.⁷

Step 5 — Integrate Supportive Parameters

Quantitative measurements should be interpreted together with markers of hemodynamic consequences and cardiac remodeling. Systolic flow reversal in the pulmonary veins is a strong supportive finding for severe MR, although its absence does not exclude severe regurgitation in the presence of eccentric jets or the Coanda effect.^{1,2,16,17}

Continuous-wave Doppler of the MR jet provides additional qualitative information about the density and

morphology of the spectral envelope. A dense and triangular envelope with early systolic peak suggests a hemodynamically relevant regurgitation. Progressive left atrial and left ventricular dilatation, elevated pulmonary artery systolic pressure, and a left ventricular ejection fraction below 60% further support significant hemodynamic consequences. In Barlow disease, a global longitudinal strain may help identify subclinical left ventricular dysfunction.^{1,2,16,17}

Step 6 — Determine When Cardiac Magnetic Resonance Should Be Performed

CMR should be considered when echocardiographic estimates of MR severity are discordant with clinical symptoms or cardiac remodeling, when acoustic windows are limited, or when echocardiographic parameters are borderline in the context of pre-interventional decision-making.⁹⁻¹²

In Barlow disease, CMR provides additional value by quantifying RV in a manner that is less dependent on regurgitant jet geometry and by enabling tissue characterization with late gadolinium enhancement, T1 mapping, and extracellular volume fraction, all of which are relevant for detecting myocardial fibrosis and stratifying arrhythmic risk. In prolapse with redundant leaflets, the volume of the prolapsed tissue should be incorporated into RV calculation to avoid underestimating the regurgitation severity.^{14,15,18}

Differential Diagnosis: Primary versus Secondary MR

The etiology of MR (i.e., primary [degenerative] or secondary [functional]) directly influences the interpretation of quantitative parameters, severity thresholds, and therapeutic strategy. In secondary MR, the EROA threshold associated with severe regurgitation is lower because of the reduced functional reserve of the remodeled left ventricle. Table 4 summarizes the main differences between these phenotypes relevant to multimodal imaging assessment.^{2,16,17}

Technical Pitfalls and How to Avoid Them

Technical expertise in three-dimensional image acquisition and analysis is fundamental to ensure an accurate quantification of MR with multiple jets. The most common sources of error include the following:^{1,3-6}

- **Summing two-dimensional widths instead of areas:** the sum of linear diameters does not correspond to the sum of the effective areas of multiple regurgitant orifices. Areas (cm²), rather than widths (mm), should always be summed. This error results in underestimation of the global EROA.³⁻⁵

- **Planimetry outside the true vena contracta:** measurements should be obtained at the smallest cross-sectional area of the jet, immediately distal to the regurgitant orifice. More distal measurements within the expanding jet in the left atrium overestimate the vena contracta area.³⁻⁵

- **Inappropriate Nyquist velocity:** excessively high Nyquist settings artificially reduce the color jet area, whereas excessively low settings promote blooming artifacts and artificial expansion of jet boundaries. For three-dimensional planimetry of the vena contracta area, a Nyquist velocity of 50 to 70 cm/s is recommended.³⁻⁶

Table 4 – Differences between primary and secondary mitral regurgitation relevant to imaging assessment

Characteristics	Primary MR (degenerative)	Secondary MR (functional)
Mechanism	Structural disease of the mitral leaflets, chordae tendineae, or mitral annulus (prolapse, flail, Barlow disease, or fibroelastic degeneration).	Left ventricular remodeling with tethering of the subvalvular apparatus
Jet pattern	Frequently eccentric; multiple jets are common in Barlow disease because of multisegment prolapse.	Central or biatrial; multiple jets may occur in asymmetric tethering.
EROA severity threshold	$\geq 0.40 \text{ cm}^2$.	$\geq 0.20 \text{ cm}^2$ (reduced myocardial reserve of the remodeled left ventricle).
Role of CMR	Reference standard in cases of borderline parameters or echocardiographic-clinical discordance; useful in Barlow disease/MAD (regurgitant volume by volumetric balance).	Particularly useful when left ventricular ejection fraction is borderline or concomitant coronary revascularization is being considered.
Interventional strategy	Mitral valve repair or replacement; timing based on symptoms, left ventricular ejection fraction, and left ventricular dimensions or volumes.	Prioritary clinical optimization; surgery is reserved for patients with high regurgitant volume and favorable repair anatomy.

MR: mitral regurgitation; EROA, effective regurgitant orifice area; CMR, cardiac magnetic resonance; MAD, mitral annular disjunction.

- **Insufficient frame rate:** a low volume rate may capture the vena contracta outside peak systole, reducing reproducibility of the measurement. A volume rate of at least 20 to 25 Hz should be prioritized with reduction of the acquisition sector and use of valvular zoom whenever possible.³⁻⁶

- **Single-beat analysis:** planimetry should be performed over multiple cardiac cycles, and the mean value should be used for analysis. Beat-to-beat variability exceeding 20% suggests technical instability, arrhythmia, or inadequate image acquisition.³⁻⁶

- **Underrecognition of commissural jets:** commissural jets are particularly common in Barlow disease and may be numerous, small, and easily overlooked by two-dimensional imaging. Summing the individual areas of the vena contracta is important in these cases, in which the total EROA may be substantially greater than initially apparent.³⁻⁶

- **Failure to document hemodynamic conditions:** blood pressure, heart rate, and cardiac rhythm should be recorded during the exam. Acute changes in afterload may substantially alter the EROA and RV.^{1,2}

- **Incorrect positioning of pulsed-wave Doppler at the mitral valve:** in volumetric methods, the mitral velocity-time integral should be measured at the level of the mitral annulus. Supravulvar sampling introduces systematic error into the calculation of mitral stroke volume.^{1,7}

- **Assuming mitral annular circularity in Barlow disease:** the mitral annulus frequently exhibits a large, dynamic, and noncircular geometry. Estimating the annular area from a single diameter underestimates the true annular area and may overestimate the calculated RV. In these cases, direct measurement of the three-dimensional mitral annular area should be preferred.^{7,14}

Conclusion

Quantifying MR with multiple jets requires methods that accurately represent the true geometry of the regurgitant orifices and their hemodynamic consequences. In this context, three-dimensional vena contracta planimetry using multiplanar reconstruction is a central tool when technically feasible and should always be interpreted in conjunction with valvular anatomy, cardiac remodeling, and supporting parameters.^{1,3-5}

In Barlow disease, the large, dynamic, and noncircular geometry of the mitral annulus substantially limits the accuracy of conventional two-dimensional methods. Incorporating true three-dimensional anatomical areas into the continuity equation is also an important advance for this complex anatomical phenotype.^{7,14}

CMR should be considered the complementary reference method in cases of discordant findings, borderline parameters, or diagnostic uncertainty, particularly in more complex phenotypes with multiple jets.^{9,10-12}

Rather than seeking a single “ideal” parameter, assessing MR with multiple jets requires a rational hierarchy of methods selected based on the valvular mechanism, regurgitant orifice geometry, hemodynamic conditions, and technical quality of image acquisition. Ultimately, understanding the physical and geometric limitations of each method is as important as mastering its technical execution.^{1,2,16,19}

Author Contributions

Conception and design of the research, acquisition of data, analysis and interpretation of the data, writing of the manuscript, critical revision of the manuscript for important intellectual content: Emerich TMS; Barros G; Gripp EA.

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Ethics Approval and Consent to Participate

This article does not contain any studies with human participants or animals performed by any of the authors.

Use of Artificial Intelligence

During the preparation of this work, the author(s) used Claude AI for spelling and bibliographic reference review. After using this tool/service, the author(s) reviewed and edited the content as needed and take full responsibility for the content of the published article.

Data Availability

The underlying content of the research text is contained in the manuscript.

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Cardiac Involvement in Fabry Disease: From Electrocardiography to Recent Advances in Cardiovascular Imaging

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Abstract

Fabry disease is an X-linked lysosomal storage disorder caused by α -galactosidase A deficiency, leading to the progressive accumulation of globotriaosylceramide (Gb3) and globotriaosylsphingosine (lyso-Gb3) in multiple organs. Cardiac involvement is the leading cause of morbidity and mortality, making early recognition of cardiomyopathy fundamental to optimizing treatment and improving prognosis. This review summarizes the current evidence on the role of electrocardiography, conventional and advanced echocardiography, and cardiac magnetic resonance (CMR) imaging in the assessment of cardiac involvement in Fabry disease. The main electrocardiographic findings, the structural and functional changes identified by echocardiography, including myocardial deformation by speckle tracking and myocardial work, as well as the contributions of magnetic resonance imaging to tissue characterization through late gadolinium enhancement (LGE), T1 and T2 mapping, extracellular volume (ECV), and feature tracking are discussed. The applications of these methods in the early detection of cardiomyopathy, differential diagnosis, risk stratification, monitoring of disease progression, and evaluation of treatment response are discussed. The integration of different imaging methods allows for a more comprehensive characterization of the pathophysiological mechanisms and stages of Fabry cardiomyopathy, contributing to early diagnosis, clinical decision-making, and longitudinal follow-up of these patients.

Introduction

Fabry disease is a hereditary lysosomal storage disorder characterized by the systemic accumulation of glycosphingolipids in multiple organs and tissues.^{1,2} The metabolic defect results from

deficient activity of α -galactosidase A, a lysosomal enzyme that catalyzes the hydrolytic cleavage of terminal galactose residues from globotriaosylceramide (Gb3).¹ Deficient α -galactosidase A activity leads to the progressive accumulation of Gb3 and related glycolipids within lysosomes, particularly in vascular endothelial cells, cardiomyocytes, and renal and neural cells, ultimately resulting in the multisystemic manifestations of the disease.^{1,2} In addition to lysosomal accumulation of Gb3, recent evidence demonstrates that secondary mechanisms, including lyso-Gb3 accumulation, inflammation, oxidative stress, mitochondrial dysfunction, and alterations in autophagy, play an important role in the progression of tissue damage and cardiomyopathy.^{1,3}

The disease is caused by pathogenic variants in the *GLA* gene, located on the X chromosome, which encodes the lysosomal enzyme α -galactosidase A.⁴ The estimated prevalence is approximately 1 case per 10,000 live births. However, this frequency varies widely depending on the population studied and the screening strategy employed. Neonatal screening studies and studies of at-risk populations have shown that the disease is significantly more frequent than previously estimated, especially in males and in carriers of late-onset variants of the *GLA* gene.^{3,4} Symptoms of Fabry disease typically begin in childhood and include neuropathic pain, gastrointestinal dysfunction, hypohidrosis, and intolerance to temperature fluctuations.⁵ Although Fabry disease presents with multisystemic manifestations, cardiac involvement represents its main cause of morbidity and mortality, making imaging methods fundamental for early diagnosis, risk stratification, and disease monitoring.^{3,6,7} This review aims to synthesize the current evidence regarding the role of electrocardiography, echocardiography, and cardiac magnetic resonance (CMR) in the assessment of cardiac involvement in Fabry disease. The central figure summarizes the natural history of Fabry cardiomyopathy and the integrated application of multimodal assessment in the different stages of the disease.

Keywords

Fabry Disease; Echocardiography; Magnetic Resonance Imaging; Electrocardiography; Cardiomyopathies

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Pathophysiology

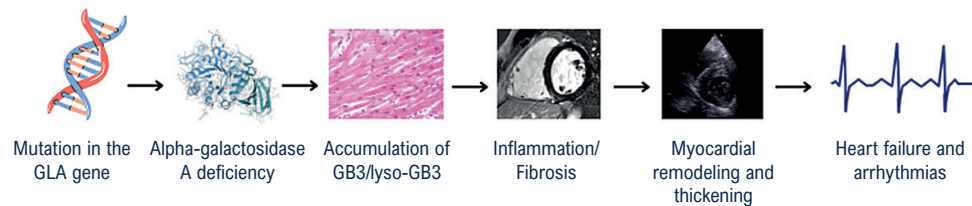
α -Galactosidase A is a lysosomal acid hydrolase responsible for the degradation of Gb3, a glycosphingolipid present in cell membranes. Under physiological conditions, this enzyme catalyzes the removal of the galactose terminal residue from the Gb3 molecule, allowing its degradation inside lysosomes.^{1,2,8,9} In Fabry disease, pathogenic variants in the *GLA* gene result in deficiency or absence of α -galactosidase A activity, interrupting the lysosomal degradation of Gb3

Central Illustration: Cardiac Involvement in Fabry Disease: From Electrocardiography to Recent Advances in Cardiovascular Imaging



Cardiac involvement in Fabry disease

NATURAL HISTORY



MULTIMODAL ASSESSMENT



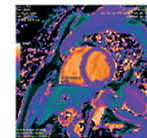
ELECTROCARDIOGRAPH

Short PR interval
Progressive expansion of the QRS
Repolarization abnormalities
Ventricular overload
QT Dispersion



ECHOCARDIOGRAM

Myocardial deformation
Myocardial work
Diastolic dysfunction
Myocardial thickening
Systolic dysfunction



CMR IMAGING

T1 Mapping
T2 Mapping
Gadolinium-induced late enhancement
Extracellular volume
Feature Tracking

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Schematic representation of the natural history of Fabry cardiomyopathy, from α -galactosidase A deficiency and Gb3/lyso-Gb3 accumulation to myocardial remodeling and its clinical manifestations, highlighting the complementary role of electrocardiography, echocardiography, and CMR imaging in the multimodal assessment of cardiac involvement. CMR: Cardiac Magnetic Resonance; Gb3: globotriaosylceramide; lyso-Gb3: globotriaosylsphingosine; ECV: Extracellular Volume.

and promoting its progressive accumulation in various cell types, particularly endothelial cells, vascular smooth muscle cells, podocytes, renal tubular cells, and cardiomyocytes.^{1,9,10} Intracellular Gb3 storage begins in intrauterine life in individuals with the classic form of the disease and precedes the appearance of clinical manifestations by many years.^{1,10}

In addition to lysosomal Gb3 storage, part of this molecule undergoes deacylation, originating globotriaosylsphingosine (lyso-Gb3), a soluble metabolite currently recognized as one of the main mediators of the pathophysiology of the disease. Lyso-Gb3 levels are markedly elevated in Fabry disease and exert several biological effects, including stimulation of cardiomyocyte hypertrophy, fibroblast activation, inflammation, vascular remodeling, and extracellular matrix deposition, thereby contributing to the progression of cardiomyopathy.^{1-3,11}

Recent evidence demonstrates that tissue damage in Fabry disease does not result exclusively from lysosomal storage of glycosphingolipids. The interaction between lyso-Gb3 accumulation, activation of inflammatory pathways, oxidative stress, mitochondrial dysfunction, and alterations in autophagy favors progressive myocardial remodeling, culminating in left ventricular hypertrophy, myocardial fibrosis, diastolic dysfunction, arrhythmias, and heart failure.^{1-3,6}

Fabry cardiomyopathy develops gradually and can be understood as a sequence of events beginning with intracellular glycosphingolipid storage, followed by early metabolic and inflammatory changes, myocardial remodeling, left ventricular hypertrophy, fibrosis, and, ultimately, ventricular dysfunction and heart failure. This pathophysiological model helps explain how cardiovascular

imaging can detect structural and functional abnormalities at different stages of the disease, often before the appearance of overt clinical manifestations.^{3,6,7,12}

Clinical Manifestations

Symptoms of the classic form of Fabry disease usually begin in childhood or adolescence and include neuropathic pain (acroparesthesia), angiokeratomas, hypohidrosis, intolerance to heat, cold, and exercise, as well as recurrent gastrointestinal manifestations.^{3,5,9,10} Small-fiber neuropathy is one of the most characteristic neurological manifestations of the disease and frequently precedes the involvement of other organs.^{10,13} Ophthalmological findings, such as cornea verticillata, and otological manifestations, including sensorineural hearing loss, tinnitus, and vertigo, are also frequent and may represent early signs of the disease.^{10,13}

Cerebrovascular involvement may occur early and represents a significant cause of morbidity. Ischemic strokes, transient ischemic attacks, and ischemic white matter lesions, frequently identified by brain magnetic resonance imaging, can occur decades earlier than in the general population, especially in men with the classic form of the disease.^{10,13,14}

Renal involvement results from the progressive deposition of Gb3 in podocytes, and tubular/vascular cells, initially manifesting as microalbuminuria and proteinuria, progressing to chronic kidney disease and end-stage renal failure when left untreated.^{9,10,13}

Although Fabry disease has multisystemic manifestations, cardiac involvement is currently the leading cause of morbidity and mortality. The progressive accumulation of Gb3 and the biological effects of lyso-Gb3 contribute to left ventricular hypertrophy, myocardial remodeling, fibrosis, valvular heart disease, microvascular disease, conduction abnormalities, and arrhythmias, leading to a substantial increase in the risk of heart failure, sudden cardiac death, and cardiovascular events.^{3,6,7,12,15,16}

Electrocardiography

Progressive accumulation of Gb3 in cardiomyocytes, the conduction system, and the microvasculature promotes early electrophysiological changes that can often be detected on the electrocardiogram before the development of left ventricular hypertrophy, making electrocardiogram an important tool for the early recognition of cardiac involvement in Fabry disease.^{6, 17-19}

One of the classic electrocardiographic changes in the disease is a shortened PR interval, measured from the onset of the P wave to the onset of the QRS complex. Initially attributed to the presence of accessory pathways, electrophysiological studies have shown that most patients do not present with anomalous atrioventricular bundles, suggesting that this finding results mainly from increased conduction velocity through the atrioventricular node and atrial conduction abnormalities related to glycosphingolipid deposition.¹⁸⁻²⁰

More recent studies have shown that, in the early stages of the disease, especially in the absence of left ventricular hypertrophy, the apparent shortening of the PR interval results

predominantly from a reduction in the duration of the P wave, reflecting early atrial involvement before ventricular remodeling is established.^{19,21}

As cardiomyopathy progresses, left ventricular hypertrophy develops, the main cardiac phenotype of Fabry disease, often mimicking sarcomeric hypertrophic cardiomyopathy or hypertensive cardiomyopathy. The progressive increase in ventricular mass is associated with an increase in QRS complex voltage and the appearance of electrocardiographic criteria for left ventricular hypertrophy, although its sensitivity remains limited.^{15,16,21}

In more advanced stages, infiltration of the His-Purkinje system and the development of myocardial fibrosis favor widening of the QRS complex, intraventricular blocks, and atrioventricular conduction disturbances. ST segment and T wave changes reflect repolarization disturbances resulting from myocardial infiltration, fibrosis, and microvascular dysfunction, and are associated with the progression of cardiac involvement.^{6,17-19}

Even in the absence of left ventricular hypertrophy, patients with Fabry disease may present with prolonged corrected QT interval (QTc), increased QT dispersion and Tpeak-Tend interval dispersion, reflecting greater ventricular electrical heterogeneity and a predisposition to the development of ventricular arrhythmias.²¹

More recently, Figliozzi *et al.* developed an electrocardiographic score comprising four parameters — the Sokolow–Lyon index, P-wave duration/PR-segment ratio, QRS duration, and QTc — that can estimate the probability of reduced native T1 on CMR imaging, potentially enabling early identification of myocardial glycosphingolipid storage before the development of left ventricular hypertrophy.²¹

Conventional Echocardiography

Transthoracic echocardiography is the first-line imaging modality for the cardiac evaluation of Fabry disease because of its wide availability, safety, and ability to characterize cardiac morphology, geometry, and function, as well as to enable longitudinal monitoring of cardiomyopathy progression and response to treatment. However, conventional echocardiographic parameters may remain normal in the early stages, so normal findings do not exclude subclinical cardiac involvement.^{3,7,22,23}

Increased thickness of the ventricular walls and left ventricular mass constitutes the most characteristic echocardiographic manifestation of Fabry cardiomyopathy. Left ventricular hypertrophy most commonly presents with a concentric pattern, with a relatively uniform increase in the thickness of the interventricular septum and posterior wall. However, asymmetrical, septal, or apical patterns can also occur, especially in more advanced stages, and may mimic sarcomeric hypertrophic cardiomyopathy or hypertensive heart disease.^{7,12,16,22,24}

Increased ventricular thickness is generally earlier and more pronounced in men, although women can also present with fibrosis and significant cardiac involvement, even without an evident increase in thickness.^{1,3,6,25}

Hypertrophy and prominence of the papillary muscles are frequent morphological findings and can significantly contribute to increased left ventricular mass. Although disproportionate papillary muscle enlargement has been proposed as a possible early marker of Fabry cardiomyopathy, this finding is not specific and should be interpreted in conjunction with the clinical context and other imaging parameters.^{7,22,23}

The binary aspect of the endocardium was initially described as a marker of Fabry disease, but it has low reproducibility and little specificity, and is not currently recommended as an isolated diagnostic criterion.^{7,22,23,26}

Left Ventricular Ejection Fraction (LVEF) generally remains preserved until advanced stages, even in the presence of significant hypertrophy. However, normal ejection fraction values do not exclude myocardial dysfunction, since alterations in longitudinal function, ventricular relaxation, and myocardial mechanics may precede the reduction of overall systolic function. As fibrosis and ventricular remodeling progress, ventricular cavity dilation, reduced ejection fraction, and heart failure may develop.^{6,7,12,16}

Impaired myocardial relaxation can be identified early in Fabry disease, particularly through reduced diastolic mitral annular velocities on tissue Doppler imaging. With the progression of cardiomyopathy, increased ventricular mass, reduced myocardial compliance, and the development of fibrosis contribute to the worsening of diastolic dysfunction, which may result in elevated filling pressures and increased left atrial volume. Conventional mitral flow parameters have limited sensitivity for identifying early involvement and should be interpreted in an integrated manner with mitral annulus velocities by tissue Doppler and myocardial deformation parameters.^{7,12,22,27}

Fabry disease should integrate parameters of mitral flow, tissue Doppler, left atrial volume, and other echocardiographic markers. The 2025 ASE update incorporated new parameters and a revised algorithm for assessing diastolic function and estimating filling pressures. However, further studies are needed to evaluate the applicability and performance of these recommendations specifically in patients with Fabry disease.²⁸⁻³⁰

Valvular involvement results primarily from thickening and infiltration of the leaflets and subvalvular apparatus, most frequently affecting the mitral and aortic valves. Mild valvular regurgitation is relatively common, while hemodynamically significant lesions are uncommon. The right ventricle may also exhibit increased wall thickness and hypertrophy, generally associated with greater severity of left ventricular hypertrophy and more advanced stages of cardiomyopathy. Despite these structural changes, conventional right ventricular systolic function often remains preserved.^{7,12,16,22}

Dilation of the aortic root and ascending aorta has also been described, particularly in men, possibly related to the accumulation of glycosphingolipids in the vascular wall and connective tissue remodeling. Although generally subtle, assessment of aortic dimensions should be included in the routine echocardiographic examination of patients with Fabry disease.^{7,22}

Speckle Tracking Echocardiography and Myocardial Deformation

Speckle tracking echocardiography allows for the quantitative assessment of myocardial deformation and can identify subclinical functional changes before ejection fraction reduction and, in some patients, before the development of left ventricular hypertrophy. Unlike tissue Doppler imaging, this technique is less dependent on the insonation angle and allows for the analysis of the longitudinal, circumferential, and radial components of ventricular deformation, in addition to the evaluation of atrial and right ventricular function. Pioneering studies with myocardial Doppler demonstrated reduced velocities and deformation indices in patients with Fabry disease, contributing to the recognition of early functional impairment.^{12,27} Subsequently, studies that include speckle tracking broadened the characterization of cardiac mechanics and demonstrated biventricular and atrial changes even in the presence of preserved conventional systolic function.^{22,31-33}

Left Ventricular Longitudinal Strain

Global Longitudinal Strain (GLS) assesses myocardial shortening along the longitudinal axis of the left ventricle and is the most studied strain parameter in Fabry disease. Early myocardial Doppler studies demonstrated impaired longitudinal function despite preserved ejection fraction, while later speckle tracking studies confirmed reduced GLS and regional changes in strain, even in patients without evident left ventricular hypertrophy.^{12,22,27,31,34}

The reduction in longitudinal strain shows a heterogeneous distribution and tends to be more pronounced in the basal segments, particularly in the inferolateral wall, a region characteristically associated with the development of myocardial inflammation and fibrosis. However, the apical segments are not completely spared, unlike the pattern of relative apical sparing frequently observed in cardiac amyloidosis. The regional reduction in strain may be related to the presence of Late Gadolinium Enhancement (LGE) and the progression of myocardial damage, although changes in deformation may also occur before fibrosis is detectable by CMR.^{22,32,33}

Radial and Circumferential Strain of the Left Ventricle

Radial strain represents myocardial thickening towards the center of the ventricular cavity during systole. Initial studies using myocardial Doppler demonstrated a reduction in radial strain, even in women with preserved left ventricular mass, while subsequent analyses by speckle tracking showed impairment of radial strain before the development of left ventricular hypertrophy and independently of the ventricular geometric pattern.^{27,35}

Circumferential strain represents myocardial shortening around the ventricular circumference and predominantly reflects the mechanics of the mid-wall myocardial fibers. In Fabry disease, regional changes in circumferential strain and a reduction in the physiological gradient from base to apex have been described even in patients without left ventricular hypertrophy. However, findings regarding global circumferential strain are less consistent, and some studies have not demonstrated significant differences compared to healthy individuals.^{22,24,36}

Left Atrial Strain

Analysis of left atrial strain allows for the evaluation of its reservoir, conduit, and contraction functions, and can identify atrial involvement before the development of significant dilation. Boyd *et al.* demonstrated increased atrial volume and reduced left atrial compliance before the onset of ventricular hypertrophy, providing early evidence of early atrial involvement in Fabry disease.³⁷

Subsequently, Pichette *et al.* demonstrated, using speckle tracking, impairment of all three phases of left atrial function and improvement in strain parameters following enzyme replacement therapy, representing an important milestone in the assessment of atrial strain in Fabry disease.³⁸ Subsequent studies confirmed the reduced atrial strain and suggested that left atrial dysfunction may reflect a combination of intrinsic atrial myopathy, ventricular diastolic dysfunction, and increased filling pressures, potentially being associated with the development of atrial fibrillation and adverse clinical events.³⁹⁻⁴²

Right Ventricular Strain

Speckle tracking allows the identification of subclinical changes in right ventricular systolic function that may not be recognized by conventional echocardiographic parameters. Initial studies with myocardial Doppler did not demonstrate a significant reduction in the longitudinal strain rate of the right ventricle, possibly due to the characteristics of the studied population and the methodological limitations of the technique.¹²

With the development of speckle tracking, Lillo *et al.* demonstrated reduced global right ventricular longitudinal strain and right ventricular free wall longitudinal strain in patients with Fabry disease and cardiac involvement, while these parameters remained preserved in patients without evidence of cardiac involvement.⁴³ Subsequent studies have demonstrated an association between reduced right ventricular free wall strain, greater severity of cardiac phenotype, and the occurrence of cardiovascular events. However, this association did not remain independent after adjustment for global left ventricular longitudinal strain and indexed left atrial volume, suggesting that right ventricular involvement accompanies the severity of cardiomyopathy, with no current evidence of incremental prognostic value in relation to left heart parameters.^{32,33,44}

Right Atrial Strain

Evaluation of the right atrium constitutes a more recent area of echocardiographic characterization in Fabry disease. Lillo *et al.* demonstrated reduced reservoir and contraction functions of the right atrium, even in patients without left ventricular hypertrophy, suggesting that right atrial involvement may be part of the early cardiac phenotype of the disease.²⁹

Echocardiogram with Myocardial Work

Myocardial work is a noninvasive echocardiographic approach that integrates left ventricular longitudinal strain with estimated systolic blood pressure through pressure-strain loop analysis, allowing assessment of ventricular mechanics while accounting for the influence of afterload. In Fabry disease, recent studies have demonstrated alterations in global and regional myocardial

work indices, with differences related to the presence of left ventricular hypertrophy and the stage of cardiac involvement. Regional analysis also revealed a heterogeneous distribution of myocardial work, adding information to the evaluation by GLS (Figure 1).^{45,46} Although promising, myocardial work still needs validation in multicenter studies before its routine incorporation.

CMR Imaging

CMR Imaging plays a central role in the evaluation of Fabry cardiomyopathy, allowing for comprehensive characterization of ventricular morphology, volumes, and function, as well as non-invasive assessment of myocardial tissue composition. Its high spatial resolution and multiparametric characterization capabilities enable the identification of different components of the pathological process, including intracellular storage of glycosphingolipids, hypertrophy, inflammation, edema, and fibrosis, contributing to differential diagnosis, disease staging, prognostic stratification, and therapeutic monitoring.^{6,7,23,47,48} The most common morphological manifestation is left ventricular hypertrophy, usually with a concentric pattern, although asymmetric patterns and other phenotypic variants may also occur. CMR is the reference standard for quantifying ventricular volumes, myocardial mass, and biventricular function, allowing more precise characterization of the distribution of hypertrophy and identification of structural abnormalities that may not be adequately detected by echocardiography.^{7,23,25,49}

LGE enables the identification of areas of extracellular space expansion related to focal myocardial fibrosis. The classic pattern of Fabry cardiomyopathy consists of mesocardial or subepicardial LGE, predominantly located in the basal and mid- inferolateral wall segments, generally with preservation of the subendocardium (Figure 2A). This pattern was initially characterized by Moon *et al.*, and constitutes an important marker of advanced heart disease, although other distributions may be observed, especially in patients with more extensive myocardial remodeling.^{7,23,49,50}

Fabry disease was subsequently demonstrated by Moon *et al.*, who directly compared CMR images with macroscopic and histological analysis of the heart. Regions with LGE showed extensive collagen deposition, confirming that late enhancement corresponds to focal myocardial fibrosis and not to intracellular storage of glycosphingolipids.⁵¹ In the study, the LGE-enhanced segments showed approximately 62% collagen, compared to 4% in the non-enhanced segments.

The presence and extent of LGE are associated with the progression of cardiomyopathy, a higher risk of ventricular arrhythmias, and adverse cardiovascular events. Myocardial fibrosis is also an important determinant of treatment response, as patients with established fibrosis have less potential for regression of hypertrophy and functional recovery after initiation of specific therapy. This finding reinforces the importance of diagnosis and treatment before the development of irreversible myocardial damage.^{7,23,52-54}

T1 Mapping

Native T1 mapping represented one of the major advances in the evaluation of Fabry cardiomyopathy, allowing for quantitative characterization of the myocardium without the need for contrast administration (Figure 2B). Unlike most

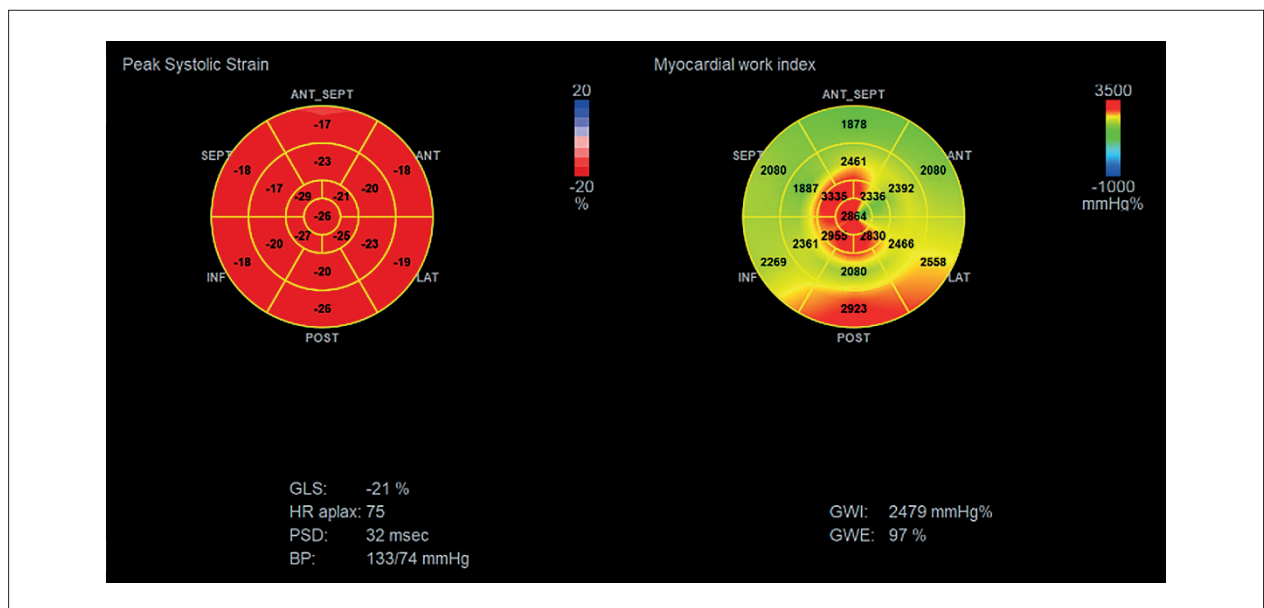


Figure 1 – Assessment of left ventricular mechanics via advanced echocardiography in a patient with Fabry disease. On the left, a polar map of systolic longitudinal strain, demonstrating a GLS of -21% . On the right, a polar map of myocardial work, with a global work index (GWI) of $2479 \text{ mmHg\%}$ and a global myocardial work efficiency (GWE) of 97% . Image from the authors' collection.

cardiomyopathies associated with ventricular hypertrophy, in which native T1 is usually elevated, Fabry disease is typically characterized by reduced T1 values, attributed to the intracellular storage of glycosphingolipids.^{23,55-58}

The pioneering studies by Sado et al. and Thompson et al. demonstrated that a reduction in native T1 has a high capacity to differentiate Fabry disease from other causes of left ventricular hypertrophy and may be present even before the development of detectable hypertrophy or fibrosis. Thus, native T1 constitutes a sensitive marker of early myocardial storage and may allow the identification of cardiac involvement in subclinical phases of the disease.⁵⁵⁻⁵⁷

However, normal T1 values do not exclude cardiac involvement. In regions with inflammation, edema, and fibrosis, particularly in the inferolateral wall, the increased water content and extracellular matrix can elevate T1 and counterbalance the reducing effect of intracellular storage, producing apparently normal values, a phenomenon called T1 pseudonormalization. In advanced stages, T1 may even present elevated values in regions with extensive fibrosis.^{6,7,23,59,60}

T1 values should be interpreted according to the equipment, the technique used, and local reference values.^{6,23,58}

T2 Mapping and Myocardial Inflammation

T2 mapping allows for the quantitative assessment of myocardial fluid content and constitutes a non-invasive marker of edema and inflammation. In Fabry disease, elevated T2 values are observed predominantly in the inferolateral wall, frequently in association with areas of LGE, suggesting the presence of chronic inflammatory activity superimposed on glycosphingolipid storage and myocardial fibrosis.

Regional T2 elevation is associated with the presence of LGE, elevated troponin, and greater severity of cardiomyopathy, and should be interpreted in conjunction with other CMR imaging parameters.^{7,23,59,60}

Extracellular Volume

Myocardial Extracellular Volume (ECV), calculated from T1 values obtained before and after contrast administration, together with hematocrit, allows estimation of the fraction of myocardium occupied by extracellular space. Unlike native T1, which in Fabry disease is typically reduced due to intracellular storage of glycosphingolipids, ECV generally remains within normal limits in the initial phases, reflecting the predominantly intracellular nature of the storage process.^{55,56,58}

With the progression of cardiomyopathy and the development of myocardial injury, inflammation, and fibrosis, expansion of the extracellular space and regional or global increase in the ECV may occur. These changes are observed mainly in regions with LGE, particularly in the inferolateral wall, and may contribute to characterizing the extent of interstitial remodeling.^{6,23,47,59}

ECV should be interpreted in conjunction with T1, T2, and LGE, as normal values do not exclude early involvement and may coexist with regional abnormalities.^{6,7,47}

Strain by CMR Imaging

Myocardial deformation analysis by feature tracking in CMR imaging allows quantification of the longitudinal, circumferential, and radial components of strain from conventional cine sequences, without the need for additional acquisitions. In

Fabry disease, alterations in myocardial deformation can be identified even in the presence of preserved ejection fraction and are associated with the severity of cardiac involvement. Zhao *et al.* demonstrated a reduction in longitudinal and radial strain of the left ventricle, with progressive impairment according to the stage of cardiomyopathy; however, circumferential strain showed less uniform behavior. Despite its potential for functional characterization and monitoring of disease progression, differences between programs, analysis methods, and reference values still limit its routine clinical application, and longitudinal studies are needed to define its prognostic value and its usefulness for therapeutic monitoring.^{47,48,61}

Conclusion

The integration of electrocardiography, echocardiography, and CMR enables early diagnosis, risk stratification, and longitudinal monitoring of Fabry cardiomyopathy. Emerging techniques, including myocardial work and CMR feature tracking, show promising potential but require further validation before their routine clinical implementation.

Author Contributions

Conception and design of the research and analysis and interpretation of the data: Volpolini LC, Mancuso FJ, Uellendahl M; acquisition of data: Volpolini LC, Cardinali MP, Uellendahl M; statistical analysis and writing of the manuscript: Volpolini LC; critical revision of the manuscript for intellectual content: Volpolini LC, Fischer CH, Moises VA, Curiati MA, Martins AM, Mancuso FJ, Uellendahl M.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the Universidade Federal de São Paulo under the protocol number 51118615.6.0000.5505. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

Use of Artificial Intelligence

During the preparation of this work, the authors used artificial intelligence to improve the text and for translation purposes, and not for the creation of the content itself. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

Availability of Research Data

The underlying content of the research text is contained within the manuscript.

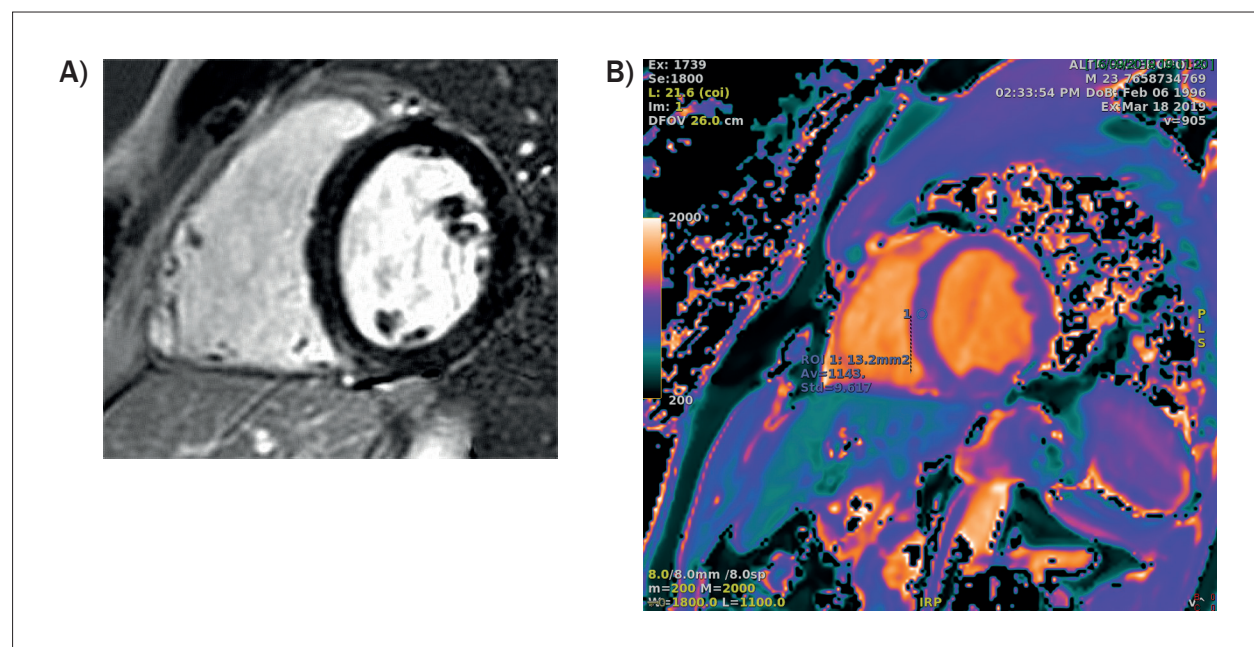


Figure 2 – Myocardial tissue characterization via CMR imaging in patients with Fabry disease. (A) Short-axis LGE image demonstrating mid-wall enhancement in the inferolateral wall of the left ventricle, consistent with myocardial fibrosis. (B) Short-axis native T1 map of the myocardium, used for the quantitative assessment of myocardial tissue properties. Images from the authors' collection.

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Equity and Representation in Cardiovascular Imaging: A Scientific Imperative, Not an Ideological One

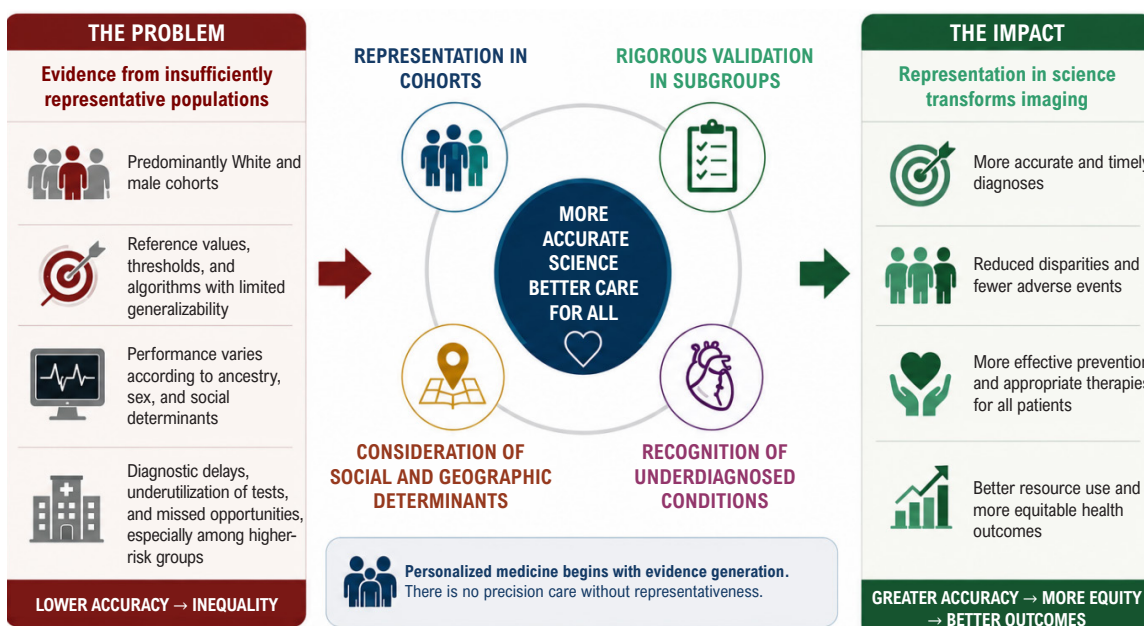
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Central Illustration: Equity and Representation in Cardiovascular Imaging: A Scientific Imperative, Not an Ideological One



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Abstract

Much of cardiovascular medicine has been built on evidence derived from predominantly White, male cohorts that do not reflect the diversity of the patient population. Consequently, reference values, devices, and algorithms may exhibit variable accuracy across groups, thereby compromising diagnostic precision. From the perspective

of cardiovascular imaging, this review examines how underrepresentation in research translates into diagnostic inequities. We discuss scenarios where representation alters what imaging reveals: transthyretin amyloidosis associated with the Val142Ile variant in older adults of African ancestry, cardiopulmonary manifestations of sickle cell disease, and conditions that predominantly affect women, including ischemia with non-obstructive coronary arteries (INOCA) and takotsubo syndrome. We also address bias in devices and algorithms, exemplified by pulse oximetry and artificial intelligence models trained on datasets lacking diversity. Finally, we propose an agenda centered on ensuring representation in normative cohorts, subgroup validation, and the equitable implementation of novel technologies.

Keywords

Equity; Diagnostic Imaging; Bias; Algorithms

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Introduction

Although changes in the therapeutic and diagnostic landscape of contemporary cardiology have brought

undeniable advances, they have also exposed a structural limitation in the knowledge upon which we have historically built our practice. Many of the reference values, diagnostic thresholds, algorithms, and even the devices at our disposal were calibrated based on predominantly White, male cohorts, which do not reflect the diversity of patients we treat. A test whose accuracy varies according to a patient's sex, ancestry, or race is, first and foremost, a less precise test, and this imprecision harms everyone.

In this context, considering equity and representation in cardiovascular imaging research and practice is not a concession to any particular ideological agenda, but rather a requirement of ethical commitment and scientific rigor. After all, equity does not compete with scientific precision; it stems from it. Here, we review some of the key issues highlighted in the recent literature.

The documented burden of disparities

Disparities in cardiovascular disease outcomes have been widely documented and directly linked to persistent inequities in access to health care worldwide, affecting populations that have historically been underrepresented in various population-based studies (Central Illustration).

Black individuals experience higher cardiovascular mortality and a substantially elevated risk of recurrent events; these disparities persist after adjusting for clinical factors and have been largely attributed to social determinants and unequal access to health care.¹⁻³ For cardiologists and cardiovascular imaging specialists, these statistics are not merely a distant backdrop; they translate into diagnostic delays, underutilization of advanced imaging, and missed opportunities for prevention strategies, populations at greater risk and vulnerability.

Such disparities are likewise not randomly distributed geographically. Place of residence, imperfectly yet revealingly summarized by ZIP code, serves as a marker of environmental exposure, socioeconomic conditions, and access to health care, to the extent that ZIP code-based analyses can predict cardiovascular outcomes better than clinical data alone.^{4,5} In a population-based cohort, a neighborhood disadvantage index alone accounted for 32% of the variation in adverse coronary artery disease events across neighborhoods, compared with only 10% accounted for by the clinical risk model.⁴ Recognizing the relationship between where one lives and risk factors has led to the incorporation of geographic factors into risk stratification tools: the American Heart Association's PREVENT calculator includes an optional ZIP code-based component to capture neighborhood socioeconomic status and refine risk prediction beyond traditional biological factors.⁶ The lesson for cardiovascular imaging is analogous: The determinants that shape who falls ill and who has access to imaging must be considered during both the indication and interpretation phases; if we fail to do so, we run the risk of reproducing in our reports the inequalities that were established long before the images were acquired.

When representation changes diagnosis

Some practical scenarios illustrate how the representation of factors such as race, ancestry, and sex can influence what cardiovascular imaging methods are capable of revealing.

Hereditary transthyretin cardiac amyloidosis associated with the Val142Ile variant (formerly Val122Ile) is an underdiagnosed cause of heart failure in older Black adults; the allele is present in approximately 3% to 4% of people of African descent in the United States, but it is practically absent among White individuals.^{7,8} It is worth noting that the frequency of this variant tracks with genetic ancestry (specifically West African ancestry) rather than race as a social category; in this case, self-identified race serves as an imperfect marker of ancestry. For decades, these patients were labeled as having hypertensive heart failure or heart failure with preserved ejection fraction of undetermined origin, precisely because this specific condition was not considered. Imaging has changed this landscape, as bone-seeking radiotracer scintigraphy, subendocardial late gadolinium enhancement, and elevated extracellular volume on T1 mapping (via cardiac magnetic resonance imaging) now enable noninvasive diagnosis. In this context, the SCAN-MP study was intentionally designed to screen for cardiac amyloidosis using nuclear imaging in Black and Hispanic populations with heart failure, an explicit recognition that representativeness in imaging research is essential for diagnosing conditions that previously went undetected.⁹ Ignoring these population did not by any means make the disease rare; instead, it merely kept it invisible.

Sickle cell disease provides a second example. Among patients with this disease, which predominantly affects individuals of African descent, cardiopulmonary complications, such as pulmonary hypertension, diastolic dysfunction, and sudden death, are the leading causes of mortality in adulthood.^{10,11} Here, too, imaging has played a decisive role in clinical decision-making, since cardiac magnetic resonance imaging studies have shown that these patients develop a distinctive restrictive cardiomyopathy characterized by atrial dilation and restrictive physiology. This phenotype was only understood once the population was studied using appropriate imaging tools.^{12,13} Cardiovascular research historically neglected these patients; had it continued to do so, we would still lack the valuable diagnostic framework needed to interpret these findings to this day.

Gender and sex provide an equally instructive perspective. For decades, ischemic heart disease was studied and defined based on the male pattern of epicardial obstruction, while mechanisms that are predominate in women were largely overlooked. Ischemia and myocardial infarction with non-obstructive coronary arteries (INOCA and MINOCA) clearly illustrate this issue. An analysis of the ISCHEMIA trial revealed that INOCA was approximately four times more common in women than in men (odds ratio of 4.2 [95% confidence interval 3.4–5.2] for women in the multivariable analysis).¹⁴ Because conventional angiography cannot visualize microcirculation, these conditions were long interpreted as non-cardiac chest pain. Today, functional imaging, including Positron Emission Tomography (PET)-based assessment of coronary flow and cardiac magnetic resonance perfusion and mapping, makes the underlying. In MINOCA, conversely, mechanisms such

as plaque rupture or erosion, spontaneous coronary artery dissection and spasm predominate, the elucidation of which relies on modalities such as cardiac magnetic resonance and intracoronary imaging.

A similar phenomenon is observed in Takotsubo syndrome, a condition predominantly affecting post-menopausal women, who account for nearly 90% of cases in an international registry.¹⁵ Recognition of this syndrome depends on patterns of ventricular ballooning identified via ventriculography, echocardiography, and cardiac magnetic resonance imaging; therefore, in this disease as well, what is observed depends on what we have decided to look for.

Bias in devices and algorithms

The third area of concern, perhaps the most urgent in the era of quantitative imaging and artificial intelligence, lies in bias embedded within devices and algorithms.

The case of pulse oximetry has become emblematic, as Black patients are approximately three times more likely to have undetected occult hypoxemia due to the interference of skin pigmentation with device readings.¹⁶ The parallel with cardiovascular imaging is direct. Artificial intelligence models trained on datasets lacking diversity tend to define what is “normal” and “abnormal” based on a narrow population and may exhibit systematic errors when applied to groups that were underrepresented in the training data.¹ Technically, these are classified as representation and aggregation biases, which have been described among the main mechanisms limiting the generalizability of artificial intelligence models in health care.¹⁷ Normative values for myocardial thickness, strain, extracellular volume, or coronary calcium scores derived from homogeneous cohorts risk misclassifying patients whose underlying physiology remains understudied. A prime example in cardiovascular imaging involves a deep learning model for cardiac magnetic resonance image segmentation that, having been trained predominantly on White individuals, exhibited consistently inferior performance in Black and mixed-race patients prior to bias-mitigation strategies.¹⁸

Diversity in training datasets is necessary, but not sufficient. Models also require external validation across distinct populations and continuous monitoring after implementation. An algorithm is only as equitable as the data on which it was trained and only as reliable as the population in which it was validated. Cardiovascular imaging, which is increasingly reliant on automated measurements, must address this limitation in a transparent manner.

From description to action: an agenda for cardiovascular imaging

It is worth clarifying a frequent misunderstanding here. Studying neglected populations is neither a favor to a specific group nor an exercise in political correctness, but rather a scientific strategy that expands knowledge applicable to all people.

It was only by investigating the Val142Ile variant in Black patients that our understanding of transthyretin amyloidosis as a whole was refined. Wild-type transthyretin amyloidosis is

now recognized as a condition affecting older patients across diverse ancestral backgrounds. The study of sickling led to the characterization of a restrictive cardiomyopathy phenotype whose relevance extends beyond that specific disease. Science that excludes populations does not become more neutral; it becomes poorer, less generalizable, and less precise. After all, personalized medicine begins before treatment: it begins with generating evidence.

Recognizing disparities is merely the first step; the contemporary challenge lies in moving from description to action. A recent joint editorial by the American College of Cardiology, the American Heart Association, the European Society of Cardiology, and the World Heart Federation proposes exactly this shift, framing health equity not as a politicized agenda, but as a scientific frontier in cardiovascular medicine that warrants the same rigor applied to any other field.¹⁹ For our cardiovascular imaging community, this framing translates into concrete commitments.

The first is ensuring the representativeness of the cohorts that define normal values. Whenever biologically plausible and clinically relevant, reference values for myocardial thickness, strain, T1 mapping, extracellular volume, coronary calcium scores, and echocardiographic parameters should be established and reported across diverse populations in terms of ancestry and sex, so that the concept of “normal” is not derived from a narrow sample.

The second is validation of devices and algorithms across subgroups. Much like the lessons learned from pulse oximetry, imaging tools and artificial intelligence models should demonstrate consistent performance across groups prior to adoption, with explicit reporting of accuracy based on relevant variables such as race, ancestry, sex, and skin tone, rather than assuming generalizability based on homogeneous training data. This assessment must include external validation and post-implementation monitoring, as performance observed in one cohort does not guarantee reproducibility in another. This effort should be structured throughout the model's lifecycle, spanning conception and data collection, preprocessing, validation, deployment, and post-deployment monitoring. Furthermore, subgroup performance must always be evaluated using explicit fairness metrics, such as demographic parity and equal opportunity.¹⁷

The third encompasses education and diagnostic vigilance. It is crucial to incorporate into the training of cardiologists and radiologists the recognition of conditions that historical homogeneity has kept in the shadows, such as transthyretin amyloidosis in older Black adults and the cardiac manifestations of sickle cell disease, as well as the routine consideration of geographic and social determinants of access when ordering and interpreting tests.

Last comes implementation. Strategies such as telemedicine, abbreviated protocols, and lower-cost technologies have the potential to bring advanced imaging closer to historically underserved populations, provided they are designed with equity in mind, so that innovation will narrow, rather than widen, the gap between those who benefit and those who remain marginalized.¹⁹ A caveat regarding scope is warranted: the framework of disparities discussed herein relies largely on

evidence from North America. Both epidemiological profiles and sociodemographic categories vary across health care systems and populations. In Brazil, for example, the high degree of genetic admixture limits the direct extrapolation of normative values and allele frequencies derived from other cohorts. Moreover, this viewpoint is a perspective article and does not constitute a systematic review of the literature.

Take-home message

Cardiovascular imaging is uniquely positioned to lead the necessary change, as it operates at the frontier between measurable physiology and clinical decision-making. The true measure of its excellence lies not only in the increasing sophistication of its methods but also in its ability to maintain accuracy across the entire population it aims to serve. Better representing human diversity does not mean tailoring science to an external agenda; it means aligning it more closely with the biological and social realities that science seeks to describe. The more diverse the evidence underpinning our methods, the more generalizable the resulting knowledge becomes, and the more precise the care offered to each patient. In this sense, equity is not at odds with scientific excellence; it is one of its most tangible expressions.

Author Contributions

Writing of the manuscript: Calheiros EC, Veloso JS; critical revision of the manuscript for intellectual content: Assunção Junior AN, Araujo-Filho JAB.

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This article does not contain any studies with human participants or animals performed by any of the authors.

Use of Artificial Intelligence

During the preparation of this work, the author(s) used ChatGPT for elaboration of Figure 1. After using this tool/service, the author(s) reviewed and edited the content as needed and take full responsibility for the content of the published article.

Availability of Research Data

The underlying content of the research text is contained within the manuscript.

Review Article

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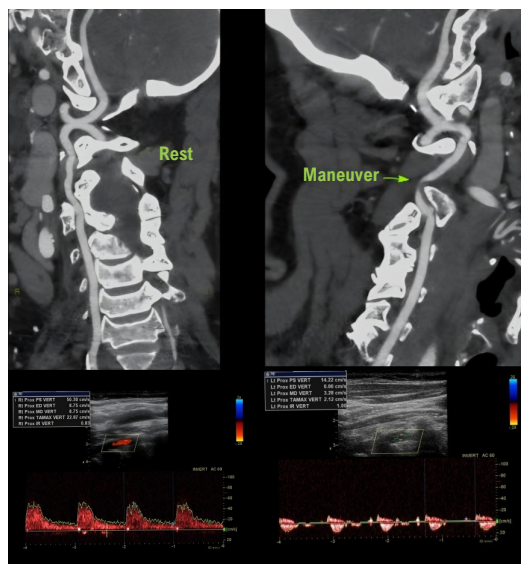
My Approach To: Bow Hunter's Syndrome

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Central Illustration: My Approach To: Bow Hunter's Syndrome



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Top left: CT angiography of the vertebral artery at rest demonstrating normal opacification. Bottom left: Vertebral Doppler ultrasound at rest showing normal blood flow. Top right: CT angiography with contralateral neck rotation demonstrating arterial compression between C1 and C2. Bottom right: Doppler ultrasound with contralateral neck rotation demonstrating a staccato flow pattern.

Abstract

Bow hunter's syndrome (BHS) is a rare and underdiagnosed condition characterized by mechanical compression or temporary occlusion of the vertebral artery due to lateral rotation or hyperextension of the neck. This mechanical stress occurs predominantly in the V3 segment (C1–C2 level) because of its high degree of mobility.

The pathophysiology involves two main mechanisms – hemodynamic, in which extreme rotation immediately reduces

local blood flow and causes paroxysmal symptoms (the triad of vertigo, dizziness, and imbalance) that resolve once the head returns to the neutral position; and thromboembolic, triggered by repeated microtrauma and chronic endothelial injury, which may lead to thrombus formation or dissections and result in cerebellar or brainstem infarctions.

Definitive diagnosis is based on dynamic digital subtraction angiography (DSA) and computed tomography angiography (CTA). However, dynamic vascular Doppler serves as an excellent non-invasive screening method, capable of recording critical real-time hemodynamic changes through positional maneuvers, such as a greater than 50% drop in peak systolic velocity (PSV) or disappearance of diastolic flow.

Therapeutic management varies according to severity. Mild cases are treated conservatively with a cervical collar, behavioral modifications, and antiplatelet therapy. Surgical interventions – such as decompression via osteophylectomy or cervical arthrodesis – and specific endovascular treatments are strictly reserved for patients with refractory symptoms or high risk of stroke.

Keywords

Vertebral Artery; Rare Diseases; Diagnosis

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Introduction

Bow hunter's syndrome (BHS), also known as rotational vertebral artery syndrome or rotational occlusion of the vertebral artery, is a rare and underdiagnosed condition in clinical practice, classified among the compressive syndromes of the vertebrobasilar system. It is characterized by compression or occlusion of the vertebral artery during lateral head rotation, resulting in transient or permanent neurological deficits.

The name derives from the posture adopted by archers when shooting arrows, during which they perform a vigorous rotation of the neck. An important variant of BHS occurs due to hyperextension of the head, known as the beauty parlor stroke syndrome, described in relation to the position assumed during hair washing in salon sinks.¹²

Incidence

The exact incidence of BHS remains unknown in the general population due to its dynamic nature and the

high rate of underdiagnosis. It is more frequent among individuals aged 50 to 79 years, with a male predominance of approximately 2:1. However, it may occur at any age, including in children.¹

Pathophysiology

To understand the pathophysiology of BHS, it is necessary to correlate the anatomical course of the vertebral artery (Figure 1) – traditionally divided into four segments – with its specific mechanical vulnerabilities during cervical kinematics (Table 1).

The V3 segment, due to its anatomical particularities, is the most frequently affected site. This occurs because the hypermobility of the atlantoaxial joint (C1–C2) accounts for approximately 50% of total cervical rotation,³ making this region particularly susceptible to dynamic compression of the vertebral artery.

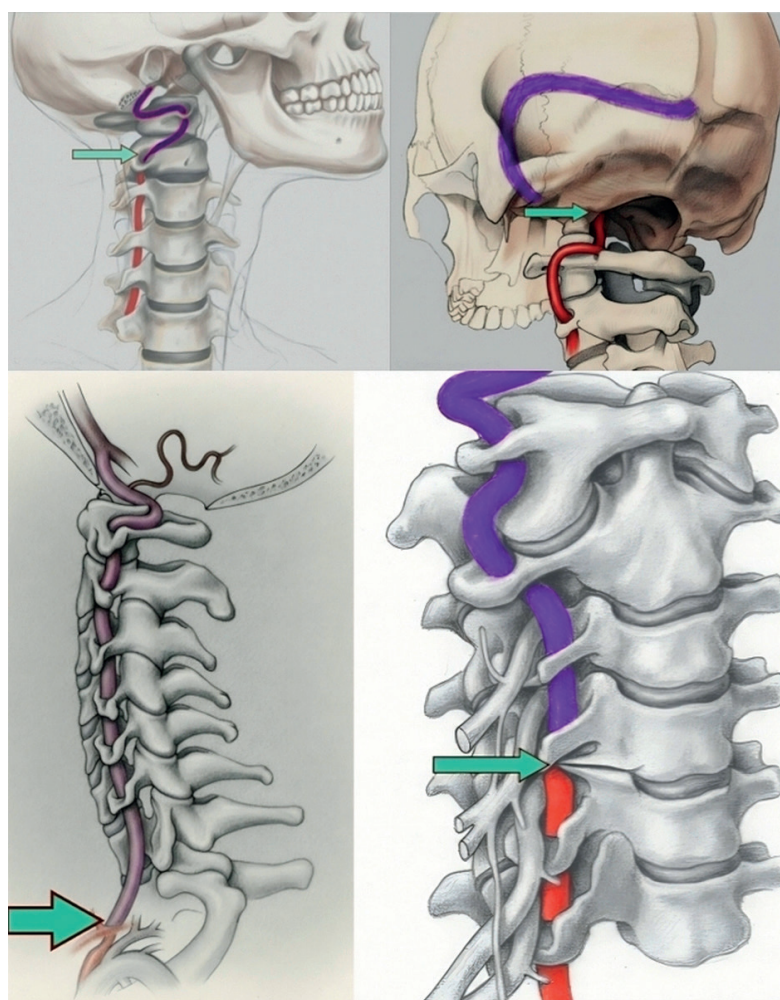


Figure 1 – Segments of the vertebral artery; bottom left: V1 segment; bottom right: V2 segment; top left: V3 segment (the most frequent site); top right: V4 segment.

Arterial dominance is another critical factor: compression of a dominant vertebral artery carries a greater potential for hemodynamic repercussions, especially when associated with hypoplasia of the contralateral vessel.

Two pathophysiological mechanisms may occur either independently or simultaneously. The hemodynamic mechanism manifests when extreme cervical rotation (generally greater than 60°) causes mechanical compression and an immediate reduction in blood flow. This drop in perfusion compromises the most vulnerable regions of the posterior circulation, resulting in transient neurological symptoms, which resolve as soon as the head returns to the neutral position and the vessel regains its patency. The severity of symptoms is directly related to the degree of dynamic stenosis, the presence of contralateral hypoplasia, and the efficiency of the circle of Willis in compensating for the deficit through the posterior communicating arteries.

The thromboembolic mechanism, in turn, is associated with chronic structural damage to the arterial endothelium. Mechanical stress and repeated compression of the vertebral artery produce endothelial microtrauma, culminating in subintimal dissections or mural thrombi. These may give rise to distal embolization, causing cerebellar or brainstem infarctions, even without sustained cervical rotation. This phenomenon is particularly observed in the pediatric population, in which cervical hypermobility predisposes to arterial dissections after minimal trauma or abrupt rotational movements.⁴

The clinical presentation of BHS is typically paroxysmal and strictly related to head position. The classic symptomatology consists of a triad of vertigo, dizziness, and imbalance triggered by lateral rotation of the neck, and may also include syncope, diplopia, auditory disturbances, or infarcts within the posterior circulation.

The differential diagnoses include benign paroxysmal positional vertigo, Ménière's disease, and vestibular migraine,

which makes it imperative to investigate transient symptoms triggered exclusively by cervical rotation.

Diagnosis

The gold standard for diagnosis is dynamic digital subtraction angiography (DSA). Dynamic computed tomography angiography (CTA) also plays an important role, as it allows three-dimensional reconstruction, assessment of the stenotic segment, and identification of the anatomical structure responsible for the compression.

Dynamic vascular Doppler emerges, in this context, as a highly effective screening tool, as it is an accessible, low-cost, radiation-free method that does not require contrast administration. The dynamic nature of the examination allows real-time assessment of the vessel's hemodynamic behavior.

The examination should be performed with the patient in a neutral position and in maximum contralateral rotation, evaluating both vertebral arteries, preferably in the V1 and V2 segments and, when accessible, V3. Neck flexion and extension may be combined with rotation to enhance the maneuver.

It is essential to maintain the position for 30 to 60 seconds to increase the sensitivity of the test, since flow alterations may exhibit a latency period. Whenever possible, the patient should be asked to adopt the exact position that typically triggers the symptoms.

Although the greatest point of arterial stretching occurs at the C1–C2 level during contralateral rotation combined with extension, some authors suggest measuring flow in up to nine different positions, combining neutral position, flexion, extension, and ipsilateral and contralateral rotations.⁵

During the procedure, velocities and flow patterns are recorded in the neutral position for later comparison during the maneuvers (Figure 2). Flow variations with a reduction greater than 50% in peak systolic velocity (PSV) are indicative of significant compression. End-diastolic velocity (EDV) often shows a marked reduction; however, the most robust criterion is the complete disappearance of diastolic flow during rotation, which reflects increased downstream vascular resistance due to distal vessel occlusion (Central Illustration).

Vascular resistance rises considerably during distal compression maneuvers and decreases during proximal ones. In severe cases, complete absence of flow may be observed, consistent with total occlusion. Another detectable parameter is reactive hyperemia, characterized by an increase greater than 10% in flow velocities after returning to the neutral position. Contralateral evaluation is mandatory, given the risk of bilateral involvement.

The flow pattern obtained provides information not only about the presence of compression but also about the segment involved. In proximal compressions, a dampened (*tardus-parvus*) pattern is observed, with increased acceleration time and reduced peak velocity. At the exact point of compression, turbulence with elevated velocities may occur. In distal segments, there may be absence of flow, reduced systolic and diastolic velocities

Parameter	Behavior in BHS (rotation)
PSV	Absence of flow or >50% reduction
EDV	Absence or marked reduction
Wave morphology	Staccato pattern – distal Tardus-parvus pattern (dampened) – proximal
RI	Reduction – proximal Increase – distal
AT	Increases in proximal obstructions

Table 1 – Flow patterns observed on vascular Doppler in BHS. PSV: Peak Systolic Velocity; EDV: End-Diastolic Velocity; RI: Resistive Index; AT: Acceleration Time; BHS: Bow Hunter's syndrome.

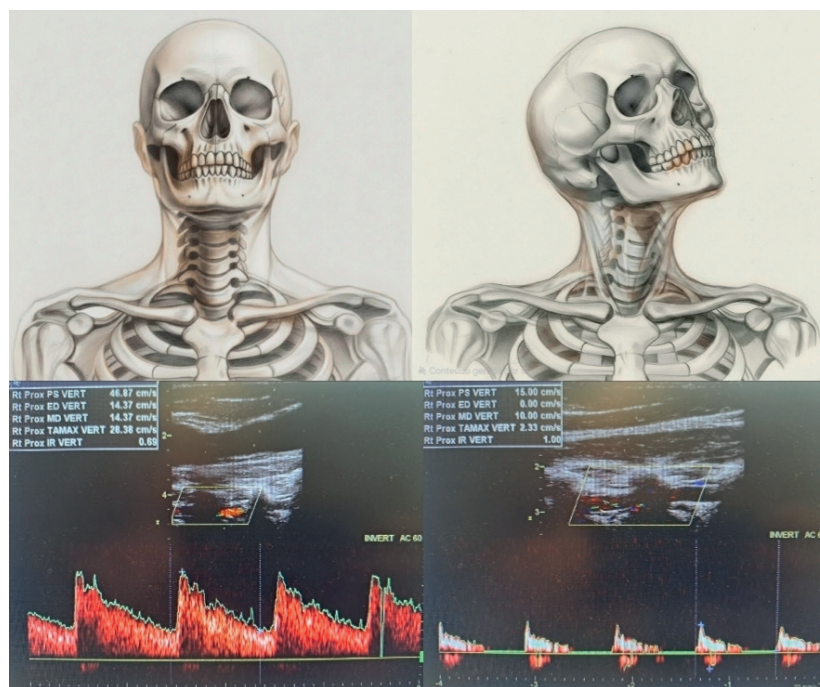


Figure 2 – Vascular Doppler of the V2 segment performed in the neutral position (left), demonstrating normal flow; on the right, the same patient shows staccato-pattern flow after contralateral rotation maneuver.

with increased resistance index (RI), or a staccato-type pattern (Table 2).

The reproduction of neurological symptoms during the maneuvers, with immediate reversal upon returning to the neutral position, supports the positivity of the test.

Treatment

The therapeutic management of BHS must be individualized based on the severity of symptoms, the risk of stroke, and the presence of cervical instability.

In patients with mild, infrequent symptoms and no structural neurological lesions, conservative management is the first-line approach. This strategy is based on behavioral modifications (avoiding the triggering position) or the use of a cervical collar. Antithrombotic therapy with antiplatelet agents (such as aspirin or clopidogrel) is indicated to prevent thromboembolic events resulting from endothelial injury. Although safe, conservative treatment shows effectiveness in controlling limiting symptoms or reducing stroke risk in only about 50% of cases.

Endovascular treatment remains controversial, as BHS results from an extrinsic compressive force that may flatten or fracture the stent structure, especially when the V3 segment is involved. Therefore, this approach should be reserved for highly selected cases.⁶

Surgical intervention is indicated for severe or refractory cases. It consists of decompression through osteophyctomy

Segment of the vertebral artery:	Anatomical description	Bow hunter's relevance
V1 (pre-apophyseal)	Origin from the subclavian artery to the transverse foramen of C6	Less common site; compression by fibrous bands or muscles
V2 (inter-apophyseal)	Course through the transverse foramina from C6 to C2	Frequently affected by osteophytes and disc herniations
V3 (atlanto-axial)	Exit at C2, looping over C1 to the foramen magnum	Most common site (C1-C2) due to the high amplitude of rotation
V4 (intracranial)	From the foramen magnum to the basilar artery junction	Rarely the primary site of extrinsic mechanical compression

Table 2 – anatomical segments of the vertebral artery and main causes of obstruction in BHS.

(removal of osteophytes), a procedure that generally preserves cervical range of motion, although it carries a risk of recurrence due to postoperative fibrosis.

An alternative is cervical arthrodesis, which shows the highest success rate in preventing permanent neurological events; however, it imposes a definitive limitation on neck mobility.¹

Discussion

BHS is a neglected and frequently underdiagnosed condition capable of causing severe limitations and permanent neurological sequelae, making early diagnosis crucial. Vascular Doppler, due to its wide availability and reproducibility, has become an indispensable tool for screening suspected patients, especially those with neurological symptoms closely related to changes in cervical position.

Clinical suspicion in cases of syncope without an apparent cause is essential, and routine dynamic positional maneuvers should be incorporated into cervical vascular examination protocols. Although methods such as dynamic CTA and DSA remain crucial for anatomical mapping and final therapeutic planning, Doppler plays a decisive role in optimizing and guiding the indication for these invasive examinations.

Author Contributions

Conception and design of the research, acquisition of data, analysis and interpretation of the data, statistical analysis, obtaining financing, writing of the manuscript and

critical revision of the manuscript for intellectual content: Visconti RB.

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Study Association

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Ethics Approval and Consent to Participate

This article does not contain any studies with human participants or animals performed by any of the authors.

Use of Artificial Intelligence

The authors did not use any artificial intelligence tools in the development of this work.

Availability of Research Data

The underlying content of the research text is contained within the manuscript.

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My Approach to Echocardiographic Guidance During Percutaneous Balloon Mitral Valvuloplasty

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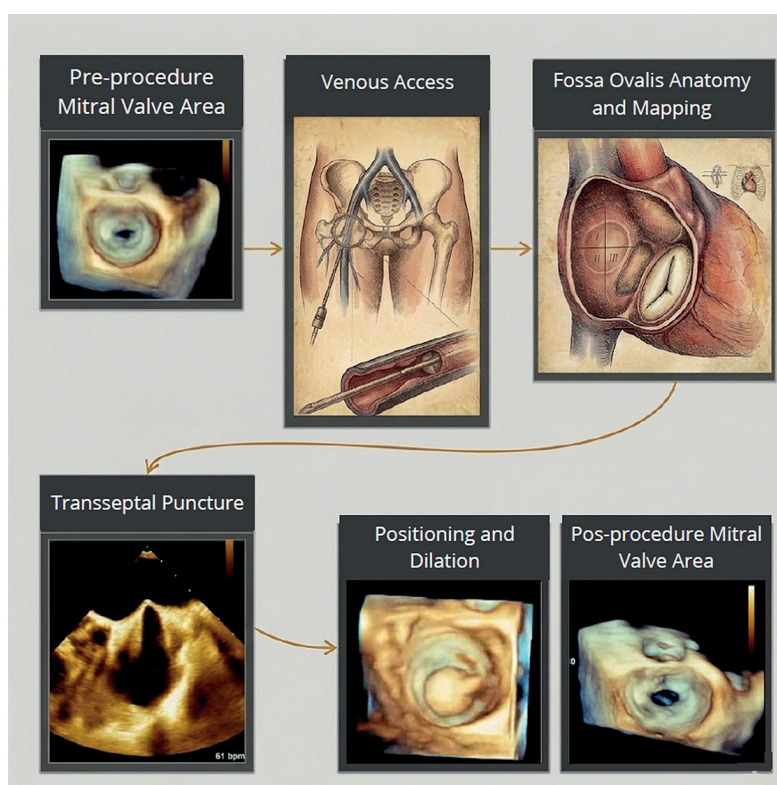
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Central Illustration: My Approach to Echocardiographic Guidance During Percutaneous Balloon Mitral Valvuloplasty



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Abstract

Rheumatic heart disease (RHD) remains a major global public health challenge because of its substantial morbidity and mortality, predominantly affecting the mitral valve. Although its prevalence is higher in developing countries, the disease continues to be diagnosed, albeit less frequently, in developed nations. Percutaneous balloon mitral valvuloplasty (PBMV) has become a highly effective therapeutic option for appropriately selected patients, with its technical and clinical success being strongly dependent on careful candidate selection. This article reviews the key aspects of

PBMV, ranging from the echocardiographic criteria used for patient selection to intraprocedural monitoring using transesophageal echocardiography (TEE).

Introduction

Rheumatic heart disease (RHD) remains one of the leading causes of cardiovascular disease worldwide and is considered the second leading cause of cardiovascular morbidity and mortality, surpassed only by atherosclerotic cardiovascular disease.¹ The prevalence of RHD remains high in developing countries; in Brazil and India, for example, it is estimated at 7 and 6 cases per 1,000 school-aged children, respectively. According to the Brazilian Institute of Geography and Statistics, approximately 10 million episodes of pharyngotonsillitis occur annually in Brazil, resulting in an estimated 30,000 new cases of acute rheumatic fever.^{2,3} Globally, approximately 30 million children and young adults are estimated to be living with the chronic form of the disease. In contrast, the incidence in developed countries is substantially lower, ranging from 0.1 to 0.4 cases per 1,000 school-aged children, as reported in the United States.⁴

In Brazil, the lack of effective rheumatic fever prevention programs places a substantial burden on the public healthcare system. This gap in care facilitates the progression to chronic valvular disease, among which mitral stenosis (MS) is the most common manifestation. Patients with severe symptomatic MS have a formal indication for intervention, which may be performed using either a percutaneous or a surgical approach.³

Historically, before the advent of percutaneous techniques, surgical commissurotomy was the standard treatment for MS. Initially, the procedure consisted of digital commissurotomy, in which the surgeon used their fingers to separate the fused valvular commissures. Subsequently, technical refinements led to the introduction of a mechanical dilator through the surgical incision, allowing more controlled dilation of the mitral valve. Closed surgical commissurotomy, introduced in the 1940s, was gradually replaced by open-heart surgery between the late 1960s and early 1970s, driven by the development of cardiopulmonary bypass. In 1982, Kanji Inoue performed the first percutaneous balloon mitral valvuloplasty (PBMV), with the original description published in 1984.^{5,6} Although alternative techniques, such as the double-balloon approach, were also developed, the Inoue balloon became the device of choice. When appropriately indicated, PBMV provides efficacy and long-term durability comparable to those of surgical commissurotomy, resulting in sustained hemodynamic and clinical improvement in both the short and long term, with an overall mortality rate of approximately 1%.⁷

Although the devices used in PBMV, such as balloon catheters, have undergone relatively modest technological changes over the past four decades, advances in cardiac imaging have profoundly transformed the procedure. Transesophageal echocardiography (TEE), particularly following the introduction of 3D imaging, has assumed a pivotal role. The high-quality images provided by TEE, combined with the expertise of the interventional

cardiologist, have made PBMV both safer and more effective. In the catheterization laboratory, the echocardiographer plays a crucial role, particularly in guiding transseptal puncture, thereby improving anatomical precision and reducing the risks associated with one of the most critical steps of the procedure.⁸

Preprocedural assessment and planning for PBMV

Appropriate patient selection for the procedure

TEE plays a pivotal role in the diagnosis, anatomical stratification, and careful selection of patients eligible for PBMV. The primary indications for the procedure include patients with severe MS and favorable valve anatomy (Class I, Level of Evidence B) as well as symptomatic patients with severe MS who are at high surgical risk (Class I, Level of Evidence C), provided that no thrombus is present in the left atrium (LA) or left atrial appendage (LAA).⁹

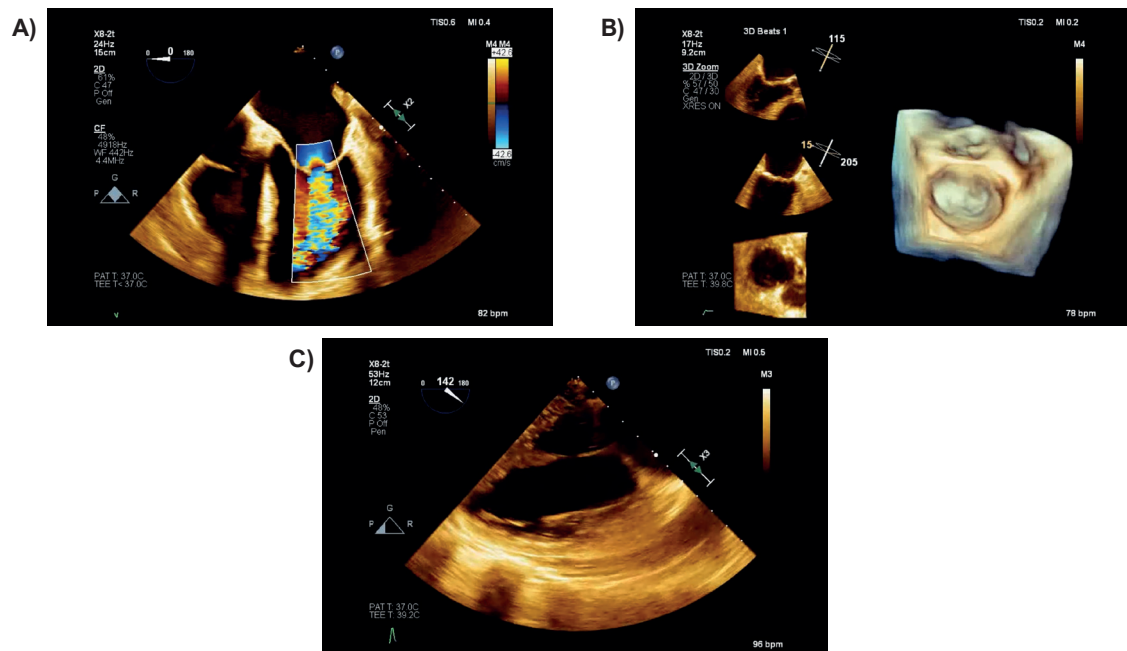
PBMV is also a safe, effective therapeutic option for pregnant women with severe MS and favorable valve anatomy, preferably after the 24th week of gestation. When performed with appropriate radiation protection, including lead shielding and minimal radiation exposure, the procedure is associated with low maternal and fetal morbidity and mortality.⁹

In contrast, mitral valve degeneration secondary to mitral annular calcification is not an indication for PBMV, as its underlying pathophysiology does not involve commissural fusion.

A systematic assessment of mitral valve anatomy and accurate measurement of the mitral valve area (MVA) constitute the cornerstone of PBMV indication. Currently, severe MS is defined based on MVA measurement, obtained using quantitative methods with 2D TEE or, more accurately, by direct planimetry with 3D TEE.¹⁰ Compared with the 2D technique, 3D planimetry provides greater accuracy and reproducibility by allowing more precise delineation of the valve orifice and complete visualization of the leaflets and commissures¹¹ (Video 1; Figure 1).

The anatomical evaluation should include a detailed assessment of leaflet morphology, including the degree of thickening and the presence of calcification, as well as commissural morphology. Characterization of the extent and symmetry of commissural fusion and the distribution of calcification is essential, given that the mechanism of PBMV is based on the mechanical separation of fused commissures, thereby increasing the MVA. The severity and pattern of commissural fusion are directly associated with the risk of clinically significant mitral regurgitation (MR) following the procedure.¹⁰ 3D TEE has revolutionized this assessment by enabling direct, real-time evaluation of the commissures from a single volumetric acquisition of the mitral valve displayed from the LA perspective (surgeon's view) (Video 1B; Figure 1B).

Assessment of the subvalvular apparatus is also mandatory. Acquisition of the 142° TEE imaging plane is recommended to quantify the degree of chordal thickening, fusion, and calcification (Video 1C; Figure 1D).



Video 1 – 1A) View: http://abcimaging.org/supplementary-material/2026/3903/ABCImag-2026-0085_AR_Video_1A.mp4. 1B) View: http://abcimaging.org/supplementary-material/2026/3903/ABCImag-2026-0085_AR_Video_1B.mp4. 1C) View: http://abcimaging.org/supplementary-material/2026/3903/ABCImag-2026-0085_AR_Video_1C.mp4.

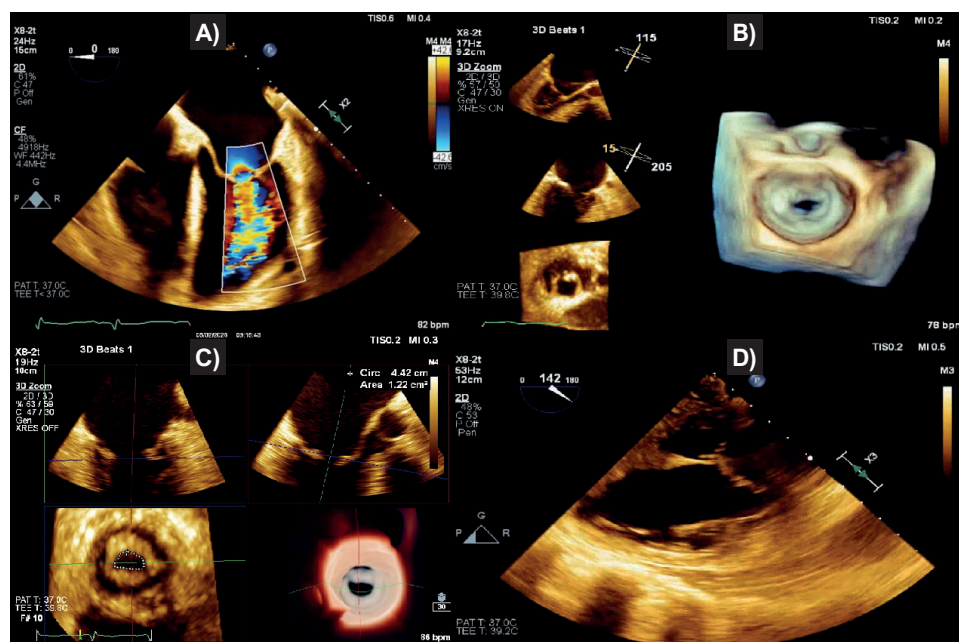


Figure 1 – Key echocardiographic findings in the preprocedural assessment for PBMV. A) Color Doppler demonstrating the PISA in a patient with isolated MS, without MR or valvular calcification. B) 3D reconstruction of the mitral valve from the LA perspective (surgeon's view), demonstrating nearly symmetrical commissural fusion. C) MVA measurement using multiplanar reconstruction (MultiVue) derived from the 3D dataset, yielding a value of 1.2 cm². D) Transgastric 142° view demonstrating the subvalvular apparatus and chordae tendineae for the assessment of thickening and calcification in patients with rheumatic involvement. LA: left atrium; MR: mitral regurgitation; MS: mitral stenosis; MVA: mitral valve area; PBMV: percutaneous balloon mitral valvuloplasty; PISA: proximal isovelocity surface area.

Several echocardiographic scoring systems have been proposed to standardize preprocedural assessment. The Wilkins score, introduced in 1988, remains the most widely used model and evaluates four structural components: leaflet mobility, leaflet thickening, calcification, and subvalvular involvement. However, this score has important limitations as it does not incorporate commissural anatomy and has limited predictive value for long-term outcomes, including the development of acute MR.¹⁰

To address such limitations, Nunes et al. proposed a more comprehensive model incorporating additional variables, including MVA, apical leaflet displacement, commissural area ratio, and subvalvular involvement.^{12, 13} Long-term outcomes after PBMV have also been shown to be strongly influenced by patient age and the quality of the immediate procedural result.¹⁴

Another key component of the preprocedural evaluation is the exclusion of contraindications to PBMV, particularly the presence of greater than mild MR. In such cases, MR severity should preferably be quantified using the quantitative methods recommended in current guidelines, rather than relying solely on qualitative parameters⁹ (Figure 2).

Other contraindications to the procedure include extensive or bicommissural mitral valve calcification, MVA > 1.5 cm², concomitant severe aortic valve disease, coronary artery disease requiring surgical revascularization, significant tricuspid stenosis or regurgitation associated with tricuspid annular dilatation, the presence of thrombus in the LA or LAA, and the absence of commissural fusion.⁹

Exclusion of LAA and left atrial thrombus

Screening for thrombus within the LA, particularly the LAA, is a mandatory component of the preprocedural

assessment. This evaluation should be performed both during the outpatient TEE examination, together with MVA measurement and application of the eligibility scores, and immediately before the intervention. The identification of an intracavitary thrombus constitutes an absolute contraindication to PBMV, requiring cancellation of the procedure and immediate initiation of anticoagulant therapy.^{9,15}

To optimize LAA assessment, the use of the biplane (X-plane) imaging modality is recommended, as it enables the simultaneous acquisition of orthogonal planes and a more comprehensive evaluation of the structure, thereby increasing the sensitivity for thrombus detection (Video 2A).

In cases of diagnostic uncertainty, particularly when differentiating thrombus from sludge and imaging artifacts, ultrasound enhancing agents (UEAs) may be used. Although dedicated software for myocardial perfusion analysis with UEAs is not yet available for TEE, current guidelines recommend their use by adapting image acquisition settings through reduction of the mechanical index (MI < 0.3). Thrombi are characterized by the absence of UEA enhancement. In contrast, sludge, a condition reflecting blood stasis and a high thromboembolic potential, demonstrates complete LAA opacification, although with delayed contrast filling consistent with reduced LAA emptying velocities. Conversely, isolated spontaneous echocardiographic contrast is characterized by rapid and homogeneous opacification of the LAA following UEA administration.¹⁶

Once an LAA thrombus has been confirmed by TEE, full anticoagulation with a vitamin K antagonist, preferably warfarin, is recommended (Class I). The recommended duration of anticoagulation before repeat echocardiographic assessment varies among guidelines and published studies,

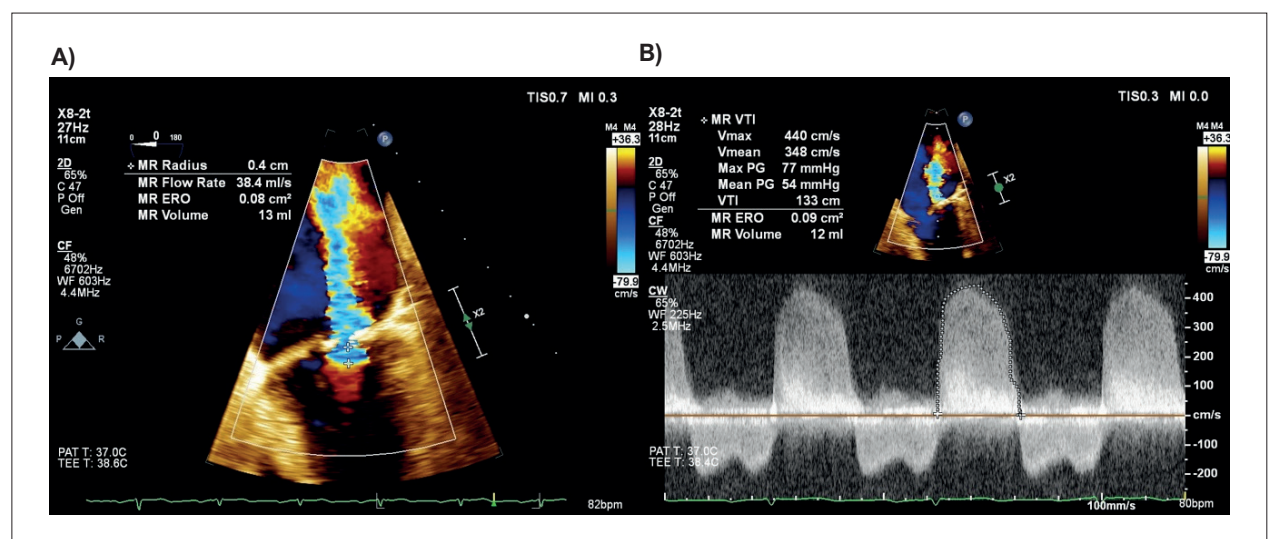
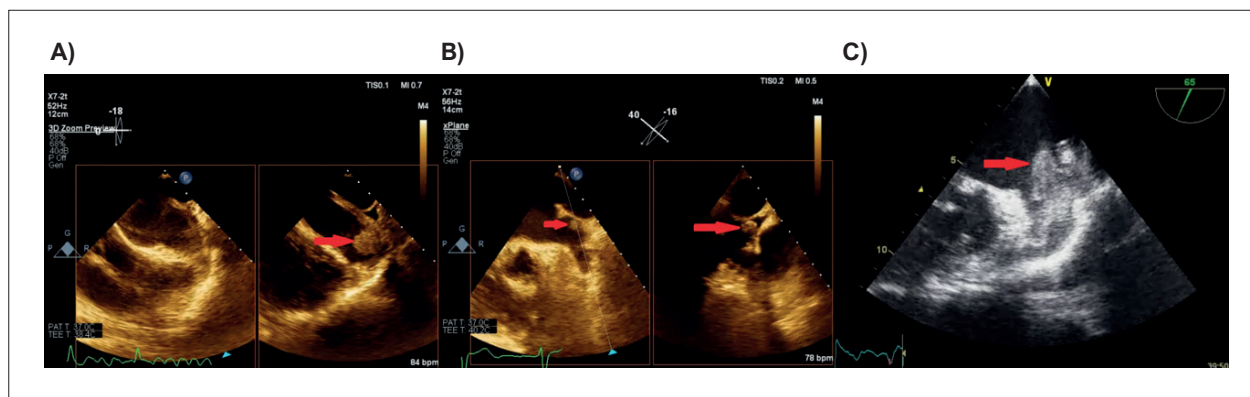


Figure 2 – Echocardiographic quantification of MR before PBMV. A) Quantification of MR using the PISA method. B) Quantification of MR using continuous-wave Doppler of the regurgitant jet, allowing calculation of the EROA and RV. The measured values (EROA = 0.09 cm² and RV = 12 mL) are consistent with mild MR. EROA: effective regurgitant orifice area; MR: mitral regurgitation; PBMV: percutaneous balloon mitral valvuloplasty; PISA: proximal isovelocity surface area; RV: regurgitant volume.



Video 2 – Different locations of thrombi within the LAA. A) Biplane (X-plane) TEE demonstrating a thrombus (red arrow) located within the body of the LAA. View: http://abcimaging.org/supplementary-material/2026/3903/ABCImag-2026-0085_AR_Video_2A.mp4. B) Example of a thrombus (red arrow) located at the LAA ostium, demonstrated using biplane (X-plane) imaging. View: http://abcimaging.org/supplementary-material/2026/3903/ABCImag-2026-0085_AR_Video_2B.mp4. C) Large thrombus (red arrow) involving both the body and the ostium of the LAA. View: http://abcimaging.org/supplementary-material/2026/3903/ABCImag-2026-0085_AR_Video_2C.mp4. LAA: left atrial appendage; TEE: transesophageal echocardiography.

generally ranging from 1 to 3 months. However, the therapeutic response is heterogeneous. Recent evidence has demonstrated that LAA morphology and thrombus location are important predictors of thrombus resolution. Cauliflower and chicken-wing morphologies, particularly when associated with thrombi located in the body or base of the LAA, are associated with a lower likelihood of resolution following anticoagulation. In contrast, cactus morphology and thrombi confined to the apical portion of the LAA are associated with higher rates of complete resolution within 3 months.^{17,18}

Assessment of interatrial septal anatomy

A thorough understanding of interatrial septal (IAS) anatomy is essential for the success and safety of transseptal puncture, a critical step in PBMV. First described in 1959, the transseptal puncture technique has become widely adopted with the expansion of percutaneous structural heart interventions, including PBMV. For this procedure, the ideal puncture site is the posteroinferior portion of the fossa ovalis (Figure 3).

TEE is indispensable for guiding transseptal puncture, reducing the risk of potentially serious complications, such as inadvertent perforation of the aortic root.²⁰

To ensure accurate needle positioning, the bicaval view (typically between 90° and 110°), combined with the biplane (X-plane) imaging modality, is particularly useful. This approach allows simultaneous visualization of the IAS and the ascending aorta in the short-axis view, providing the interventional cardiologist with anatomical landmarks that help maintain the needle-catheter assembly at a safe distance from this adjacent vascular structure²⁰⁻²² (Video 3A; Figure 4A).

During this stage, the echocardiographer should identify anatomical variations that may increase the complexity of transseptal puncture, such as a prominent Eustachian valve

or an IAS aneurysm. In the presence of an IAS aneurysm, excessive septal mobility may create the false impression that the needle has already entered the LA. However, fluoroscopy demonstrates that the needle remains within the right atrium, without complete traversal of the IAS.

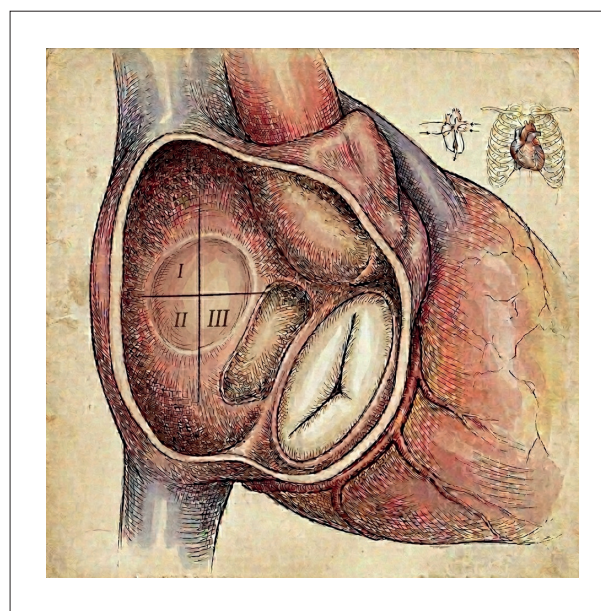
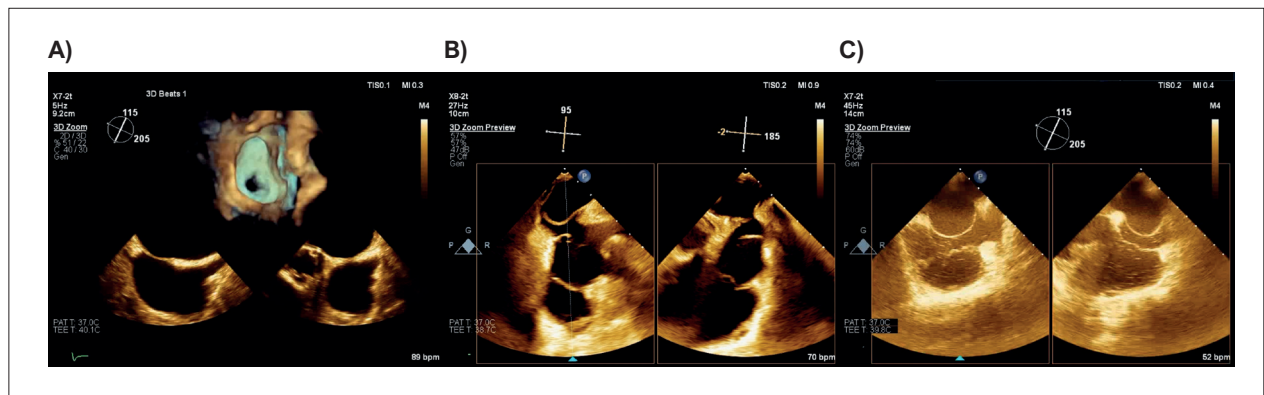


Figure 3 – Anatomy of the IAS and the principal transseptal puncture sites. Region I corresponds to the posterosuperior portion of the fossa ovalis and is preferentially used for procedures such as transcatheter mitral valve repair (MitraClip) and closure of paravalvular leaks. Region II corresponds to the posteroinferior portion of the fossa ovalis and is considered the ideal site for transseptal puncture during PBMV. Region III corresponds to the anteroinferior portion of the fossa ovalis and is typically used for pulmonary vein isolation procedures. IAS: interatrial septum; PBMV: percutaneous balloon mitral valvuloplasty.



Video 3 – 3A) View: http://abcimaging.org/supplementary-material/2026/3903/ABCImag-2026-0085_AR_Video_3A.mp4. **3B)** View: http://abcimaging.org/supplementary-material/2026/3903/ABCImag-2026-0085_AR_Video_3B.mp4. **3C)** View: http://abcimaging.org/supplementary-material/2026/3903/ABCImag-2026-0085_AR_Video_3C.mp4.

Identification of a patent foramen ovale (PFO) is another important aspect of the preprocedural assessment. Although its presence may complicate transseptal puncture, a PFO may be used as an access route to the LA when this is the sole objective of the procedure. In contrast, in interventions such as MitraClip® implantation and percutaneous LAA closure, its use is not recommended, as its marked mobility and anatomical location frequently result in suboptimal positioning of the transseptal system²¹ (Video 3A; Video 3B; Figure 4).

Selection of the appropriate balloon size

Selection of the appropriate Inoue balloon size is a critical step in PBMV, as an inappropriate device size may result in inadequate commissural splitting or injury to the leaflets and subvalvular apparatus, leading to severe MR requiring surgical treatment. Traditionally, balloon diameter is estimated using the following height-based formula:

$$\text{Balloon diameter (mm)} = \text{height (cm)} / 10 + 10$$

However, the lack of a linear relationship between patient height and MVA must be emphasised^{24,25} (Figure 5A-C).

As an alternative to height-based formulas, balloon catheter size can be individualized using TEE. This approach is based on measurement of the mitral annular diameter in the apical four-chamber and two-chamber views, preferably during midsystole or end-systole. From an anatomical standpoint, the measurement obtained in the apical two-chamber view is particularly relevant because it corresponds to the largest intercommissural diameter of the mitral valve, providing a more reliable parameter for device selection and reducing the risk of overdilatation and severe MR.^{26,27}

Inoue balloons are available in different diameters, and initial selection may be guided by patient height:

- 24 mm balloon: dilation range of 20–24 mm; recommended for patients with a height ≤ 140 cm.

- 26 mm balloon: dilation range of 22–26 mm; recommended for patients with a height ≤ 160 cm.
- 28 mm balloon: dilation range of 24–28 mm; recommended for patients with a height of 160–180 cm.
- 30 mm balloon: dilation range of 26–30 mm; recommended for patients with a height > 180 cm.

Procedure

Objective

Successful PBMV is defined as achievement of an MVA > 1.5 cm² without induction of moderate or severe MR (grade > 2+). Achieving this outcome requires the echocardiographer to have a detailed understanding of all procedural steps and to maintain continuous communication with the interventional cardiologist throughout the procedure (Central Illustration).^{14,26}

Procedural steps

Step 1 – Image-guided transseptal puncture

The first step of PBMV is transseptal puncture, performed via femoral venous access. Using the biplane (X-plane) imaging modality in the bicaval TEE view, the echocardiographer guides the interventional cardiologist to puncture the posteroinferior portion of the IAS (Video 4A-B; Figure 6A-B). This puncture site is critical because it provides a safe distance from the aortic root, an adequate working height within the LA, and coaxial alignment of the delivery system with the mitral valve.

A pigtail catheter may be positioned in the aortic root to facilitate determination of the optimal puncture height, thereby reducing the risk of inadvertent aortic perforation. Subsequently, after being repositioned in the left ventricle (LV), the same catheter can be used to measure the transmitral pressure gradient following PBMV^{7,26} (Figure 6C).

Before transseptal puncture, the echocardiographer should identify and communicate any anatomical variations that may interfere with the procedure, such as an IAS aneurysm, PFO, or a prominent Eustachian valve. Successful traversal of the IAS is confirmed by visualization of the characteristic tenting of the fossa ovalis at the intended puncture site²⁰ (Video 4B; Figure 6B).

After successful transseptal puncture, the Inoue guidewire, featuring a pigtail-shaped distal tip, is advanced into the LA. The dilator is then introduced, followed by sequential advancement of the Inoue balloon across the IAS, minimizing the risk of injury to adjacent cardiac structures^{6,27} (Video 5A-B; Figure 7A-B).

Step 2 – Introduction of the balloon delivery system

After the appropriate balloon size has been selected, the Inoue balloon is prepared and assembled. The IAS is then

dilated using the 14-Fr rigid dilator included in the Inoue system, allowing advancement of the balloon into the LA^{6,27} (Video 5A-F; Figure 7).

Step 3 – Valve dilation and immediate echocardiographic assessment

Inflation of the Inoue balloon is performed in three sequential stages. Using a mixture of saline and iodinated contrast to increase radiopacity, the distal portion of the balloon is inflated first, followed by the proximal portion and, finally, the balloon waist (Video 5C-E; Figure 8C-E). The balloon waist remains positioned at the level of the mitral valve and represents the region of greatest radial force, responsible for separating the fused commissures.^{7,27}

More specifically, once the Inoue balloon has been positioned within the LA, approximately 2 mL of the saline-

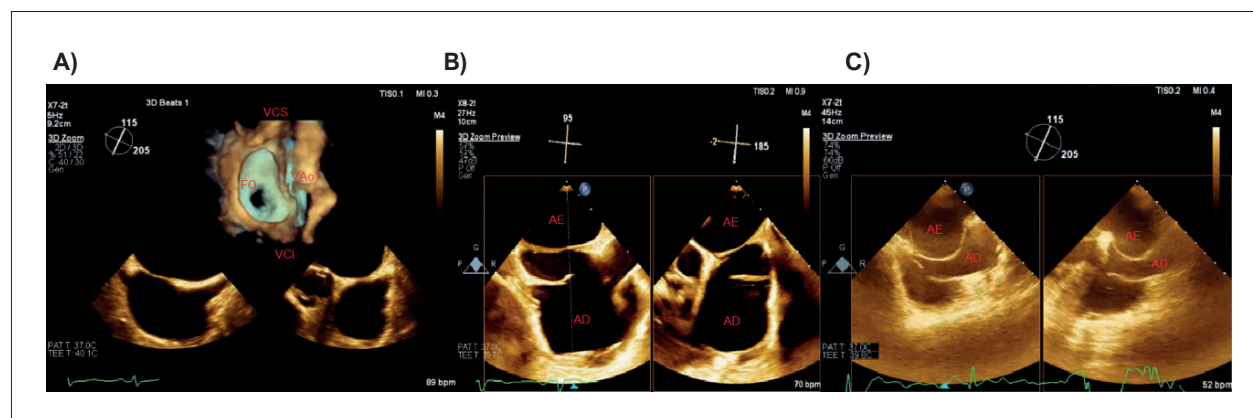


Figure 4 – Anatomical features of the IAS relevant to transseptal puncture. A) 3D reconstruction of the IAS obtained using the 3D Zoom acquisition mode from the RA perspective, demonstrating the normal anatomy of the fossa ovalis, represented by the dropout, as well as the AV, SVC, and IVC. B) Redundant Eustachian valve, an anatomical feature that may complicate transseptal puncture. C) IAS aneurysm, an important anatomical variant that should be identified before the procedure because it increases the technical complexity of transseptal puncture. AV: aortic valve; IAS: interatrial septum; IVC: inferior vena cava; RA: right atrium; SVC: superior vena cava.

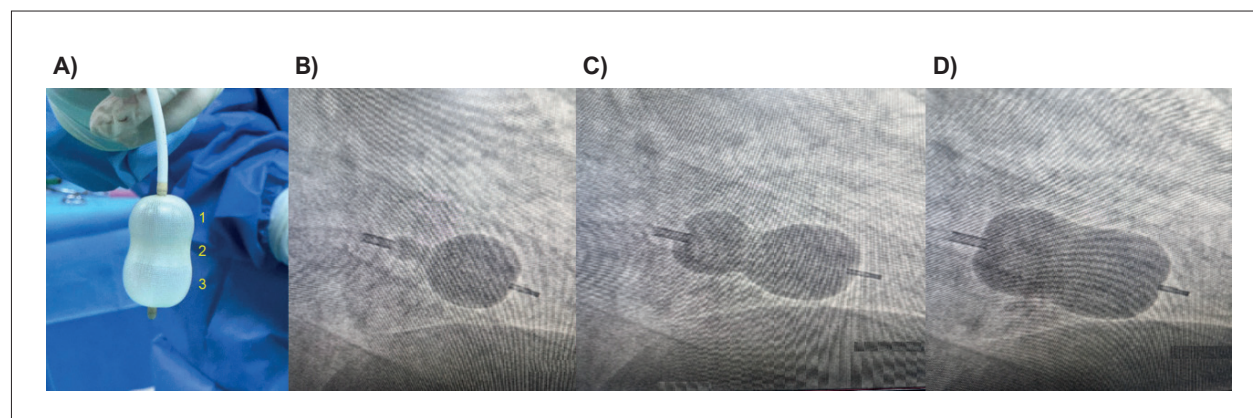


Figure 5 – Structure and inflation sequence of the Inoue balloon. A) Inoue balloon showing the proximal segment (1), the waist (2), and the distal segment (3). The waist corresponds to the region of greatest radial force and is responsible for commissural splitting during PBMV. B-D) Balloon inflation sequence during the procedure: the distal segment is inflated first, followed by the proximal segment and, finally, the waist, thereby producing commissural splitting. PBMV: percutaneous balloon mitral valvuloplasty.

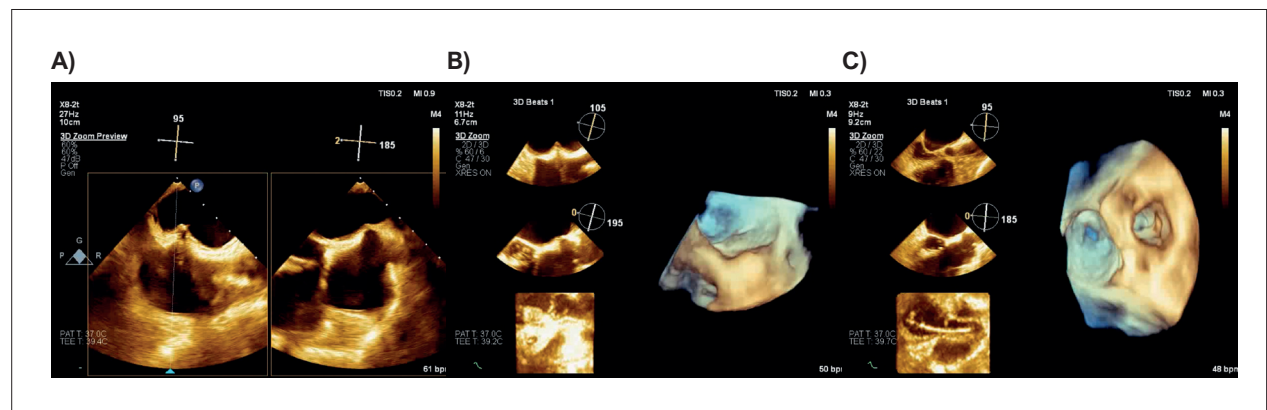
contrast mixture is initially injected to produce slight expansion of the distal balloon segment. This maneuver facilitates crossing of the mitral valve and reduces the risk of balloon entrapment within the chordae tendineae (Video 5D; Figure 7D).

After the balloon has crossed the mitral valve and has been positioned within the LV, the distal segment is fully inflated. At this stage, TEE guidance is essential. Failure of the distal segment to assume a fully spherical configuration should raise suspicion of significant resistance from the subvalvular apparatus or entrapment within the chordae tendineae. Once an appropriate spherical configuration has been confirmed, the balloon is gently retracted until the waist is positioned at the level of the mitral valve, after which full inflation is maintained for approximately 3-5 seconds (Video 5E; Figure 7E).

Following valve dilation, the balloon is repositioned in the LA, and immediate echocardiographic assessment of the

PBMV results is performed. This evaluation should include measurement of the MVA by 3D planimetry, assessment of valve and commissural morphology, characterization of the commissural splitting pattern (symmetric or asymmetric), detection of new or worsened MR, identification of its anatomical location, and evaluation for pericardial effusion, including its hemodynamic consequences. Although transmitral pressure gradients decrease immediately after the procedure, they should be interpreted with caution because they may increase during the subsequent hours as hemodynamic conditions normalize and the effects of anesthetic induction resolve. Therefore, the primary criterion for procedural success remains the achievement of an MVA $> 1.5 \text{ cm}^2$.^{26,21}

In routine practice, the initial balloon inflation is typically performed using a diameter 2-3 mm smaller than the



Video 4 – 4A) View: http://abcimaging.org/supplementary-material/2026/3903/ABCImag-2026-0085_AR_Video_4A.mp4. 4B) View: http://abcimaging.org/supplementary-material/2026/3903/ABCImag-2026-0085_AR_Video_4B.mp4. 4C) View: http://abcimaging.org/supplementary-material/2026/3903/ABCImag-2026-0085_AR_Video_4C.mp4.

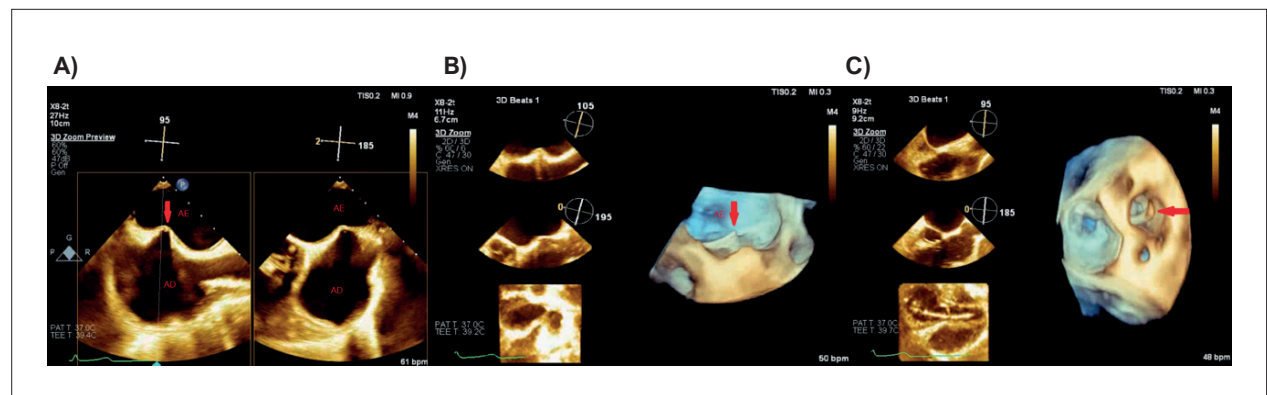
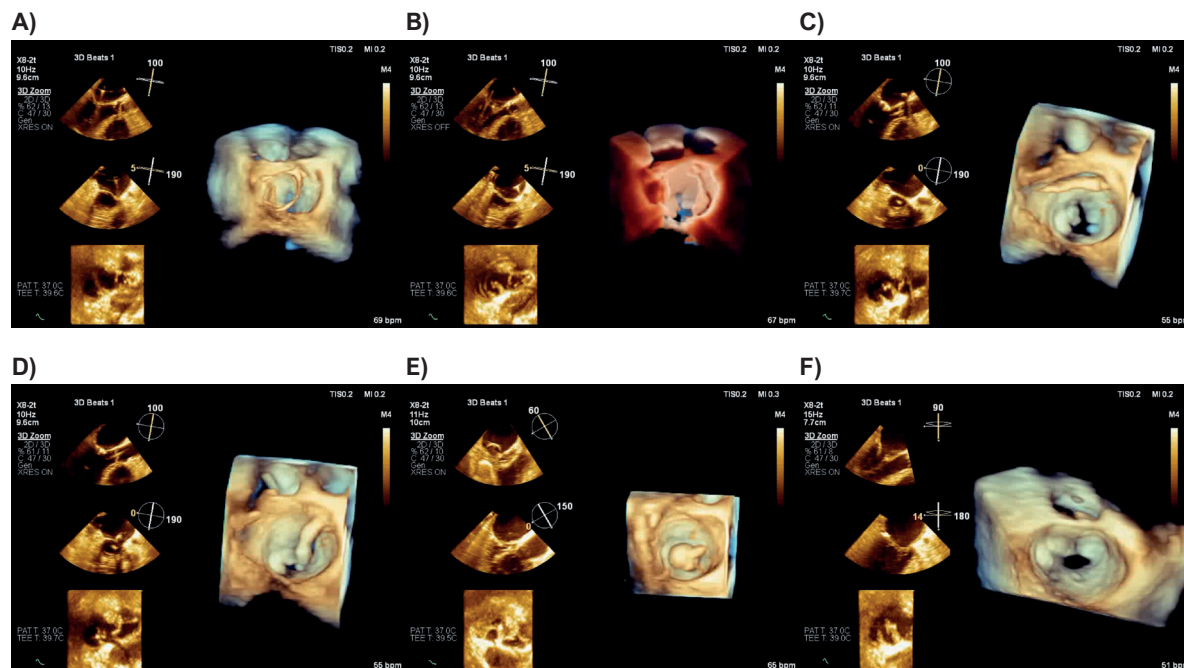


Figure 6 – Echocardiographic guidance of transseptal puncture during PBMV. A) Bicaval view combined with the biplane (X-plane) imaging mode, allowing simultaneous visualization of the IAS and the AA in orthogonal planes. This approach assists the interventional cardiologist in directing the puncture toward the posteroinferior portion of the IAS, away from the AA and toward the IVC (red arrow). B) 3D reconstruction (3D Zoom) demonstrating tenting of the IAS caused by the transseptal needle immediately before septal traversal (red arrow). C) 3D reconstruction (3D Zoom) demonstrating the pigtail catheter positioned in the AA (red arrow), serving as an anatomical landmark during transseptal puncture. AA: ascending aorta; IAS: interatrial septum; IVC: inferior vena cava; PBMV: percutaneous balloon mitral valvuloplasty.



Video 5 – 5A) View: http://abcimaging.org/supplementary-material/2026/3903/ABCIImag-2026-0085_AR_Video_5A.mp4. 5B) View: http://abcimaging.org/supplementary-material/2026/3903/ABCIImag-2026-0085_AR_Video_5B.mp4. 5C) View: http://abcimaging.org/supplementary-material/2026/3903/ABCIImag-2026-0085_AR_Video_5C.mp4. 5D) View: http://abcimaging.org/supplementary-material/2026/3903/ABCIImag-2026-0085_AR_Video_5D.mp4. 5E) View: http://abcimaging.org/supplementary-material/2026/3903/ABCIImag-2026-0085_AR_Video_5E.mp4. 5F) View: http://abcimaging.org/supplementary-material/2026/3903/ABCIImag-2026-0085_AR_Video_5F.mp4.

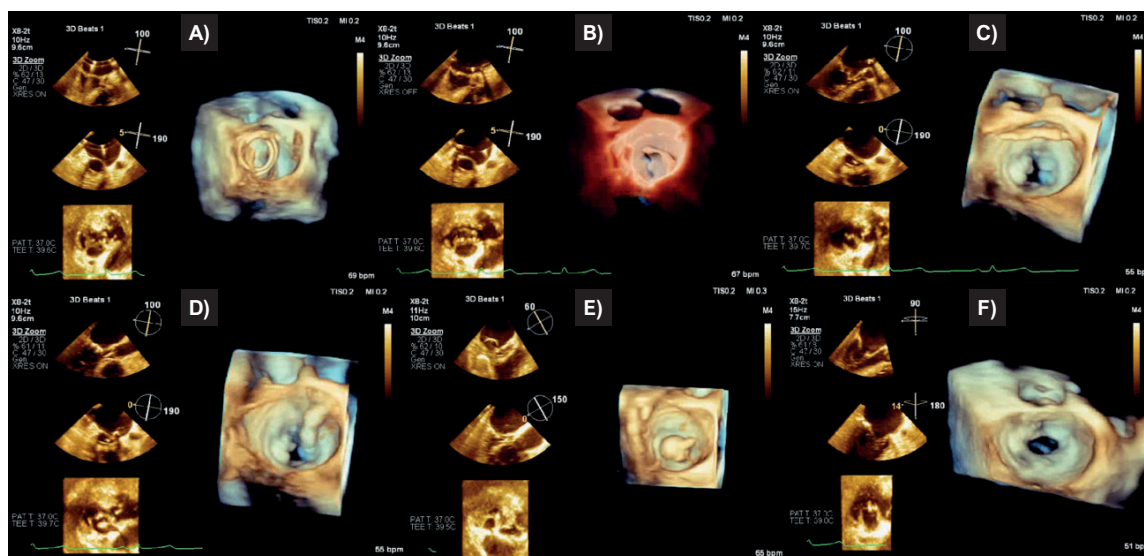


Figure 8 – Steps of Inoue balloon advancement and positioning during PBMV. A) Inoue guidewire with a pigtail-shaped distal tip designed to minimize the risk of LA injury. B) Withdrawal of the guidewire after positioning the Inoue balloon within the LA. C) Advancement of the balloon system toward the mitral valve. D) Positioning of the Inoue balloon with the waist at the level of the mitral valve. E) Inflation of the proximal segment of the balloon within the LA. F) Final appearance of the mitral valve after PBMV, demonstrating an increase in MVA compared with Figure 1B. LA: left atrium; MVA: mitral valve area; PBMV: percutaneous balloon mitral valvuloplasty.

patient's estimated final balloon diameter. Two or three additional inflations are then performed with progressive increases in balloon volume until the planned diameter is reached, while MR severity is reassessed after each inflation. The development of new or significant worsening of MR constitutes an indication for immediate termination of the procedure, and additional inflations with larger balloon volumes are not recommended.^{20,27}

Significant MR following PBMV may occur in up to 15% of patients, depending on the diagnostic criteria adopted. According to its anatomical location, MR can be classified into four patterns:

- Isolated commissural: 34.4% of cases.
- Commissural MR associated with posterior leaflet involvement: 25.0% of cases.
- Central MR resulting from extensive valve opening: 17.0% of cases.
- Central MR secondary to rupture or flail of the A2/P2 scallops: 23.4% of cases.²⁸

Acute MR is one of the most serious complications of PBMV and may result from inadequate commissural splitting, leaflet perforation, or papillary muscle rupture, frequently requiring surgical intervention. On TEE, the regurgitant jet is often eccentric, potentially leading to underestimation of MR severity. Furthermore, it is important to recognize that the criteria used to quantify chronic MR should not be applied to the assessment of acute MR.¹⁴

The most accurate measurement of MVA is obtained by direct planimetry using 3D TEE. Pressure half-time-derived MVA should not be used immediately after PBMV because acute changes in atrial and ventricular compliance compromise its accuracy. Accordingly, this method becomes more reliable approximately 48-72 hours after the procedure.^{14,27,28}

At the end of the intervention, the echocardiographer monitors balloon withdrawal to exclude iatrogenic injury and performs a repeat assessment of the IAS to identify residual atrial septal defects resulting from transseptal puncture as well as the presence of pericardial effusion. Small IAS defects with left-to-right shunting are frequently detected by TEE immediately after PBMV and, in most cases, decrease in size progressively or close spontaneously within 6-12 months. In contrast, right-to-left shunting is generally associated with significant pulmonary hypertension and may persist temporarily until pulmonary pressures decline following the procedure.^{7,14,27-29}

Outcomes

Immediate procedural success rates following PBMV are high, exceeding 90% when patients are appropriately selected. Echocardiographic and hemodynamic success is classically defined as the achievement of a final MVA ≥ 1.5 cm² in the absence of moderate or severe MR (grade ≥ 2 +).^{11,34} Procedure-related mortality is remarkably low (0%-3%).⁸

Improvements in MVA and hemodynamic status are generally sustained in patients with favorable valve anatomy, particularly younger individuals. In this subgroup, event-

free survival at 5, 10, and 15 years reaches 89%, 79%, and 43%, respectively.³¹⁻³³ In contrast, older patients or those with unfavorable valve anatomy, particularly in developed countries, experience less favorable long-term outcomes, with event-free survival rates of 56% at 10 years and 30% at 20 years.

The incidence of periprocedural complications has declined substantially over recent decades. This reduction reflects increasing operator experience, advances in cardiac imaging, and the continuous involvement of the echocardiographer throughout the procedure. The most common complications include cardiac tamponade (0.5%-12%) and embolic events, including stroke (0.5%-5%). Acute myocardial infarction occurs less frequently and is generally attributable to inadequate anticoagulation or embolization to the right coronary artery during the procedure. Structural complications include leaflet laceration, perforation of the cardiac chambers (LA or LV), and rupture of the subvalvular apparatus involving the chordae tendineae and papillary muscles. However, severe MR remains the most clinically significant complication, with an incidence of up to 15%.^{28,33}

Conclusion

Careful patient selection, combined with favorable valve anatomy, is the principal determinant of immediate procedural success and favorable long-term outcomes following PBMV. In this context, a thorough understanding of mitral valve anatomy, with particular attention to the commissures, together with objective assessment of MR severity, is essential for appropriate procedural planning and intraprocedural guidance.

The presence of the echocardiographer in the catheterization laboratory is essential for enhancing procedural safety, particularly during transseptal puncture guidance. Furthermore, immediate echocardiographic assessment after each balloon inflation allows evaluation of commissural splitting, measurement of the MVA, and early detection of new or worsening MR, the principal complication of PBMV.

In developing countries such as Brazil, where RHD remains highly prevalent, PBMV continues to play an established role in the management of rheumatic MS by relieving valvular obstruction, improving quality of life, and, in many cases, delaying the need for surgical intervention.

Author Contributions

Conception and design of the research: Gripp EA, Lourenço BN, Carestiato LR, Côrtes LA, Rabischoffsky A; acquisition of data: Gripp EA, Lourenço BN, Carestiato LR, Ribeiro ML, Rabischoffsky A; analysis and interpretation of the data: Gripp EA; writing of the manuscript: Gripp EA, Lourenço BN, Carestiato LR, Ribeiro ML, Côrtes LA, Rabischoffsky A; critical revision of the manuscript for intellectual content: Gripp EA, Lourenço BN, Ribeiro ML, Côrtes LA, Rabischoffsky A.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any thesis or dissertation work.

Ethics Approval and Consent to Participate

This article does not contain any studies with human participants or animals performed by any of the authors.

Use of Artificial Intelligence

During the preparation of this work, the authors used Gemini 1.5 to create an artistic representation of the fossa ovalis depicted in Figure 4 and the Central Illustration (atrial septal aneurysm and fossa ovalis). After using this tool, the authors reviewed and edited the content as necessary and take full responsibility for the content of the published article.

Availability of Research Data

The underlying content of the research text is contained within the manuscript.

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Biventricular Noncompaction Cardiomyopathy Associated With Neuropathy in a Young Patient: A Case Report

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Introduction

Ventricular hypertrabeculation, also known as ventricular noncompaction, is a myocardial phenotype characterized by excessive trabeculation and deep intertrabecular recesses caused by incomplete myocardial compaction during embryonic development. The earliest reported cases were associated with congenital heart defects, including ventricular outflow tract obstruction, complex cyanotic congenital heart disease, and coronary artery anomalies.^{1,2}

The clinical presentation is highly heterogeneous and may include heart failure (HF), arrhythmias, thromboembolic events, and sudden cardiac death. In addition to ventricular structural abnormalities, ventricular hypertrabeculation may be associated with cardiac conduction disorders, atrial arrhythmias, and functional valvular regurgitation (FVR) secondary to cardiac chamber dilatation, all of which contribute to greater clinical complexity and a poorer prognosis.³

Furthermore, ventricular hypertrabeculation is a well-recognized feature of several neuromuscular disorders, suggesting a shared genetic basis and a syndromic phenotype in a subset of patients. Diagnosis may be challenging because of its marked phenotypic variability and overlap with other cardiomyopathies. Cardiac magnetic resonance (CMR) plays a particularly important role in confirming the diagnosis and providing detailed anatomical characterization.⁴

We report the case of a young patient with biventricular noncompaction associated with significant valvular heart disease, cardiac conduction disease requiring permanent pacemaker implantation, who is undergoing investigation for an underlying neuromuscular disorder. The patient is enrolled in a study approved by the Human Research Ethics Committee of the Universidade do Estado do Amazonas (approval no. 7,108,530; CAAE no. 55200322.5.3009.516).

Keywords

Left Ventricular Hypertrophy; Mitral Valve Insufficiency; Case Reports

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Case report

A 21-year-old woman from the city of Tefé, state of Amazonas, Brazil, was referred to a specialized cardiomyopathy clinic with a diagnosis of biventricular noncompaction associated with severe mitral regurgitation (MR) and tricuspid regurgitation (TR) secondary to annular dilatation. Her medical history included permanent atrial fibrillation (AF) (CHA₂DS₂-VA score = 3; HAS-BLED score = 0), complete atrioventricular (AV) block with prior implantation of a dual-chamber permanent pacemaker, and a previous episode of compensated cardiogenic ascites. A neuromuscular disorder under investigation was the most relevant comorbidity.

Her clinical history revealed symptom onset during childhood, beginning with progressive ascites at 11 years of age. She was initially managed at a local health care facility but showed no satisfactory response to medical therapy. At that time, both cardiac and hepatic etiologies were considered, prompting referral to a tertiary referral center, where she remained hospitalized for approximately 3 months. Thereafter, outpatient follow-up was irregular, partly because it relied on telemedicine.

At 20 years of age, she experienced recurrent massive ascites refractory to diuretic therapy, with subsequent clinical improvement following evaluation at a private health care facility. At 21 years of age, she developed another episode of decompensation characterized by ascites and dyspnea, requiring hospitalization and referral to a tertiary care center. During this admission, the diagnosis of biventricular noncompaction cardiomyopathy was established.

On physical examination, the patient appeared underweight, with normal skin coloration, no cyanosis, and hypotension (blood pressure: 88/58 mmHg; heart rate: 71 bpm), without signs of peripheral congestion. Cardiac auscultation revealed a regular two-sound rhythm and a systolic murmur best heard at the pulmonary area. Pulmonary auscultation demonstrated normal vesicular breath sounds without adventitious findings, and no lower-extremity edema was present. Electrocardiography showed a junctional rhythm, extreme axis deviation, and left bundle branch block (Figure 1).

Transthoracic echocardiography demonstrated biatrial enlargement and mild eccentric left ventricular (LV) hypertrophy. Global LV systolic function was preserved (left ventricular ejection fraction [LVEF], 51%). Additional findings included myxomatous degeneration with prolapse

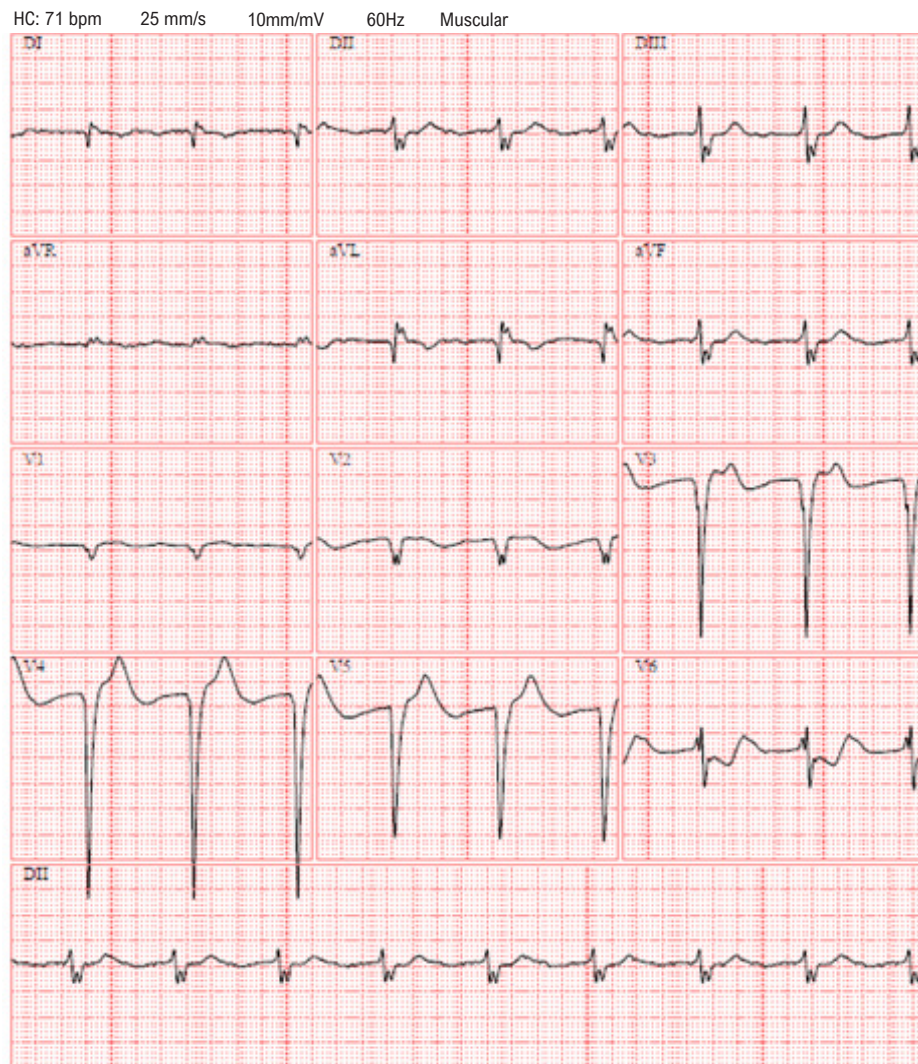


Figure 1 – Electrocardiogram demonstrating a junctional rhythm, extreme axis deviation, and left bundle branch block. HR: heart rate.

of the anterior mitral leaflet, resulting in severe MR, mild pulmonary hypertension, spontaneous echo contrast in the right atrium, and ventricular hypertrabeculation.

CMR demonstrated biventricular chamber enlargement (Figure 3), with indexed LV and right ventricular (RV) end-diastolic volumes of 110.33 mL/m² and 119.37 mL/m², respectively. Prominent LV myocardial trabeculation was observed, with a noncompacted-to-compacted myocardium ratio > 2.3, meeting the Petersen diagnostic criterion. LVEF was preserved (56%), whereas the RV exhibited systolic dysfunction (ejection fraction, 30%), accompanied by biatrial enlargement, functional MR, and a small pericardial effusion, without evidence of late gadolinium enhancement or intracardiac thrombi.

Neurological evaluation revealed a motor deficit syndrome involving all four limbs, muscle atrophy, and

findings suggestive of a neuromuscular disorder with probable X-linked inheritance. Emery-Dreifuss muscular dystrophy (EDMD) was considered the leading diagnostic hypothesis. As part of the etiological investigation, G-banded karyotyping was performed and demonstrated a normal female chromosomal complement without detectable abnormalities.

At 25 years of age, the patient underwent dual-chamber permanent pacemaker implantation because of complete AV block. At her most recent outpatient follow-up, she reported occasional palpitations but denied chest pain, dyspnea, or peripheral edema. She also reported good adherence to guideline-directed medical therapy, consisting of enalapril, carvedilol, dapagliflozin, furosemide, and spironolactone, together with anticoagulation with rivaroxaban and fluid restriction.

Case Report

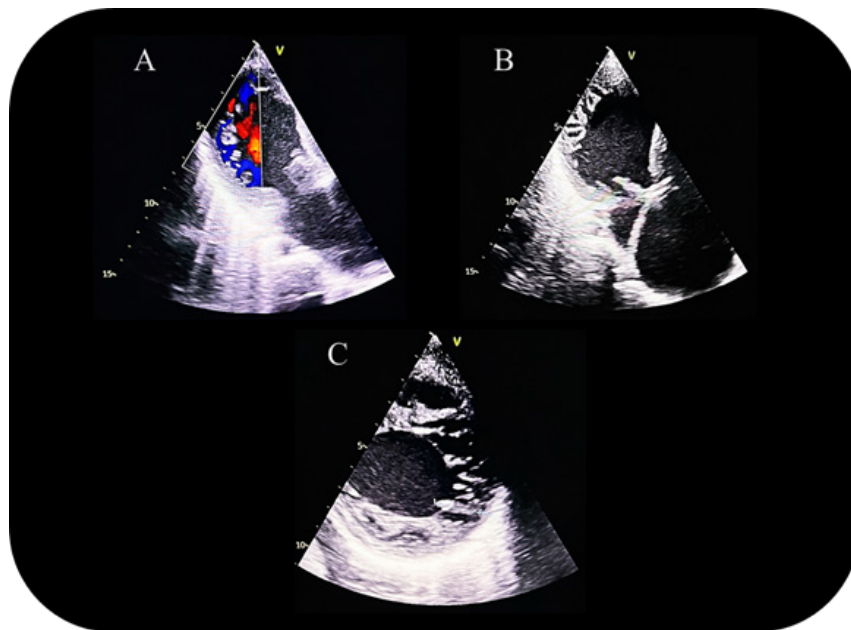


Figure 2 – Transthoracic echocardiography demonstrating hypertrabeculation of the RV free wall. A) Apical view with color Doppler imaging. B) Two-dimensional apical view demonstrating prominent trabeculations. C) Parasternal short-axis view demonstrating hypertrabeculation of the RV free wall. RV: right ventricle.

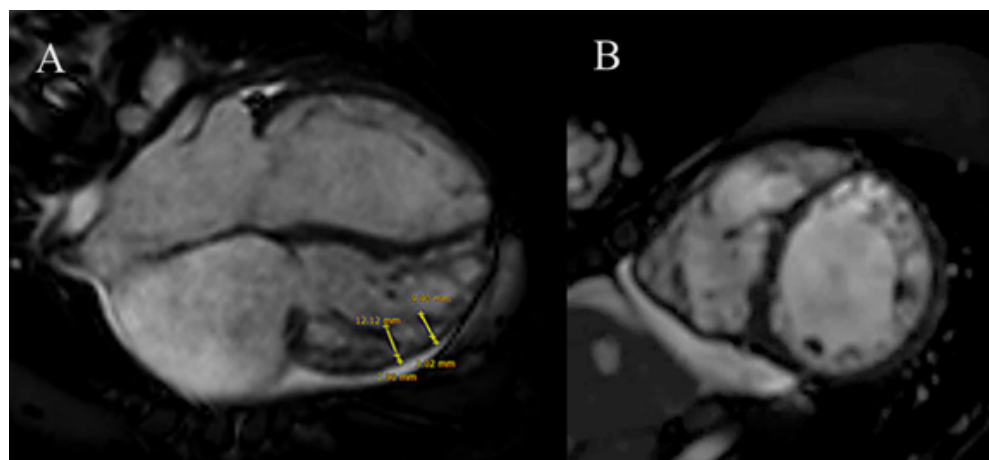


Figure 3 — CMR demonstrating ventricular hypertrabeculation. A) Four-chamber view demonstrating a noncompacted-to-compacted myocardium ratio of 4.17, exceeding the cutoff value of 2.3 established by the Petersen criterion. B) Short-axis view demonstrating prominent LV myocardial trabeculation.

Discussion

Ventricular hypertrabeculation predominantly affects the LV, whereas biventricular involvement is less common and is generally associated with greater clinical complexity and a higher incidence of adverse outcomes. In the present case, cardiac chamber dilatation, FVR, and evidence of RV

dysfunction underscore the phenotypic heterogeneity of the disease and the potential for a more severe clinical course when both ventricles are involved.^{5,6}

Cardiac chamber dilatation in ventricular hypertrabeculation may lead to FVR, particularly MR and TR, as observed in this patient. This mechanism is driven by

annular dilatation and distortion of ventricular geometry, contributing to worsening HF symptoms and an increased risk of clinical decompensation.⁶

Patients with ventricular hypertrabeculation have a high prevalence of arrhythmias and cardiac conduction abnormalities, including AF and advanced AV block. The need for permanent pacemaker implantation at a young age, together with permanent AF, highlights the arrhythmogenic potential of this condition and the impact of myocardial remodeling on the cardiac conduction system.^{7,8}

The American College of Medical Genetics and Genomics recommends genetic evaluation in patients with cardiomyopathies, particularly in the presence of early disease onset, an arrhythmic phenotype, or concomitant neuromuscular disorders.⁹ Ventricular hypertrabeculation has been associated with muscular dystrophies, myotonic dystrophy, EDMD, and mitochondrial myopathies. In the present case, the patient remains under etiological investigation for her neuromuscular disorder, and G-banded karyotyping has not identified any chromosomal abnormalities to date.¹⁰

Biventricular hypertrabeculation is a rare manifestation of the disease. Previous reports have described adults presenting with HF and a family history suggestive of cardiomyopathy, patients in whom the diagnosis was established only after CMR, and young individuals presenting with severe arrhythmias or initially noncardiac manifestations.¹¹⁻¹³ These findings highlight the marked phenotypic variability of biventricular involvement, its substantial arrhythmogenic potential, and the pivotal role of advanced cardiac imaging in establishing the diagnosis.

Conclusion

This case highlights the diagnostic complexity of biventricular hypertrabeculation and its association with neuromuscular manifestations, emphasizing the importance of a comprehensive etiological investigation and a multidisciplinary approach. Early recognition of the disease and follow-up at specialized centers are essential to optimize treatment, facilitate monitoring for disease-related complications, and expand our understanding of the clinical spectrum of this condition, particularly in

patients with neuromuscular disorders that remain under etiological investigation.

Author Contributions

Conception and design of the research: Gonçalo MO, Couceiro KN, Ferreira JMBB; acquisition of data: Gomes AAS, Monteiro MM, Cavalcante NB, Bezerra FA; analysis and interpretation of the data: Machado MA, Miranda DCC, Couceiro KN, Ferreira JMBB; writing of the manuscript: Gonçalo MO, Monteiro MM; critical revision of the manuscript for intellectual content: Couceiro KN, Ferreira JMBB.

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Study Association

This study is not associated with any thesis or dissertation work.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the Universidade do Estado do Amazonas under protocol number 7.106.271. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

Use of Artificial Intelligence

The authors did not use any artificial intelligence tools in the development of this work.

Availability of Research Data

The underlying content of the research text is contained within the manuscript.

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Coronary Artery Disease In A Rare Anatomical Scenario: Type IV Duplicated Left Anterior Descending Artery

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Introduction

Congenital coronary anomalies comprise a heterogeneous group of anatomical variations, most often identified incidentally during non-invasive imaging studies or invasive diagnostic and therapeutic procedures. Studies show that approximately 1.3% of individuals undergoing coronary angiography present some form of coronary anomaly.¹ Although most are considered benign, certain anomalies may be associated with myocardial ischemia, ventricular arrhythmias, and, in rare cases, sudden cardiac death. It is important to emphasize that coexistence with obstructive coronary artery disease (CAD) may amplify their clinical impact.

Among these variations, duplication of the left anterior descending (LAD) artery stands out due to its rarity and diagnostic relevance. According to the classification proposed by Spindola-Franco et al.² (Table 1), this anomaly is divided into four types based on the origin and course of the branches. In Type I, the most frequent form, the short and long LAD originate from the bifurcation of the main LAD artery; the short LAD artery follows the anterior interventricular groove and terminates early, whereas the long LAD artery runs parallel along the left ventricular surface before rejoining the distal groove. In Type II, the short and long LAD also arise from the bifurcation of the main LAD artery; however, the long LAD artery courses to the right of the anterior interventricular groove before reaching the apex. In Type III, the long LAD artery has an initial intramyocardial trajectory before emerging distally on the epicardial surface. Finally, in Type IV, the rarest type, a short LAD artery originates from the left coronary artery, while a long LAD artery arises anomalously from the right coronary artery (RCA) or its sinus of Valsalva.² This long branch follows an intraseptal course before emerging in the anterior interventricular groove and reaching the apex, occurring in approximately 0.2% of patients undergoing coronary angiography.³

Keywords

Coronary Artery Disease; Percutaneous Coronary Intervention; Drug-Eluting Stents; Interventional Ultrasonography

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In this context, we present the case of a patient who underwent percutaneous coronary intervention (PCI) for multivessel CAD, in whom a type IV LAD duplication was identified. This is a rare finding, with primarily diagnostic and prognostic relevance, illustrating the importance of accurately recognizing coronary anatomical variations during invasive evaluation.

Case Presentation

A 59-year-old female patient with a history of systemic arterial hypertension, type 2 diabetes mellitus, dyslipidemia, obesity, and chronic kidney disease. In December 2024, she experienced an acute myocardial infarction treated at another institution, where total occlusion of the RCA and the LAD artery was reported, in addition to a moderate lesion in the left circumflex artery (LCx). She underwent PCI with implantation of three drug-eluting stents in the RCA and one in the LCx in January 2025.

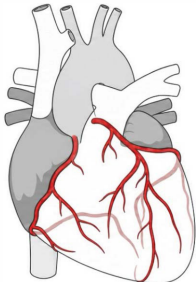
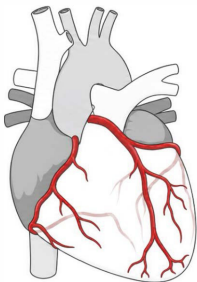
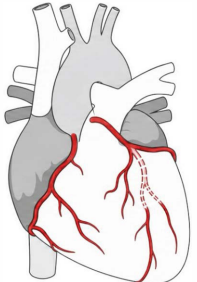
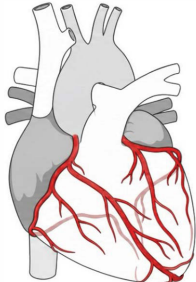
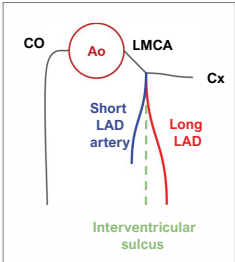
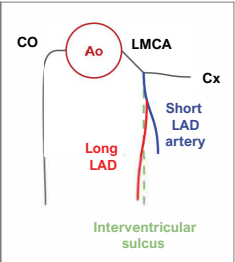
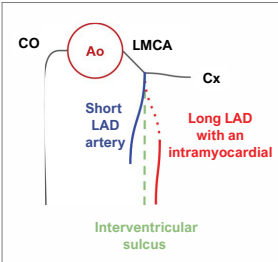
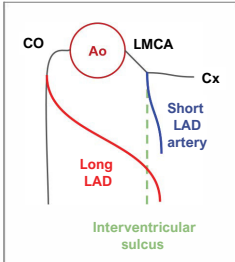
The initial echocardiogram showed preserved left ventricular ejection fraction (59%), eccentric hypertrophy, and mild hypokinesia of the inferior wall. Approximately three months after the intervention, the patient developed progressive dyspnea, orthopnea, and exertional angina (CCS functional class II). A repeat echocardiogram revealed a decrease in ejection fraction to 38%, akinesia of the inferior and inferoseptal walls, anteroseptal hypokinesia, and moderate mitral regurgitation.

Myocardial perfusion scintigraphy with dipyridamole demonstrated marked persistent hypoperfusion of the inferior wall and moderate transient hypoperfusion of the inferolateral wall, with an estimated ischemic burden of 11%. Given the persistence of symptoms and findings suggestive of ischemia, a new coronary angiography was performed at our institution. The examination revealed the RCA with overlapping stents, showing a moderate lesion in the proximal third extending to the beginning of the stent, followed by a 70% in-stent restenosis in the mid segment, and preserved stent results in the LCx (Figure 1).

During the procedure, an anomalous LAD originating from the right coronary sinus with a long course was identified – an artery not visualized in the previous angiographic study—without significant lesions (Figure 2).

Intracoronary ultrasound (IVUS) evaluation revealed underexpansion of the previously implanted stents in the proximal and mid segments of the RCA. Two new drug-eluting stents were implanted in the aforementioned segments, with good angiographic results and no complications. Adequate strut apposition and expansion were confirmed by IVUS (Figure 3).

Table 1 – Classification of Duplicated Left Anterior Descending Coronary Artery

				
				
Characteristics	Type I	Type II	Type III	Type IV
Origin of the short LAD artery	Bifurcation of the main LAD artery	Bifurcation of the main LAD artery	Left main coronary artery	Left main coronary artery
Origin of the long LAD artery	Bifurcation of the main LAD artery	Bifurcation of the main LAD artery	Left main coronary artery	RCA or right coronary sinus
Course of the long LAD	Epicardial, descending parallel to the short LAD artery in the anterior interventricular sulcus toward the apex	Epicardial, descending to the right of the anterior interventricular sulcus and returning to the distal anterior interventricular sulcus	Proximal intramyocardial (intraseptal); emerges in the distal anterior interventricular sulcus	Anômalo (intraseptal ou pré-pulmonar); alcança o sulco interventricular anterior distal
Frequency	More common	Uncommon	Rare	Very rare (~0.2%)

LAD: left anterior descending (artery); LMCA: left main coronary artery; RCA: right coronary; LCx: left circumflex artery.

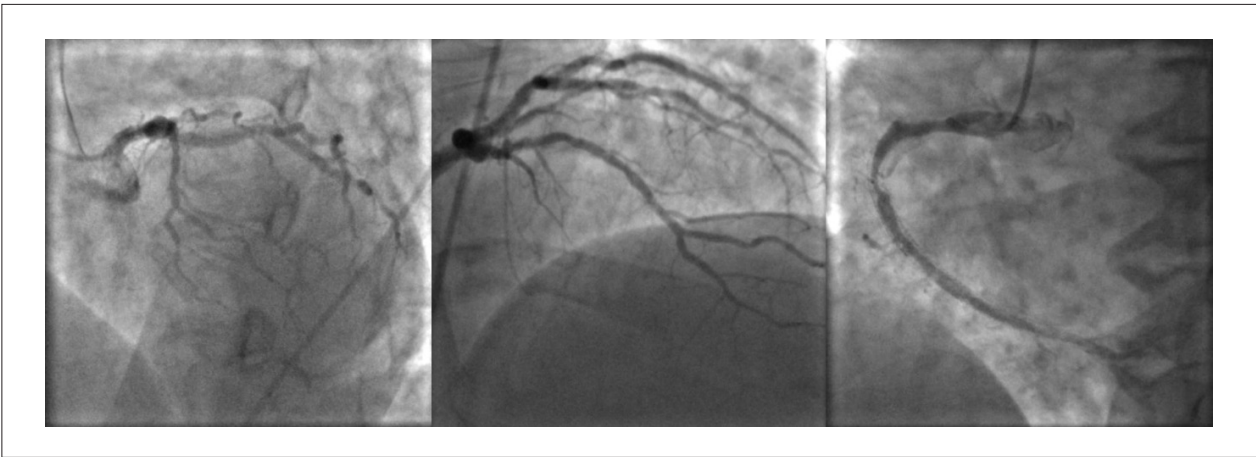


Figure 1 – Coronary angiography. Images in left anterior oblique cranial (A), right anterior oblique cranial (B), and left anterior oblique (C) projections: (A–B) visualization of the left main coronary artery, the short LAD artery, and the circumflex artery, with the previously implanted stent preserved; (C) visualization of the right coronary artery, showing a 50% lesion in the proximal third, a stent implanted from the proximal to the mid segment, and up to 70% in-stent restenosis in the mid segment.

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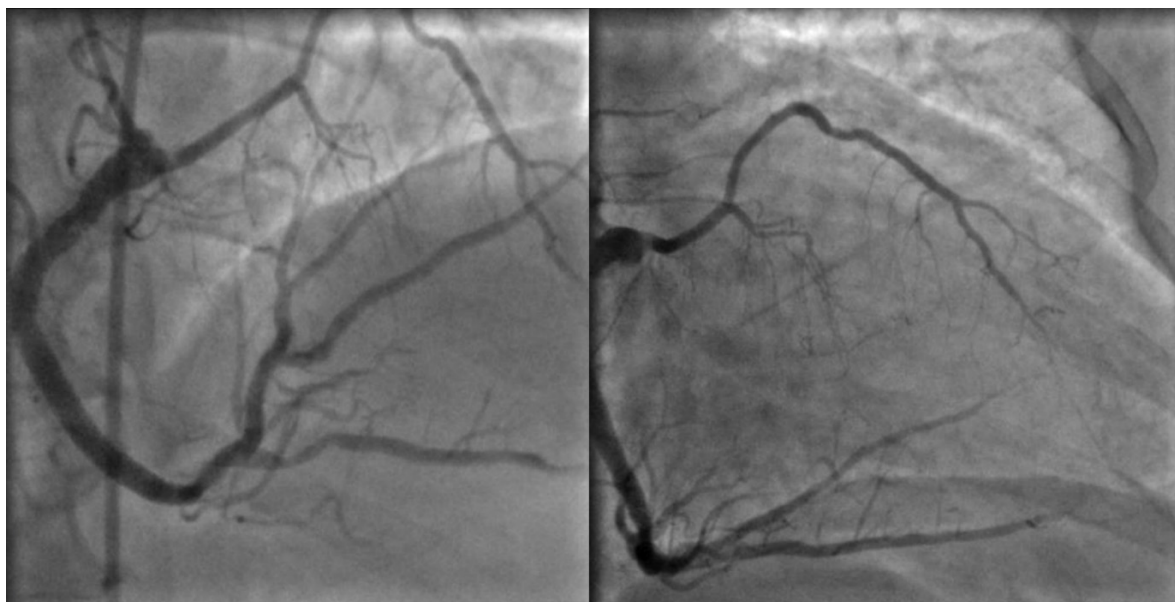


Figure 2 – Coronary angiography. Visualization of an anomalous LAD artery originating from the right coronary artery

To achieve a better understanding of the coronary anatomy, a coronary computed tomography angiography (CCTA) was performed, which confirmed the presence of a type IV dual LAD according to the Spindola-Franco classification. The examination demonstrated a short, thin vessel originating from the left main coronary artery and terminating before reaching the left ventricular apex, as well as a long vessel originating from the proximal third of the RCA, following an intraseptal course before emerging in the anterior interventricular groove and extending to the apex (Figure 4). The long LAD artery displayed a small calcified plaque in the mid segment, without significant obstruction, and no malignant courses were identified.

During outpatient follow-up, the patient remained on optimized medical therapy, including dual antiplatelet therapy for six months. Her clinical course was marked by complete remission of angina and significant improvement in heart failure symptoms, with only mild exertional dyspnea persisting during routine activities.

Discussion

Type IV LAD duplication is an extremely rare congenital anomaly, generally identified as an incidental finding on cardiac imaging. Its angiographic appearance may resemble unusual bifurcations or other anomalous courses on coronary angiography. In such cases, CCTA plays a fundamental role by characterizing the origin and course of the artery, allowing differentiation between typically benign variants — such as intraseptal, retroaortic, or prepulmonic courses — and those associated with a higher risk of arrhythmia and sudden cardiac death, particularly the interarterial course, in which the vessel passes between the aorta and the pulmonary artery.⁴

In the present case, the anomaly coexisted with multivessel CAD, in a clinical context suggestive of restenosis, later confirmed angiographically, along with significant ventricular dysfunction. This scenario is likely related to the extensive territory supplied by the dominant RCA, which exhibited significant in-stent obstructive disease, as well as to the anomalous origin of the LAD artery from the right coronary sinus.

The use of IVUS was essential to identify the mechanism of RCA restenosis and is recommended by national and international guidelines in this setting. The method demonstrated stent underexpansion, enabling differential diagnosis from other causes such as intimal hyperplasia or neoatherosclerosis. Additionally, intravascular imaging techniques assist in therapeutic planning for repeat intervention, defining the need for a new stent and determining its diameter and length. This strategy is crucial to reduce the need for repeat revascularization procedures and, consequently, major adverse cardiac events during follow-up.^{5,6}

It is worth emphasizing that the integration of non-invasive imaging methods (echocardiography, scintigraphy, and CCTA) with invasive techniques (angiography and IVUS) is central to the characterization and management of patients with CAD and coronary anomalies. In situations such as the one described, this combined approach allows identification of the mechanisms of restenosis after PCI and recognition of rare, detailed anatomical variants of the LAD, avoiding misinterpretation and guiding safer, individualized revascularization strategies.⁷

Conclusion

Type IV LAD artery duplication is a rare anatomical variant, generally asymptomatic and benign, whose clinical relevance increases when it coexists with CAD, as it may lead to misinterpretation on angiography and mimic occlusion of

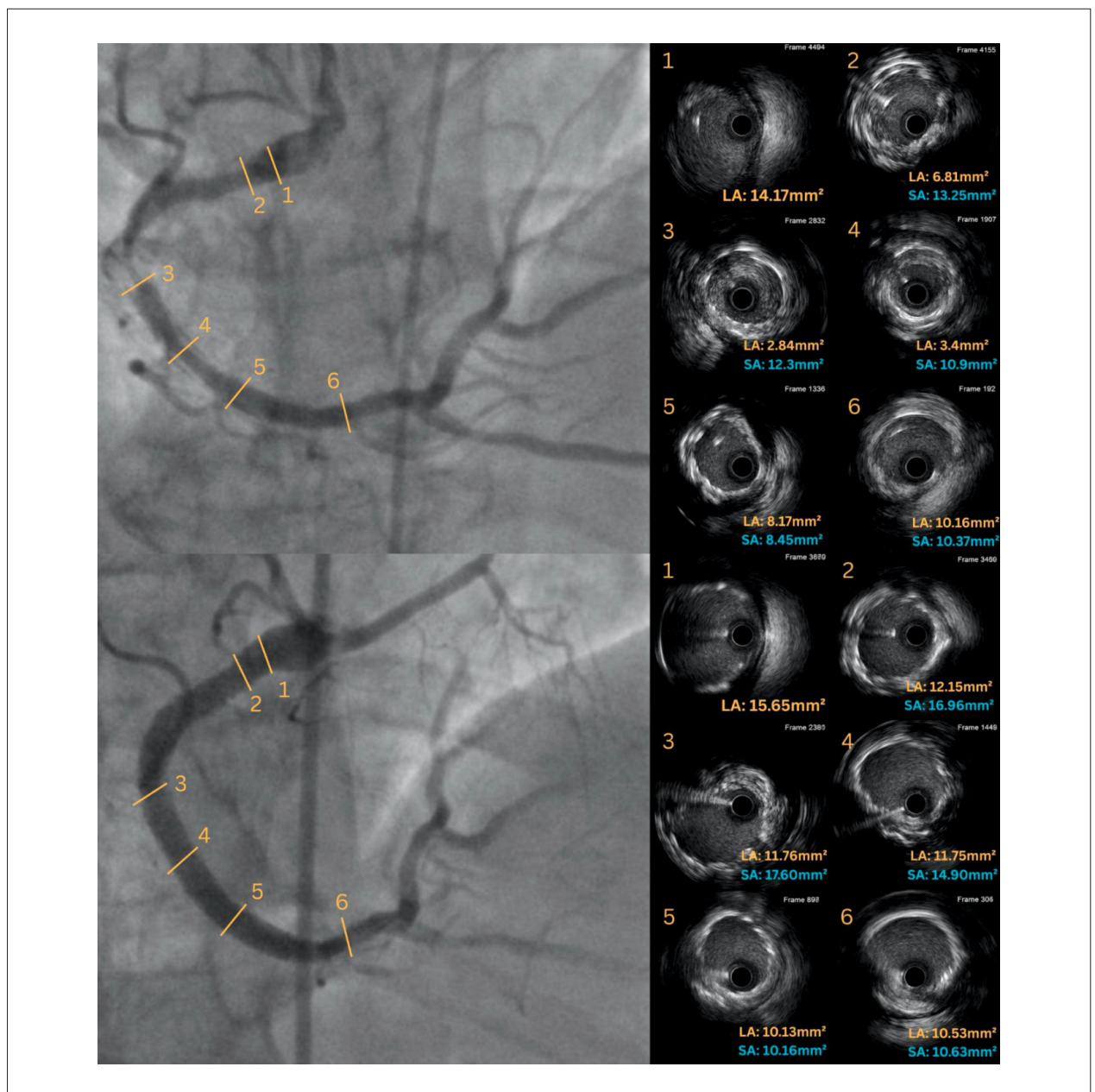


Figure 3 – Intravascular ultrasound of the right coronary artery. Pre-angioplasty: stent with underexpansion of its struts. Post-angioplasty: implantation of one drug-eluting stent (4.0 × 38 mm) in the mid right coronary artery and one drug-eluting stent (4.0 × 33 mm) in the proximal right coronary artery, with overlap and adequate strut expansion.

a major vessel. This clinical case illustrates how an integrated diagnostic and therapeutic approach – using both invasive and non-invasive methods, including IVUS and CCTA to define the mechanism of restenosis and the anomalous anatomical course – was essential for understanding the case and guiding appropriate therapeutic management.

Author Contributions

Conception and design of the research, acquisition of data and analysis and interpretation of the data:

Cruz ARC, Martins BL, Caliano MH, Magalhães PS, Centemero MP; writing of the manuscript: Cruz ARC, Martins BL, Caliano MH, Magalhães PS, Bandeira D, Costa RA, Centemero MP; and critical revision of the manuscript for intellectual content: Bandeira D, Costa RA, Centemero MP.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Case Report

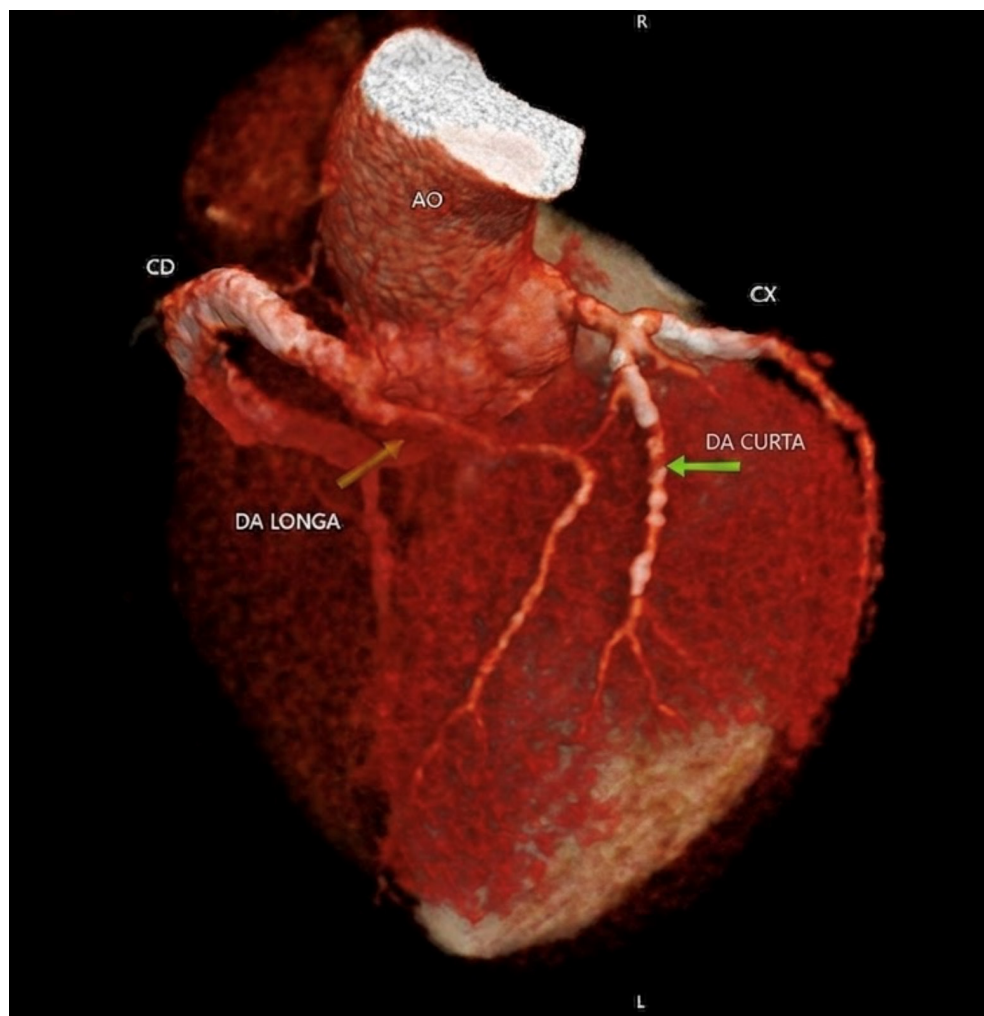


Figure 4 – CCTA. Duplicated LAD artery (long course – type IV LAD artery), showing anomalous origin from the proximal third of the right coronary artery. Its proximal third follows an intraseptal course, without luminal narrowing; the mid third reaches the anterior interventricular groove and displays a calcified plaque causing mild luminal reduction; the distal third reaches the apex, with no plaques or luminal narrowing. AO: Aorta; RCA: Right Coronary Artery; LCx: Left Circumflex Artery; Long LAD: Long Left Anterior Descending Artery; Short LAD: Short Left Anterior Descending Artery.

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There were no external funding sources for this study.

Study Association

This study is not associated with any thesis or dissertation work.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of Instituto Dante Pazzanese de Cardiologia under protocol number 8.270.800. All procedures in this study were in accordance

with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

Use of Artificial Intelligence

The authors did not use any artificial intelligence tools in the development of this work.

Availability of Research Data

The underlying content of the research is contained within the manuscript.

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Combined Minimally Invasive Transcatheter Approach for Aortic Stenosis and Abdominal Aortic Aneurysm: A Case Report

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Introduction

An aortic aneurysm is defined as a localized arterial dilation exceeding the normal vessel diameter by more than 50% or the expected diameter of the specific aortic segment by more than 2 standard deviations.^{1,2} The prevalence of abdominal aortic aneurysm (AAA) among individuals aged > 65 years is significantly higher in men.³⁻⁵ AAA rupture is associated with high mortality, estimated at 80%-90%, particularly when prehospital deaths are taken into account.⁶ The management of this condition has advanced substantially, particularly following the development of vascular endografts with improved safety and flexibility profiles.^{7,8} These technological advances have expanded therapeutic options for patients considered to be at high surgical risk or with anatomical characteristics unfavorable for open surgical repair.^{3-5,7,8}

Severe aortic stenosis (AS) is the leading cause of left ventricular (LV) outflow tract obstruction and most commonly manifests clinically as dyspnea, dizziness or syncope, and angina pectoris.^{9,10} Symptomatic severe AS, even when clinical manifestations are mild, requires intervention because, in the absence of valve replacement, it is associated with a poor prognosis, with a mean survival of only 2-3 years and a high risk of sudden cardiac death.¹⁰ In patients with severe calcific AS, surgical aortic valve replacement (SAVR) and transcatheter aortic valve implantation (TAVI) are the mainstays of treatment, providing symptom relief and improved survival.¹¹ The coexistence of severe AS and AAA has been increasingly observed, a phenomenon attributed in part to population aging.¹²

In patients with multiple comorbidities, including non-dialysis-dependent chronic kidney disease (CKD), who undergo combined percutaneous interventions, exposure to iodinated contrast medium (ICM) may contribute to deterioration of kidney function. In this setting, carbon dioxide

digital subtraction angiography (CO₂-DSA) has been used as a strategy to reduce the ICM burden and consequently minimize the risk of postprocedural deterioration of kidney function.^{13,14}

We report the case of a 79-year-old man with multiple comorbidities who was diagnosed with symptomatic severe AS and AAA and had a history of SAVR with a bioprosthetic valve. The therapeutic strategy consisted of TAVI followed by endovascular aneurysm repair (EVAR) of the abdominal aorta, both performed during the same procedure.

This case report was reviewed and approved by the Human Research Ethics Committee at Centro de Excelência em Ensino, Pesquisa e Projetos “Leide das Neves Ferreira” under CAEE No. 92462825.6.0000.5082.

Case report

A 79-year-old man was electively admitted for combined treatment of symptomatic severe AS and an infrarenal AAA. His medical history was complex and included non-dialysis-dependent CKD, chronic obstructive pulmonary disease, and paroxysmal atrial fibrillation. In 2014, he had undergone SAVR with a bioprosthetic valve. During the immediate postoperative period, he experienced two successfully resuscitated cardiac arrests and a stroke of presumed cardioembolic etiology, resulting in permanent right-sided hemiparesis. Regarding lifestyle factors, he was a former smoker and reported occasional alcohol consumption.

Following discussion by the multidisciplinary Heart Team and given the persistence of symptoms despite optimal medical therapy, a sequential percutaneous strategy was selected, with both procedures performed during the same operative session. The procedure was performed under general anesthesia. Vascular access was obtained through the right femoral vein for temporary pacemaker insertion, the left femoral artery for ancillary devices, and the right radial artery for invasive blood pressure monitoring. For the main right femoral arterial access, an 8-F introducer sheath was used, followed by preclosure with two ProGlide® devices (Abbott) according to a standardized ultrasound-guided technique.

A stiff hydrophilic guidewire, supported by a 5-F JR catheter, was then advanced into the thoracic aorta, carefully traversing the infrarenal aneurysm and allowing placement of an 18-F introducer sheath. The dysfunctional aortic bioprosthesis was crossed using a JR catheter and hydrophilic guidewire, which were subsequently exchanged for a pigtail catheter and a 0.035" × 260-cm Confida® guidewire positioned at the LV apex.

Keywords

Abdominal Aortic Aneurysm; Endovascular Aneurysm Repair; Aortic Valve Stenosis; Transcatheter Aortic Valve Replacement; Heart Valve Diseases

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After confirmation of the transvalvular gradient by simultaneous LV and aortic pressure measurements, a 26-mm SAPIEN 3 prosthesis was implanted in a valve-in-valve configuration. Under rapid ventricular pacing at 180 bpm and continuous angiographic and transesophageal echocardiographic monitoring, the prosthesis was successfully deployed and expanded. Postdilation was subsequently performed using a 26-mm balloon (+2 mL), while maintaining the rapid ventricular pacing protocol. Postimplantation assessment showed no paravalvular leak, valvular regurgitation, or pericardial effusion, with appropriate positioning and stability of the prosthesis. Final pressure measurements demonstrated a marked reduction in the mean transvalvular gradient to 4.0 mmHg (Figures 1A, 1B, and 1C).

Endovascular treatment of the infrarenal AAA was then performed. Because of preexisting CKD, a nephroprotective strategy using CO₂ delivered through the Angiodroid® system as the primary contrast agent was adopted. This strategy enabled angiographic mapping and endograft positioning with minimal exposure to ICM, with the aim of reducing the risk of acute kidney injury (Figures 2A and 2B). Over an extra-stiff Lunderquist® guidewire, a 25 × 103-mm Endurant® bifurcated endograft was deployed with preservation of the renal arteries. The reconstruction was extended bilaterally into the common iliac arteries using ETLW® endografts, while preserving the internal iliac arteries. Final angiography demonstrated complete exclusion of the aneurysm sac, no endoleaks, and preserved arterial flow (Figures 3A and 3B). Vascular access sites were closed percutaneously using suture-mediated closure devices, with additional ProGlide® devices required to control bleeding at the access site.

Postoperatively, the patient remained in the intensive care unit and was hemodynamically stable, in sinus rhythm, with improvement in dyspnea. Transient thrombocytopenia was observed, with a nadir platelet count of 85,000/μL and spontaneous recovery. The patient was discharged on

postoperative day 2 in good overall condition, with outpatient follow-up scheduled.

Discussion

Degenerative cardiovascular diseases, such as severe AS and AAA, are prevalent among older adults and may coexist in the same patient.¹² The present case falls within this context, as the patient not only had both conditions but also had multiple comorbidities that conferred high cardiovascular risk and increased the complexity of the therapeutic strategy.

Traditionally, TAVI for AS and EVAR of the abdominal aorta are performed as separate procedures. However, sequential performance of both interventions during a single session has emerged as an alternative for selected high-risk patients, with the potential to reduce exposure to multiple procedures and facilitate faster recovery.¹² Severe AS is associated with an increased risk of complications during noncardiac surgery, and its coexistence with AAA adds complexity to hemodynamic management during aneurysm repair, underscoring the importance of an individualized and integrated therapeutic strategy.^{12,15,16}

Case reports and small case series have demonstrated the technical feasibility of concomitant TAVI and EVAR during the same session.¹⁷⁻¹⁹ This strategy may be associated with a shorter overall hospital stay and potentially fewer perioperative complications. In a multicenter retrospective study involving 44 patients, 25 of whom underwent concomitant procedures, Gallito et al.¹⁷ observed a shorter hospital stay and fewer pulmonary complications with the simultaneous approach, with no apparent difference in survival during follow-up. Although promising, these findings should be interpreted with caution given the small sample size and observational nature of data.

Alternatively, TAVI and EVAR may be performed as staged procedures, and the sequence of interventions should be

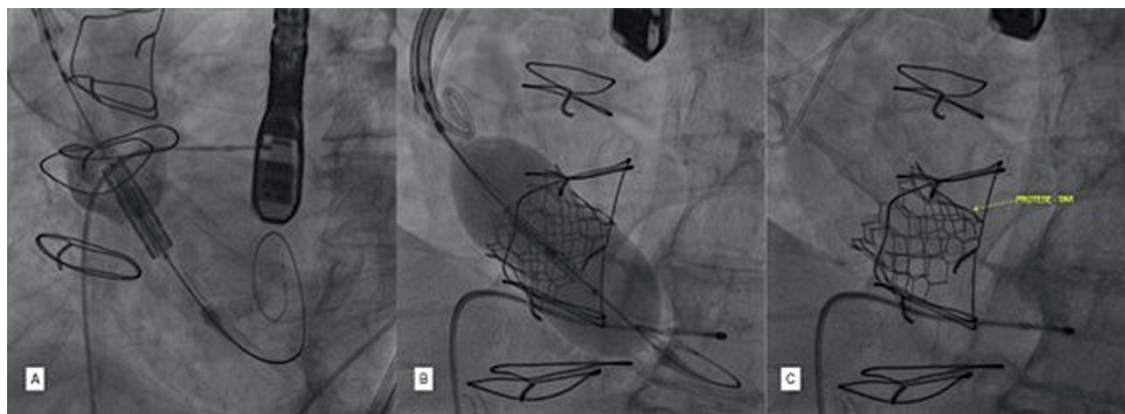


Figure 1 – Steps of TAVI in a valve-in-valve configuration. A) Positioning of the SAPIEN 3 prosthesis within the dysfunctional aortic bioprosthesis. B) Expansion of the SAPIEN 3 prosthesis by balloon inflation. C) Postimplantation result demonstrating appropriate prosthesis positioning.

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determined by the predominant clinical condition, vascular anatomy, risk of aneurysm rupture, and severity of AS, preferably following multidisciplinary evaluation.²⁰ In some circumstances, EVAR may be performed first because of the theoretical concern that an increase in systemic blood pressure after correction of AS could increase the risk of aneurysm rupture. Conversely, TAVI may be prioritized when AS is the primary determinant of symptoms or immediate clinical risk.²¹ In the present case, sequential

TAVI and EVAR were performed during a single operative session, a strategy associated with a favorable clinical course and hospital discharge on postoperative day 2.

Despite its potential advantages, performing TAVI and EVAR during a single session poses technical and logistical challenges and requires careful planning and an experienced multidisciplinary team. The sequence of interventions should be determined by factors including the severity of AS, risk of AAA rupture, and individual

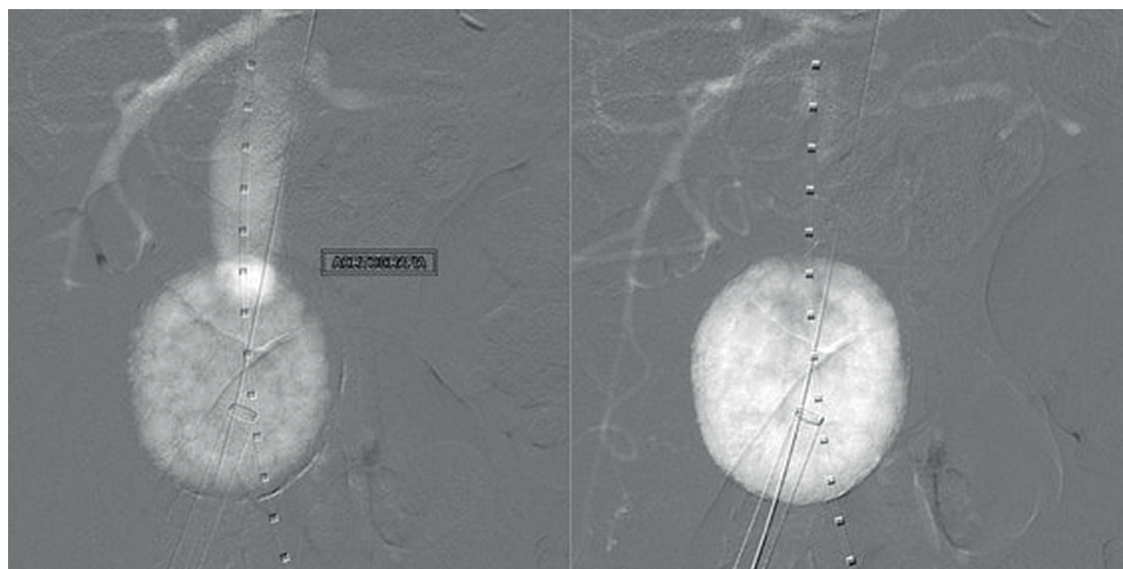


Figure 2 – CO₂-DSA before the intervention demonstrating a large infrarenal AAA.

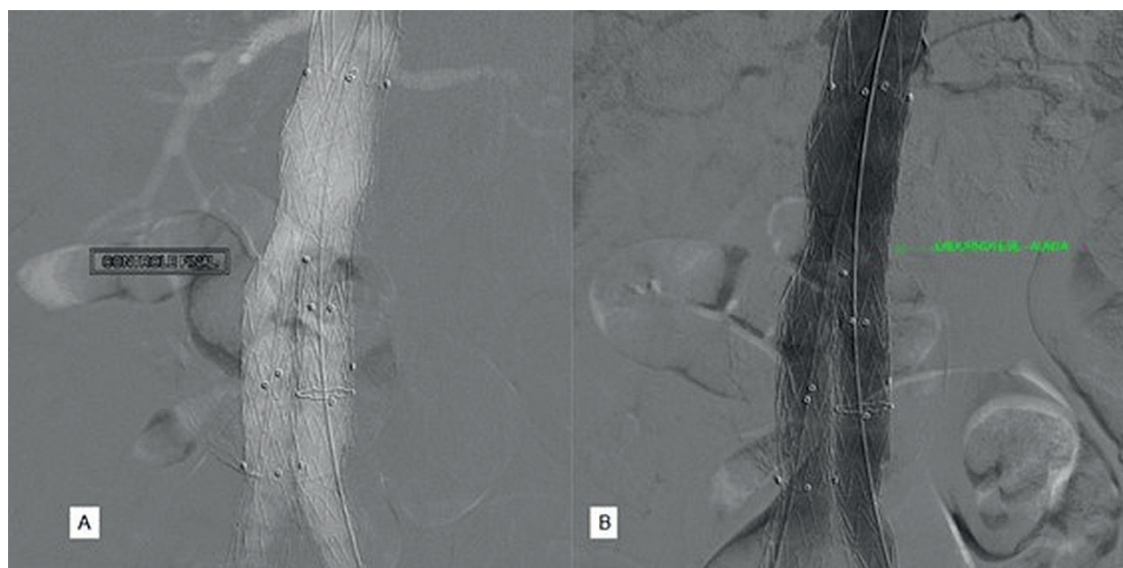


Figure 3 – EVAR of the AAA. A) Control angiography after endograft deployment, demonstrating appropriate positioning and preserved flow in the renal and iliac arteries. B) Angiography demonstrating the final result.

anatomical characteristics.^{16,21} In addition, appropriate management of antithrombotic therapy is important to balance the risks of thrombotic and bleeding events,^{16,22} while advanced imaging modalities contribute to procedural planning and accurate device deployment.^{16,21} Heart Team discussion therefore plays a pivotal role in patient selection and in determining the most appropriate therapeutic strategy.

Performing both procedures during a single session offers potential advantages, particularly the possibility of reducing hospital length of stay and accelerating recovery, which are especially relevant for older, frail patients with multiple comorbidities.^{12,15} This strategy also avoids repeated exposure to anesthesia and the risks inherent in two separate procedures.²² In the current case, preservation of kidney function was an additional concern because of non-dialysis-dependent CKD. The use of CO₂-DSA with reduced exposure to ICM represents a useful strategy for minimizing contrast burden in patients with impaired kidney function.^{13,14}

Conversely, the single-session approach has inherent limitations related to greater technical complexity and the need for a specialized team, detailed planning, and availability of specific resources.^{12,15} The longer procedural duration may increase exposure to anesthesia and radiation,^{16,22} while the need for specialized devices, materials, and infrastructure may increase procedure-related costs.²¹

The prognosis after sequential TAVI and EVAR is multifactorial and depends largely on careful patient selection and the experience of the treating team.^{16,21} This approach is generally considered for patients at high surgical risk, in whom performing separate procedures may entail greater risk because of the coexistence of both conditions.^{12,15} Preliminary evidence suggests favorable periprocedural outcomes in carefully selected patients, with acceptable morbidity and mortality rates.^{16,21}

Long-term survival is influenced by procedural success, preexisting comorbidities, and the patient's overall clinical status. Thus, regular postoperative follow-up is essential to assess prosthetic device performance and monitor cardiovascular outcomes.^{12,22} Future studies involving larger cohorts and longer follow-up periods are needed to more accurately determine the impact of this strategy on the prognosis of patients with complex clinical conditions.^{12,22}

This case report has several limitations that should be considered. No electrocardiogram was obtained before the interventions, which limited characterization of the patient's baseline electrocardiographic findings. In addition, quality of life was not systematically assessed using specific validated instruments before the procedures or during early and late postoperative follow-up.

Conclusion

This case report demonstrates the feasibility and successful combined use of TAVI and EVAR for the concomitant treatment of severe AS and AAA in an older patient with multiple comorbidities and high surgical risk. The single-session minimally invasive approach enabled treatment of both conditions, with a favorable clinical course, short hospital stay, and early recovery. These findings support the potential of this strategy as a therapeutic alternative for carefully selected patients, particularly those in whom conventional surgical procedures are associated with high risk.

Author Contributions

Conception and design of the research: Silva NA; acquisition of data: Silva NA, Trindade VT, Carrijo ENA, Carrijo LBS; analysis and interpretation of the data: Silva NA, Garcia NJM, Trindade VT, Carrijo ENA, Carrijo LBS, Gardenghi G, Prudente ML; writing of the manuscript: Silva NA, Garcia NJM, Gardenghi G; critical revision of the manuscript for intellectual content: Neto JM, Gardenghi G, Prudente ML.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

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Study Association

This study is not associated with any thesis or dissertation work.

Ethics Approval and Consent to Participate

This study was approved by the Research Ethics Committee Leide das Neves Ferreira – LNF under protocol number 92462825.6.0000.5082, dated 10/14/2025. All procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

Use of Artificial Intelligence

The authors did not use any artificial intelligence tools in the development of this work.

Availability of Research Data

The data cannot be made publicly available.

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First Colombian Experience with Mavacamten in Obstructive Hypertrophic Cardiomyopathy: A Brief Imaging Report

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Introduction

Hypertrophic cardiomyopathy (HCM) is a myocardial disease, usually of genetic origin, characterized by increased left ventricular wall thickness unexplained by abnormal loading conditions.¹ Dynamic left ventricular outflow tract (LVOT) obstruction occurs in approximately 70% of patients, either at rest or with provocation, and is closely associated with symptoms and adverse clinical outcomes.^{2,3}

The relief of the obstructive gradient remains a major therapeutic goal in obstructive HCM. Mavacamten, a cardiac myosin inhibitor, has been shown to reduce LVOT gradients and improve symptoms and functional capacity in symptomatic obstructive HCM.^{4,5} After its regulatory authorization in Colombia in August 2025, mavacamten became a new therapeutic option in this setting.

We present, to our knowledge, the first published Colombian case of obstructive HCM treated with mavacamten, with serial clinical and echocardiographic follow-up during the first 10 weeks of therapy.

Case Presentation

A 74-year-old man was referred for exertional dyspnea, chest pain, and presyncope for more than three months. On examination, blood pressure was 110/60 mmHg, heart rate was 84 beats/min, respiratory rate was 15 breaths/min, and oxygen saturation on room air was 96%. Cardiac auscultation revealed a mid-systolic ejection murmur that increased with Valsalva and transition from squatting to standing.

Transthoracic echocardiography showed asymmetric hypertrophy, predominantly involving the interventricular septum, with a diastolic septal thickness of 15 mm (Table 1). Left ventricular ejection fraction (LVEF) was 65%, whereas global longitudinal strain (GLS) was at the lower limit of normal, with segmental impairment involving the septal and lateral walls

(Video 1). Elongated mitral valve leaflets with systolic anterior motion (SAM) were observed, with an end-systolic mitral coaptation-to-septum distance of 9 mm, suggesting a high likelihood of dynamic obstruction (Figure 1). Color Doppler showed LVOT flow acceleration, with a resting peak gradient of 18.3 mmHg that increased to 78.7 mmHg with Valsalva (Figure 2 and Video 2). Genetic testing identified a MYBPC3 variant.

Initial treatment with metoprolol succinate (100 mg daily) achieved heart rates of 55 to 60 beats/min but was poorly tolerated because of persistent symptoms, cold extremities, diaphoresis, and systolic blood pressure of 90 to 100 mmHg, limiting further optimization of conventional therapy. Because of persistent symptoms and dynamic LVOT obstruction, septal myectomy was considered. However, after a second opinion abroad, the patient started mavacamten 5 mg once daily, obtained in North America before local availability in Colombia. During follow-up, metoprolol was replaced with bisoprolol (5 mg daily) due to better tolerability.

After six weeks, echocardiography showed a modest reduction in septal thickness and indexed left ventricular mass, while LVEF and GLS remained stable (Table 1 and Video 3). SAM persisted, with continued LVOT flow acceleration. The resting peak gradient was 29.6 mmHg and increased to 39.6 mmHg with Valsalva (Figure 3). At that time, the patient was receiving bisoprolol (5 mg daily). Clinically, chest pain had resolved, dyspnea had improved, and no hypotensive episodes were reported.

At ten-week follow-up, while receiving mavacamten (5 mg daily) and bisoprolol (5 mg daily), the patient was asymptomatic, in New York Heart Association (NYHA) functional class I, and exercising regularly four times per week. A new echocardiography showed further reduction in septal thickness and indexed left ventricular mass (Table 1). The mitral coaptation-to-septum distance increased to 13 mm, consistent with a lower likelihood of dynamic obstruction, while LVOT flow acceleration markedly decreased. The resting peak gradient was 18.2 mmHg and did not increase with provocative maneuvers (Figure 4 and Video 4); LVEF and GLS remained stable (Video 5). Given the favorable clinical and hemodynamic response, the same regimen was continued, with periodic follow-up planned.

Discussion

This case is relevant not only because it represents, to our knowledge, the first published Colombian case of mavacamten use in obstructive HCM, but also because it illustrates appropriate real-world patient selection, limitations of conventional therapy, and the value of serial echocardiography for treatment decisions (Figure 5 and Table 1).

Keywords

Hypertrophic Cardiomyopathy; Ventricular Outflow Obstruction; Myosins; Echocardiography

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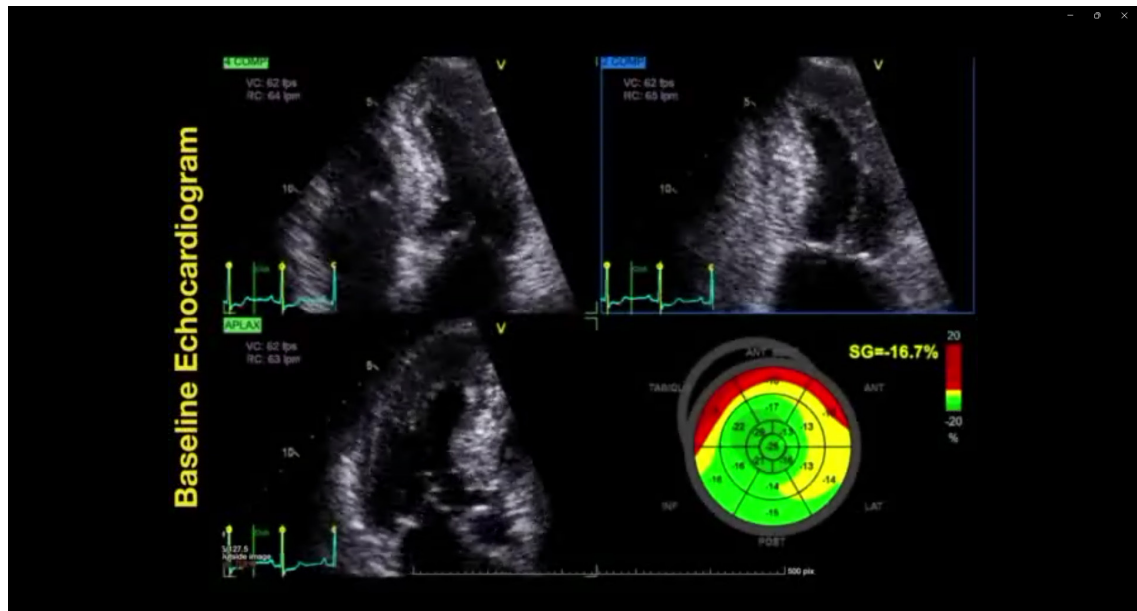
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Video 1 – Baseline left ventricular systolic function. Link: http://abcimaging.org/supplementary-material/2026/3903/2026-0061_video_01.mp4

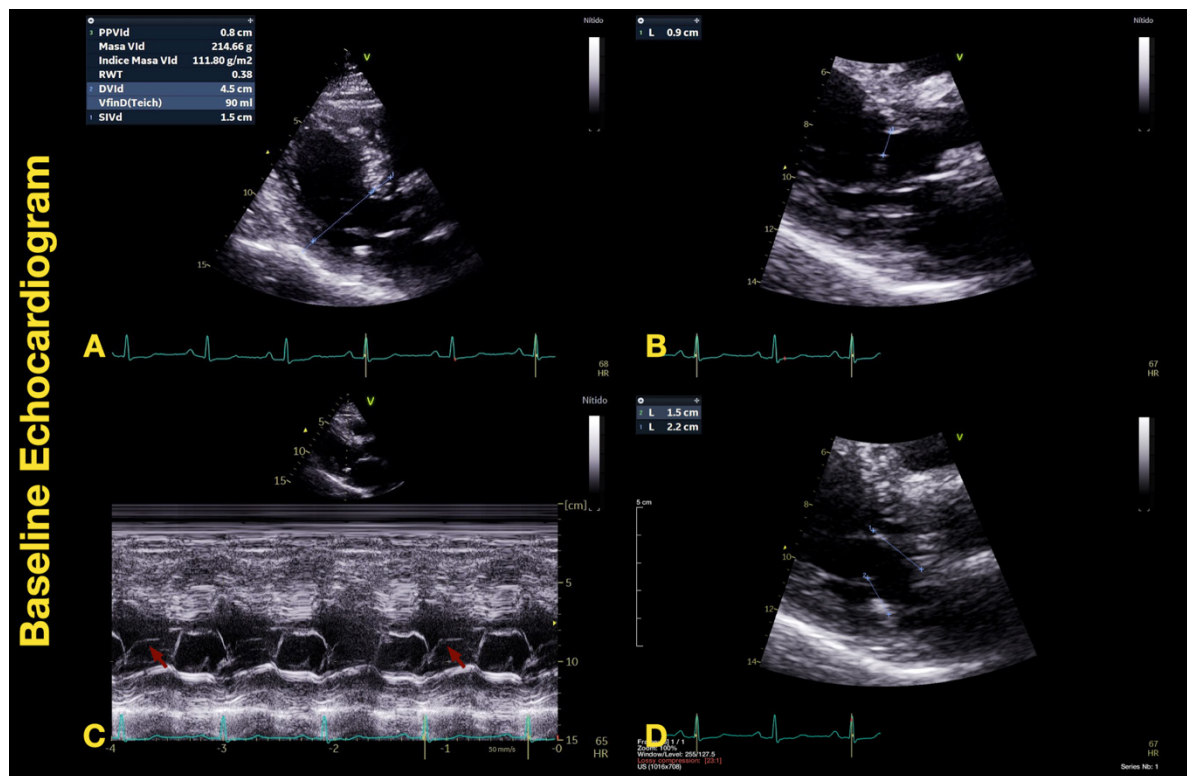


Figure 1 – Baseline echocardiogram. A. Basal septal hypertrophy (15 mm) and mildly increased left ventricular mass (112 g/m²); B. Coaptation-to-septum distance of 9 mm; C. SAM on M-mode (red arrows); D. Elongated mitral leaflets.

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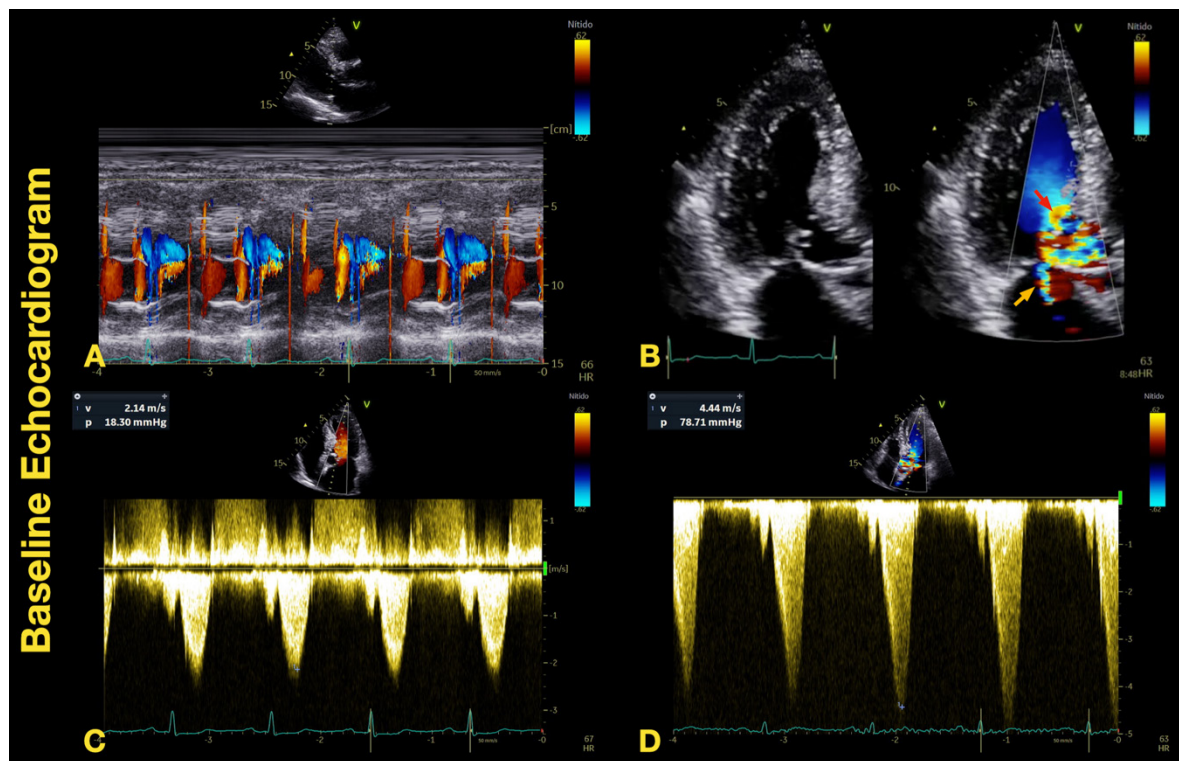
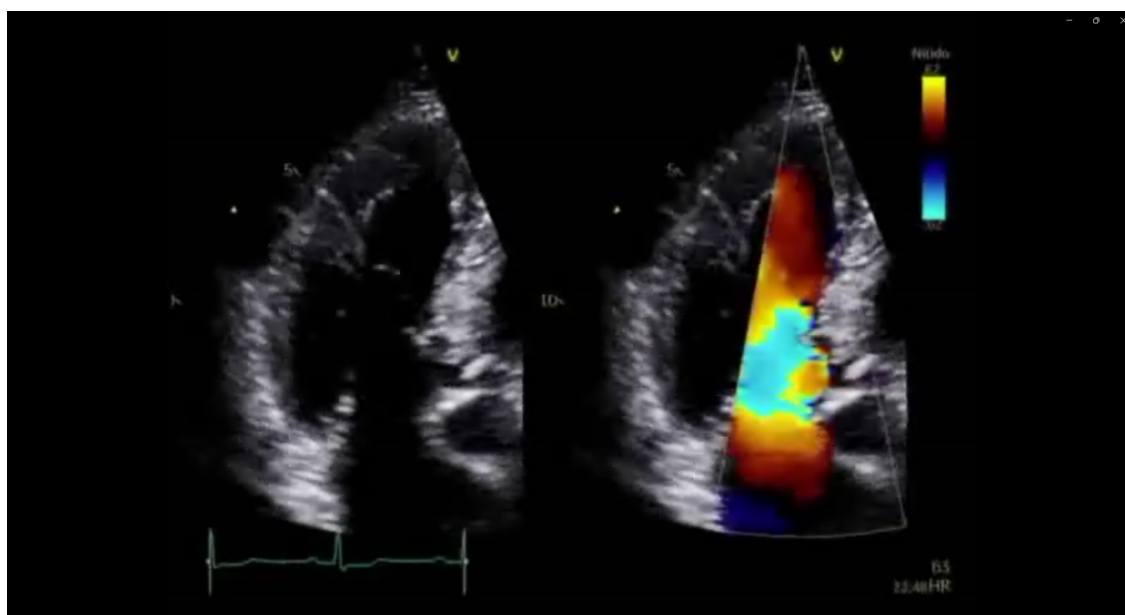


Figure 2 – Baseline LVOT obstruction. A. Flow acceleration related to SAM; B. Apical 3-chamber LVOT flow acceleration; C. Resting peak gradient (18.3 mmHg); D. Valsalva peak gradient (78.7 mmHg).



Video 2 – Baseline LVOT obstruction. Link: http://abcimaging.org/supplementary-material/2026/3903/2026-0061_video_02.mp4

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Table 1 – Echocardiographic Variables Across Follow-Up

Parameter	Baseline echocardiogram	6-Week Follow-Up	10-Week Follow-Up
LV wall thickness (mm)	15	12	11
Indexed LV mass (g/m ²)	112	81	79
LVEF (%)	65	66	60
GLS (%)	−16.7	−17.2	−16.9
Resting LVOT peak gradient (mmHg)	18.3	29.6	18.22
Valsalva LVOT peak gradient (mmHg)	78.7	39.6	18.62
Mitral-to-septum end-systolic distance (mm)	9	5	13

GLS: global longitudinal strain; LVEF: left ventricular ejection fraction; LV: left ventricular; LVOT: left ventricular outflow tract.



Video 3 – Six-week follow-up echocardiogram. Link: http://abcimaging.org/supplementary-material/2026/3903/2026-0061_video_03.mp4

A major clinical concern in HCM is its association with heart failure symptoms and sudden cardiac death. Among prognostic markers, maximal left ventricular wall thickness and dynamic LVOT obstruction are particularly relevant. In a meta-analysis including 12,146 patients, both variables were associated with cardiovascular death (Hazard Ratio [HR]: 1.42, 95%CI 1.06 to 1.89, and HR: 1.52, 95%CI 1.11 to 2.07, respectively) and sudden cardiac death (HR: 3.17, 95%CI 1.64 to 6.13, and HR: 2.41, 95%CI 1.55 to 3.73, respectively), underscoring the importance of recognizing and treating the obstructive phenotype.⁶

Mavacamten, the first myosin inhibitor approved for HCM, reduces excessive contractility, lessens dynamic LVOT

obstruction, and has shown consistent benefits in symptomatic obstructive HCM, including improved symptoms, functional capacity, and quality of life under close echocardiographic monitoring.^{5,7} A central teaching point of this case is the role of serial echocardiography during therapy. The follow-up showed early clinical and hemodynamic improvements, with progressive reduction in the provoked LVOT gradient, preserved LVEF, stable GLS, less prominent SAM, increased mitral coaptation-to-septum distance, and reduced LVOT flow acceleration. This behavior is consistent with results of the EXPLORER-HCM trial, in which mavacamten reduced post-exercise LVOT gradient by 36 mmHg versus placebo and improved symptoms, exercise capacity, and NYHA functional class.⁸

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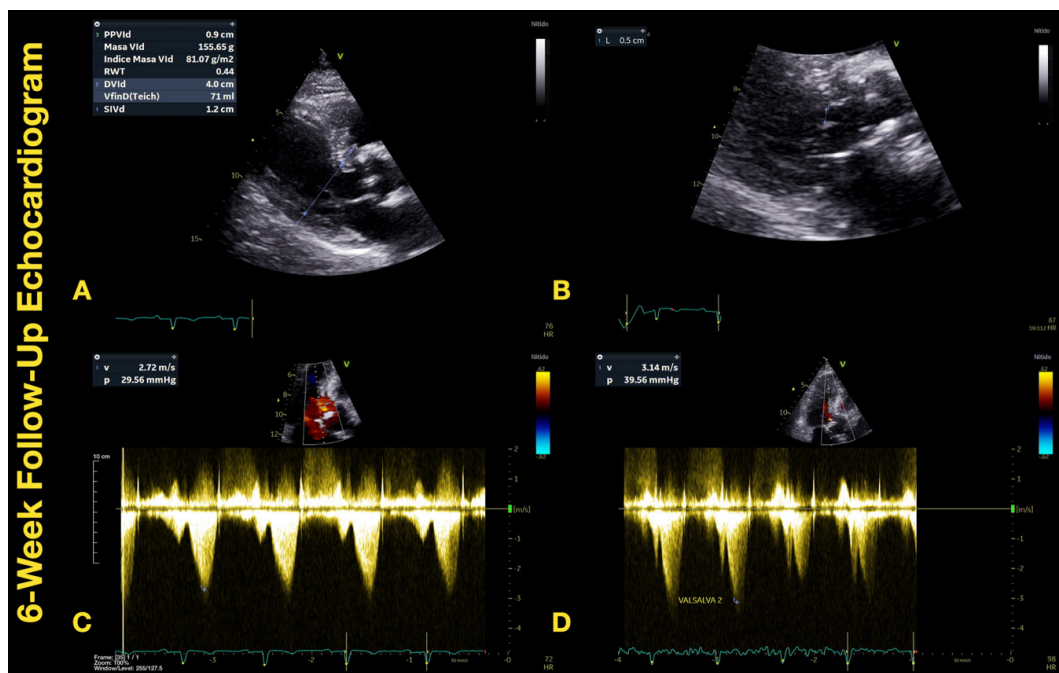


Figure 3 – Six-week follow-up echocardiogram. A. Septal thickness (12 mm) and indexed left ventricular mass (81 g/m²); B. Coaptation-to-septum distance (5 mm); C. Resting peak gradient (29.6 mmHg); D. Valsalva peak gradient (39.6 mmHg).

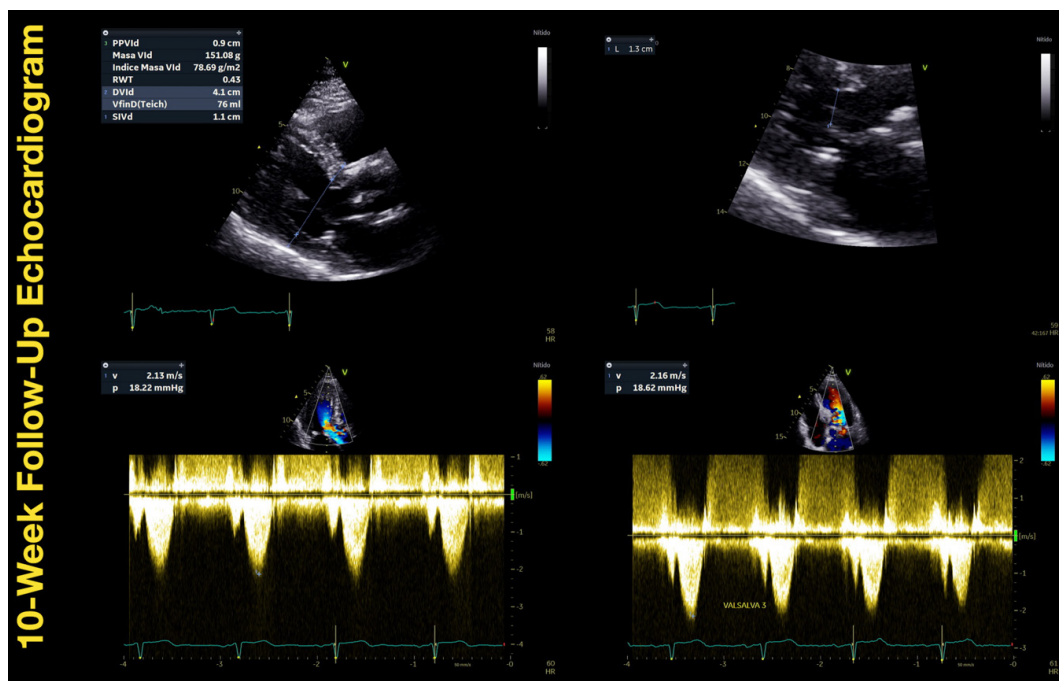
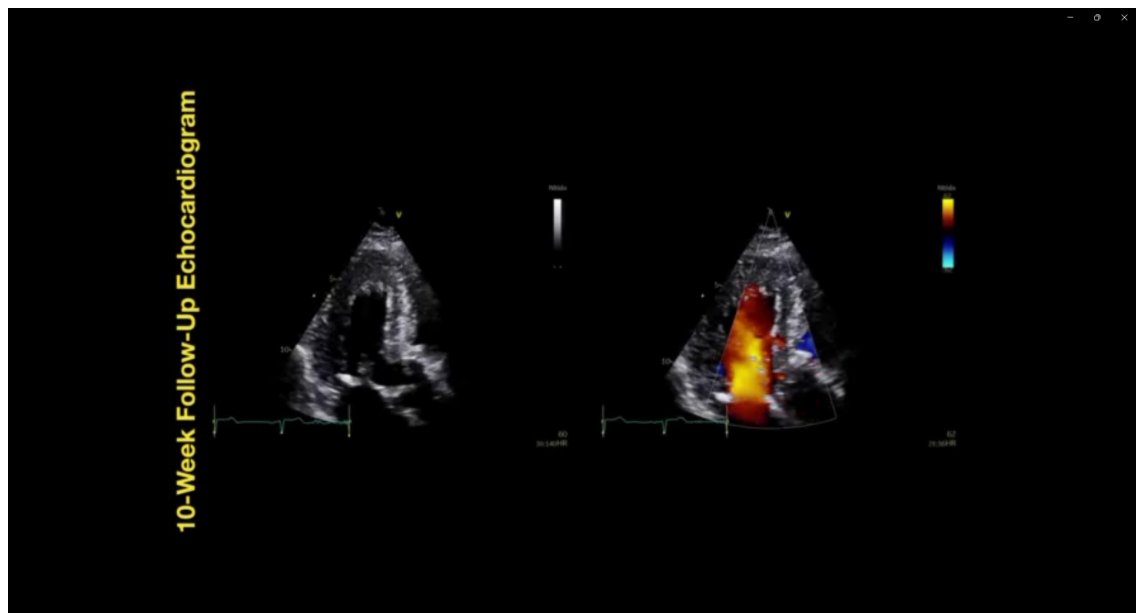
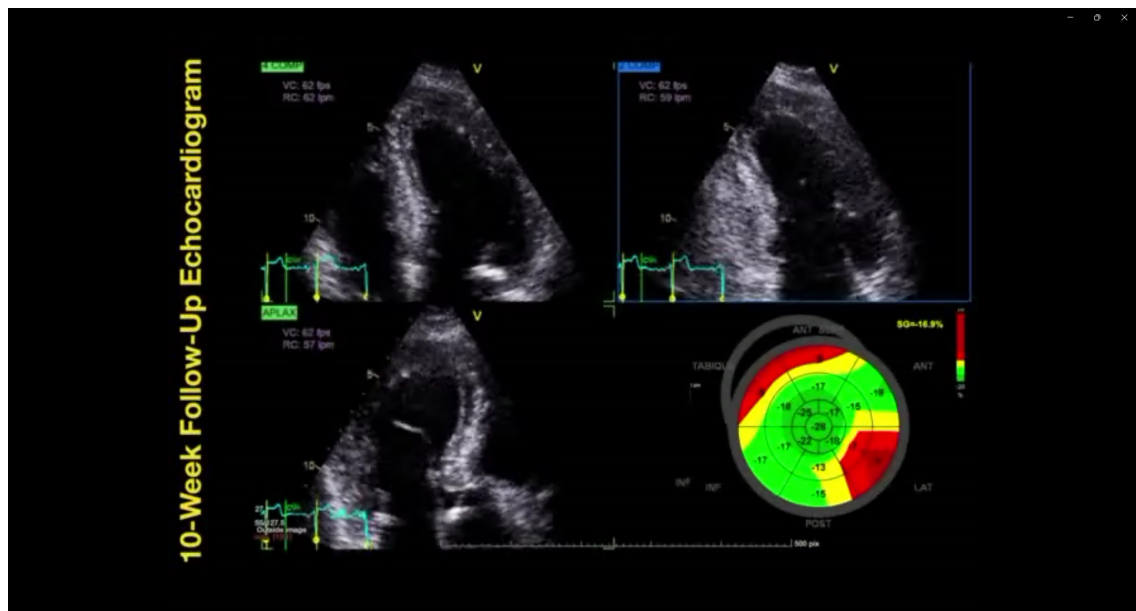


Figure 4 – Ten-week follow-up echocardiogram. A. Septal thickness (11 mm) and indexed left ventricular mass (78.69 g/m²); B. Coaptation-to-septum distance (13 mm); C. Resting gradient (18.22 mmHg); D. Valsalva gradient (18.62 mmHg).



Video 4 – Ten-week follow-up echocardiogram. Link: http://abcimaging.org/supplementary-material/2026/3903/2026-0061_video_04.mp4



Video 5 – Ten-week follow-up left ventricular systolic function. http://abcimaging.org/supplementary-material/2026/3903/2026-0061_video_05.mp4

Another interesting finding was the downward trend in septal thickness and indexed left ventricular mass. Similar structural changes have been reported in an EXPLORER-HCM substudy assessed by cardiac magnetic resonance.⁹ In our patient, a comparable pattern was observed during follow-

up. Although this is a single-case observation and should be interpreted cautiously, it remains illustrative.

From a practical standpoint, this case supports the concept that echocardiography-guided follow-up facilitates real-world initiation and monitoring of mavacamten in

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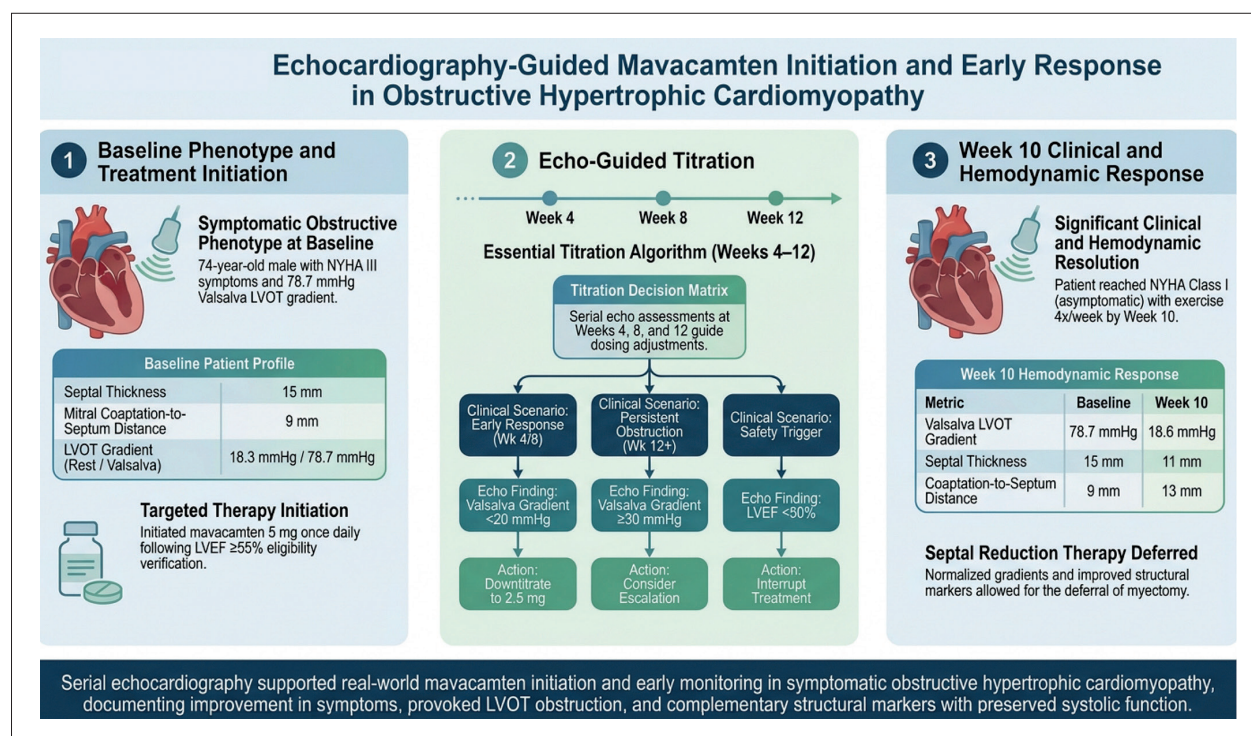


Figure 5 – Echocardiography-guided initiation and early dose adjustment of mavacamten in a patient with symptomatic obstructive HCM, showing improved symptoms, reduced provoked LVOT gradient, and increased mitral leaflet–septal distance with preserved left ventricular systolic function. LVEF: left ventricular ejection fraction.

selected patients with symptomatic obstructive HCM. In this setting, symptoms, LVEF, provoked LVOT gradient, SAM, and mitral coaptation-to-septum distance may provide a useful framework for longitudinal assessment.

Conclusion

This case illustrates that mavacamten may provide early clinical and hemodynamic benefits in selected patients with symptomatic obstructive HCM. In our patient, improvement in symptoms and LVOT obstruction occurred with preserved LVEF and stable GLS, supporting the value of an echocardiography-guided approach in real-world care.

Author Contributions

Conception and design of the research: Vasquez-Rodriguez JF, Idrovo-Turbay A, Reyes-Toledo RE, David-Pardo DG, Acuña-Olmos J; acquisition of data: Vasquez-Rodriguez JF, Idrovo-Turbay A, Acuña-Olmos J; analysis and interpretation of the data: Vasquez-Rodriguez JF, Reyes-Toledo RE; statistical analysis: Vasquez-Rodriguez JF; writing of the manuscript: Vasquez-Rodriguez JF, Reyes-Toledo RE, David-Pardo DG; critical revision of the manuscript for intellectual content: Vasquez-Rodriguez JF, Idrovo-Turbay A, David-Pardo DG, Acuña-Olmos J.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

This study received no external funding.

Study Association

This study is not associated with any thesis or dissertation work.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the Fundación Cardioinfantil – Instituto de Cardiología under the protocol number 32-2026. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

Use of Artificial Intelligence

During the preparation of this work, the author(s) used ChatGPT (OpenAI) for English language editing and grammar review, and to assist in creating the original Figure 5 layout from author-provided content and instructions. The author(s) reviewed and edited the content as necessary and assume full responsibility for the article's content.

Availability of Research Data

Data cannot be made publicly available because this manuscript is a single-patient case report. No additional research

dataset was generated. Public sharing of patient-level data could compromise confidentiality despite de-identification. All data necessary to interpret the case are included in the manuscript.

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Apical Hypertrophic Cardiomyopathy with Microfistulas: Correlation Between Coronary Flow Steal, Positive Inotropic Effect, and Normalization of T-Wave Polarity

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Introduction

Apical hypertrophic cardiomyopathy (HCM) with microfistulas is a rare condition, and the incidence of multiple microfistulas draining into the left ventricle (LV) ranges from 0.07% to 0.09%.^{1,2} Diagnosis can be established via contrast ventriculography, coronary angiography, and echocardiography.³⁻⁶

Two-dimensional echocardiography with color and pulsed-wave Doppler allows visualization of microfistula flow and measurement of diastolic flow velocity (DFV) using the same approach as for the left anterior descending artery (LAD).⁷

In apical HCM with microfistulas, electrocardiography (ECG) may show negative T waves of varying depths; this finding has been attributed to LV hypertrophy itself, myocardial ischemia, and coronary flow steal caused by the microfistulas.⁸⁻¹⁰

The interpretation of changes in T-wave polarity, whether at rest or under increased metabolic demand, remains controversial, limiting the utility of this finding as an indicator of ischemia.¹¹⁻¹³ In this context, negative T waves may become positive during physical or pharmacological stress echocardiography; however, the mechanism underlying this phenomenon remains uncertain.¹⁴

Case report

We report the case of a 61-year-old woman with hypertension and dyslipidemia who smoked and was undergoing irregular medical treatment. She sought cardiology assessment due to fatigue during strenuous exertion, without chest pain. She was in good general condition, with normal lung sounds, regular heart rhythm, a heart rate (HR) of 60

bpm, an audible fourth heart sound, no murmurs, and no edema; her blood pressure measured 190/90 mmHg. ECG showed sinus rhythm with T-wave inversion (Figure 1A). Echocardiography revealed marked HCM, predominantly apical, without dynamic obstruction. The patient was prescribed losartan, amlodipine, and a statin and advised to quit smoking.

Four months later, she was referred for dobutamine stress echocardiography to assess myocardial ischemia. At baseline, myocardial contractility was normal. The LAD was clearly visualized, and DFV measured 54 cm/s (Figure 2A). Multiple other flow signals were observed in the LV apical region, but DFV was not recorded.

During stress, DFV in the LAD was recorded at a HR of 127 bpm and measured 99 cm/s (Figure 2B), whereas color flow in the microfistulas appeared attenuated or suppressed. The test concluded at a HR of 151 bpm; no ischemic manifestations or arrhythmias occurred (Video 1), and the negative T waves seen on the baseline ECG became positive (Figure 1B). Despite these results, the attending physician requested coronary angiography, which showed normal, large-caliber coronary arteries; ventriculography was not performed at that time (Figure 3).

She remained stable over the following five years, despite reporting fatigue during strenuous exertion. She maintained controlled blood pressure, normal LV ejection fraction, and normal LV global longitudinal strain, with grade II diastolic dysfunction (Table 1). The ECG showed marked T-wave inversion (Figure 1C), with variations in T-wave depth compared to the ECG performed five years earlier. She was referred for repeat supine bicycle stress echocardiography; the test began with a HR of 62 bpm, reached a workload of 75 watts, and achieved a peak HR of 115 bpm. The test was terminated due to physical exhaustion; no arrhythmias or signs of myocardial ischemia occurred, and the T waves progressively became positive on ECG (Figure 1D).

The highest flow velocities were obtained by optimizing alignment with the Doppler cursor. At baseline, DFV measured 56 cm/s in the LAD and 140 cm/s in the microfistula (Figures 2C and 2D). The prominent diastolic flow through the microfistula (Figure 2E) was completely suppressed when the HR reached 108 bpm, whereas flow through the LAD remained clearly visible in the LV apical region (Figure 2F and Video 2).

Keywords

Hypertrophic Cardiomyopathy; Stress Echocardiography; Electrocardiography.

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Figure 1 – Electrocardiographic tracings. Ventricular repolarization abnormality at baseline (A) and normalization of T-wave polarity during dobutamine stress echocardiography (B). After five years, the ventricular repolarization abnormality persists at baseline (C), and T waves become positive during physical exertion (D).

Discussion

Microfistulas constitute a vascular labyrinth, representing the persistence of embryonic sinusoids that are typically obliterated over the course of normal development. In apical HCM with microfistulas, a plexiform communication occurs between the coronary artery and the LV cavity, a rare

association that often raises the possibility of myocardial ischemia. Symptoms suggestive of angina and the presence of a murmur may or may not be observed.^{2-4, 6, 14}

The ratio of stress DFV to resting DFV yields coronary flow velocity reserve, which was low (< 2) in the LAD, a finding that could have resulted from impairment of either

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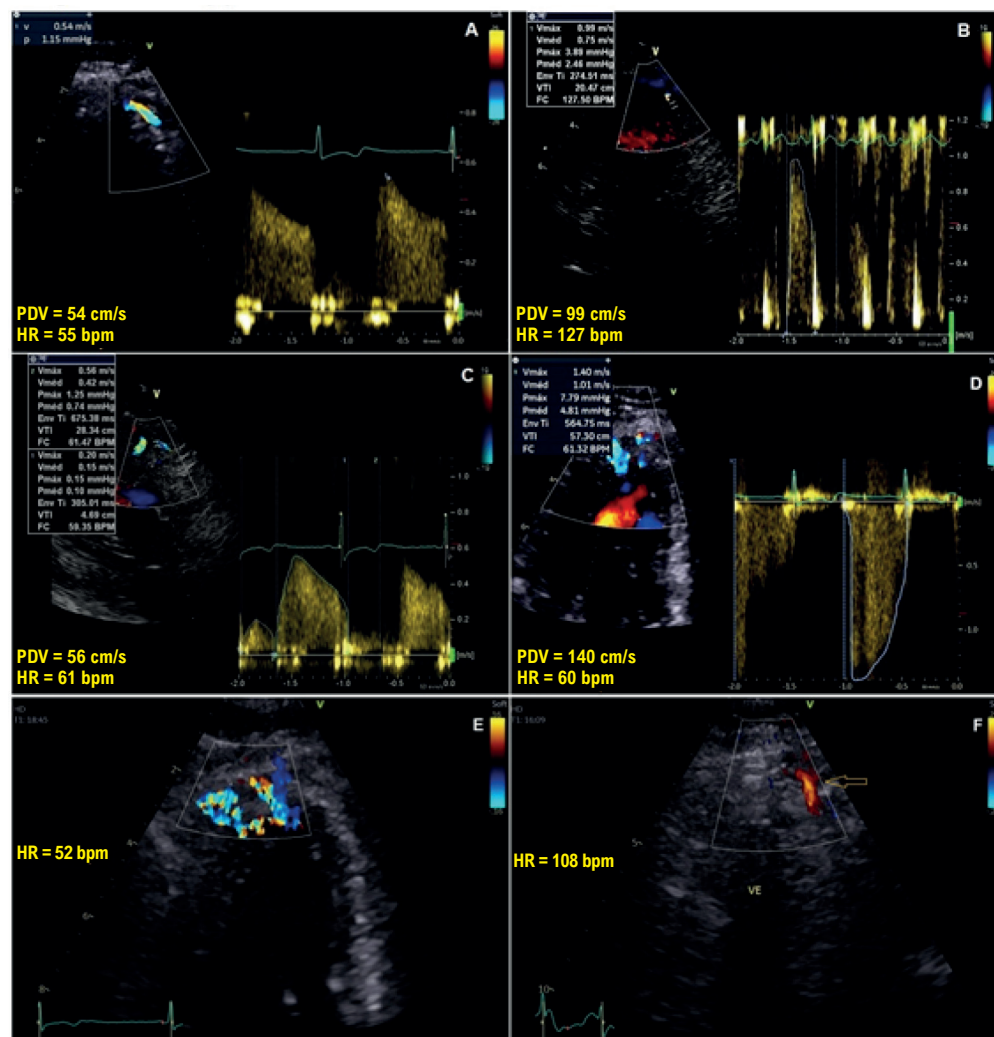


Figure 2 – Pulsed-wave Doppler echocardiography of the LAD at baseline (A) and during dobutamine stress (B). Baseline pulsed-wave Doppler measurements in the LAD (C) and the microfistula (D). Prominent color Doppler flow through the microfistulas into the LV at baseline (E) is completely suppressed by the positive inotropic effect during physical exertion, whereas flow in the LAD (arrow) is preserved (F). HR: heart rate; PDV: peak diastolic velocity.

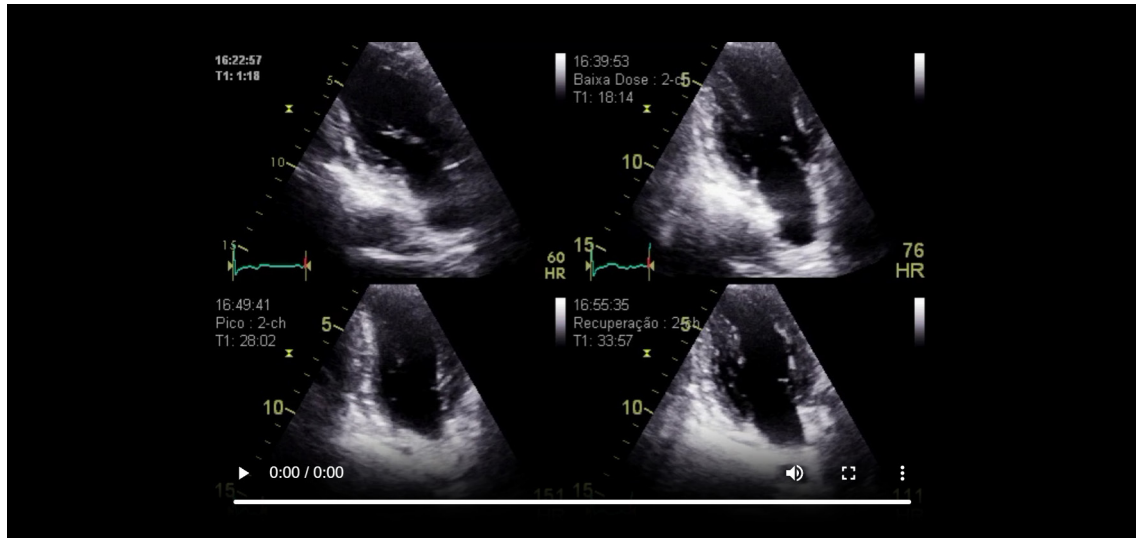
the epicardial coronary arteries or the microcirculation.⁷ In our case, although dobutamine stress echocardiography at maximal HR was negative for ischemia, a false-negative result was suspected.

Given the possibility of myocardial ischemia in the presence of ECG T-wave pseudonormalization, coronary angiography was a plausible indication; however, it revealed large, normal epicardial coronary arteries.

The value of T-wave polarity changes as an indicator of myocardial ischemia during stress is controversial. However, even at rest, conditions that might cause some form of ischemic memory are absent in our case.¹⁵ False-positive diagnoses of

ischemia based on prominent ECG abnormalities should be avoided in patients with apical HCM and microfistulas. It is worth noting that the depth of these negative T waves can vary over time during routine follow-up.^{8,14} This was observed in our case, although no specific explanation for these changes was identified.

During dobutamine stress echocardiography, flow through the microfistulas appeared to be suppressed, but this was not given due attention at that time. Exercise stress echocardiography was performed using a supine bicycle, allowing for real-time echocardiographic monitoring. Once the HR reached 108 bpm, microfistula flow was completely suppressed; simultaneously, the T waves became positive



Video 1 – Dobutamine stress echocardiography was negative for myocardial ischemia at maximal heart rate. Link: http://abcimaging.org/supplementary-material/2026/3903/2026-0090_video_01.mp4

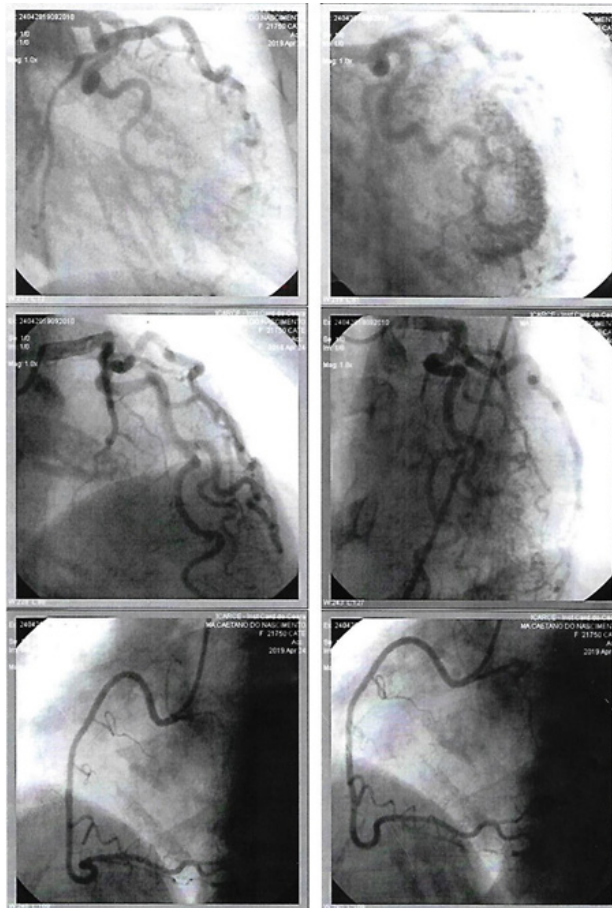
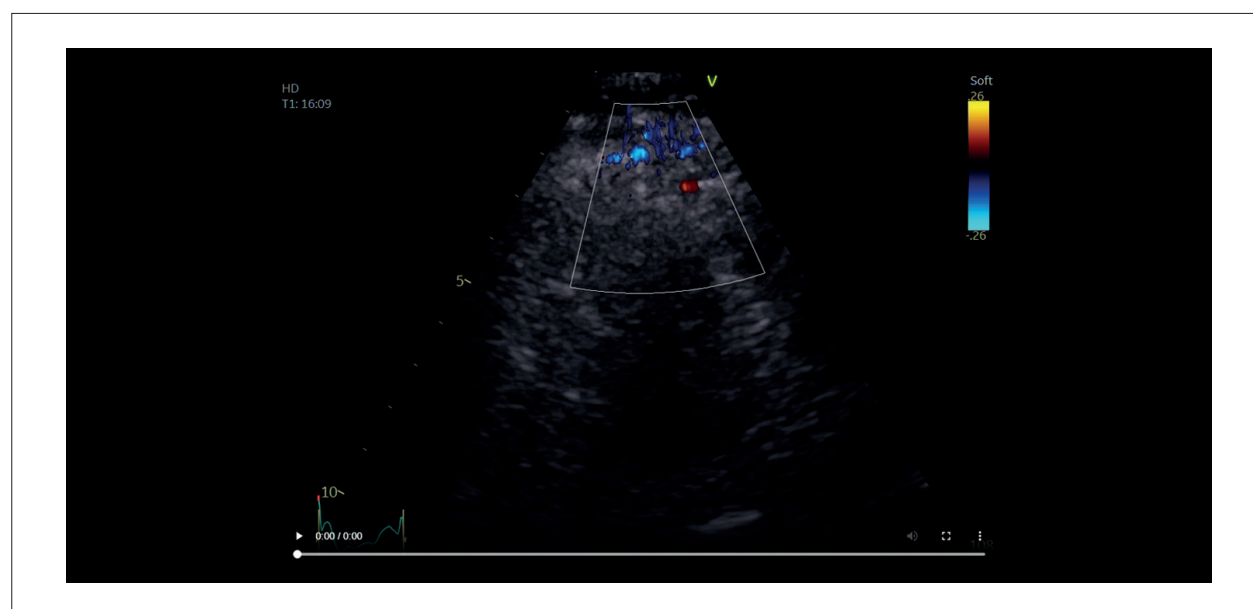


Figure 3 – Normal epicardial coronary arteries.

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Table 1 – Baseline echocardiographic variables measured before exercise stress echocardiography

Left ventricular ejection fraction, Simpson's method (%)	65
Left ventricular global longitudinal strain (%)	−18.7
Left atrial volume index (mL/m ²)	31
Left atrial reservoir strain (%)	27
Mitral Doppler E wave (cm/s)	9
Mitral E/A ratio	1.21
Mitral E/E' ratio	16



Video 2 – During physical exertion, flow through the microfistulas is completely suppressed, whereas flow through the LAD is preserved.
Link: http://abcimaging.org/supplementary-material/2026/3903/2026-0090_video_02.mp4

on ECG, suggesting a correlation between these events. Conversely, flow through the LAD remained clearly evident.

Even in the presence of grade II diastolic dysfunction, the positive inotropic effect on the LV during exercise stress echocardiography did not result in the suppression of diastolic flow through the epicardial coronary artery. However, the consequent rise in intracavitary pressure and the shortening of diastole likely contributed to the complete suppression of flow within the microfistulas. This microfistula flow has been considered coronary flow steal because there is no communication with the coronary network; rather, blood flows directly into the LV cavity without perfusing the myocytes.^{4,10}

In our case report, we observed, for the first time, that this flow steal ceased following a moderate increase in LV contractile performance, which could contribute to the magnitude of clinical manifestations and the prognosis. However, we cannot infer that the suppression of flow steal is the sole determinant of normalization of T-wave polarity on ECG.¹⁶

Conclusion

In this case of apical HCM with microfistulas, the change in ECG T-wave polarity was not consistent with pseudonormalization or myocardial ischemia, as it occurred in the presence of normal epicardial coronary arteries and coincided with suppression of coronary flow steal through the microfistulas, despite the positive inotropic effect.

Author Contributions

Conception and design of the research and writing of the manuscript: Abreu JS; acquisition of data: Abreu JS, Diógenes TCP; analysis and interpretation of the data: Abreu JS, Abreu MEB; critical revision of the manuscript for intellectual content: Chagas ISM, Feitosa MPM.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

Ethics Approval and Consent to Participate

This study was approved by the Research Ethics Committee of Universidade Estadual do Ceará under protocol number 6.312.526 (approved on 09/20/2023). All the procedures

in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

Use of Artificial Intelligence

The authors did not use any artificial intelligence tools in the development of this work.

Availability of Research Data

The underlying content of the research text is contained within the manuscript.

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Unicuspid Aortic Valve in a Young Woman Associated with Aortopathy and Atrial Septal Defect: Therapeutic Implications

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Abstract

Unicuspid aortic valve (UAV) is a rare congenital anomaly, frequently associated with early progression to severe aortic stenosis and aortopathy. We report the case of a 38-year-old woman who presented with difficult-to-control hypertension and progressive exertional dyspnea. Transthoracic echocardiography revealed critical aortic stenosis (peak gradient of 183 mmHg, mean gradient of 125 mmHg, and valve area of 0.59 cm²), associated with mild aortic regurgitation and ascending aortic dilation (45–46 mm). Three-dimensional transesophageal echocardiography confirmed a unicommissural UAV, as well as an ostium secundum atrial septal defect with a left-to-right shunt (Qp/Qs = 2.3). Given the significant hemodynamic impact, aortic valve replacement with a bioprosthetic valve was performed. The patient developed a conduction disturbance during the postoperative period, requiring permanent pacemaker implantation. At the 6-month follow-up, she was asymptomatic, and the prosthetic valve was functioning normally. This case illustrates the importance of advanced echocardiography in identifying rare valvular anomalies and highlights the uncommon association between UAV, aortopathy, and atrial septal defect in a young woman, with relevant implications for clinical and surgical management.

Introduction

Unicuspid aortic valve (UAV) is a rare congenital malformation, with an estimated prevalence of less than 0.02% in the general population.^{1,2} It is characterized by a more aggressive clinical course than that associated with bicuspid aortic valve, with early degeneration and rapid progression to severe aortic stenosis in young individuals.^{2,3} UAV is frequently associated with ascending aortic dilation and, more rarely, with other congenital heart defects, posing a diagnostic challenge. Transesophageal echocardiography, especially with three-dimensional reconstruction, plays a fundamental role in identifying this anomaly and differentiating it from a calcified bicuspid valve.^{4,5} The association of UAV, aortopathy, and other congenital

anomalies in a young woman is uncommon, underscoring the clinical relevance of this case report.

Case report

We report the case of a 38-year-old woman with difficult-to-control hypertension who presented with progressive dyspnea upon moderate exertion. As shown in Figure 1, transthoracic echocardiography revealed critical aortic stenosis (peak gradient of 183 mmHg, mean gradient of 125 mmHg, and valve area of 0.59 cm²), associated with mild aortic regurgitation and ascending aortic dilation (46 mm). Concentric left ventricular hypertrophy, preserved ejection fraction, grade I diastolic dysfunction, reduced global longitudinal strain (13%), mild left atrial dilation, and signs of right heart volume overload were also observed. Another echocardiogram confirmed elevated transvalvular velocities and a significant reduction in valve area (Figure 2). Three-dimensional transesophageal echocardiography confirmed a unicommissural UAV (Figure 3) and an ostium secundum atrial septal defect (14 mm), with a left-to-right shunt and a Qp/Qs ratio of 2.3, indicating a significant hemodynamic impact. Given this clinical condition, aortic valve replacement was indicated. Following shared decision-making, taking the patient's age, preferences, and desire to avoid chronic anticoagulation into account, a bioprosthetic valve was selected, which is considered an acceptable strategy under current guidelines.^{1,4} Although the ascending aorta was dilated, its diameter was within the borderline range for isolated surgical intervention; therefore, clinical follow-up and serial imaging were chosen. During the postoperative period, she developed a conduction disturbance, requiring permanent pacemaker implantation. At the 6-month outpatient follow-up, she was asymptomatic, with a normally functioning prosthetic valve.

Discussion

UAV is an extremely rare congenital malformation, often associated with a more aggressive clinical course than bicuspid aortic valve, and requiring early intervention.^{2,3} Consistent with the findings described by Roberts et al.,² presentation in young adulthood with critical aortic stenosis underscores the accelerated nature of valvular degeneration in these patients. From an anatomical perspective, the unicommissural type is the most commonly seen in patients who survive into adulthood.³ Identifying this anomaly via transthoracic echocardiography can be challenging; transesophageal echocardiography, particularly with three-dimensional reconstruction, is crucial for differential diagnosis, in accordance with current guidelines.^{4,5} The association between UAV and ascending aortic dilation suggests an underlying intrinsic aortopathy, possibly related to structural alterations in the extracellular matrix of the vascular wall. This mechanism is similar to that observed in bicuspid aortic valve.^{6,7}

Keywords

Aortic Valve; Aortic Valve Stenosis; Aortic Aneurysm; Congenital Heart Defects

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Case Report

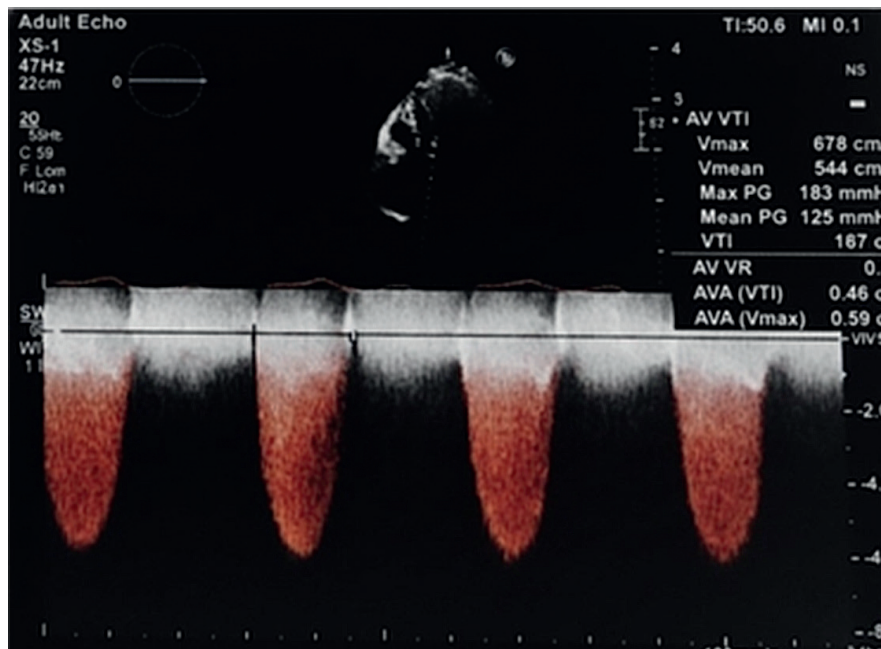


Figure 1 – Transthoracic echocardiography with continuous-wave Doppler (apical five-chamber view) demonstrating transvalvular aortic flow with significantly elevated velocities, consistent with critical aortic stenosis. Peak systolic gradient: 183 mmHg; mean gradient: 125 mmHg; aortic valve area: 0.59 cm². AV VTI: Aortic Valve Velocity-Time Integral; AV: Aortic Valve; VR: Velocity Ratio; AVA: Aortic Valve Area.

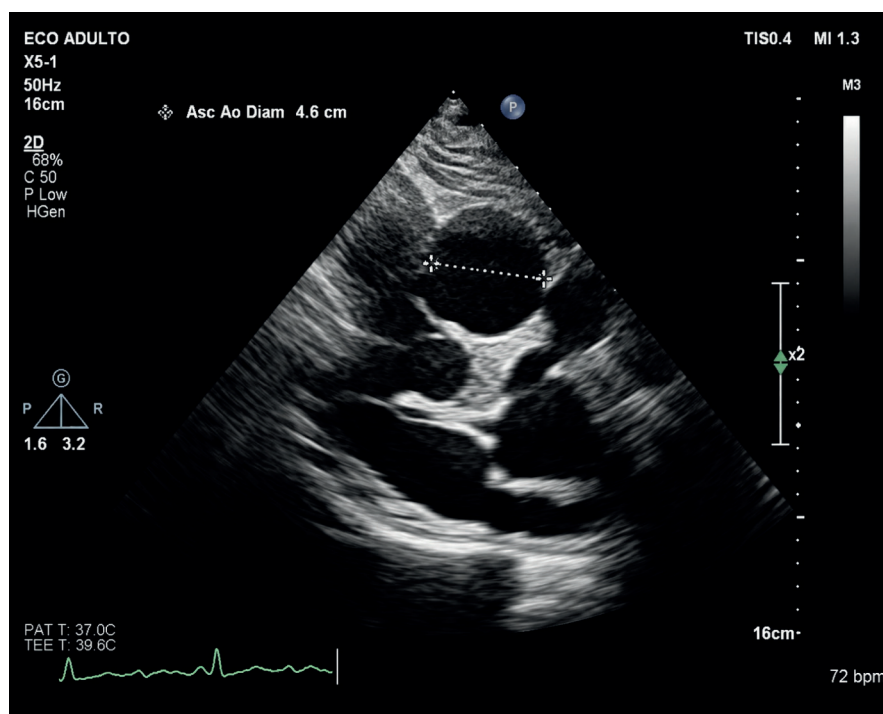


Figure 2 – Transthoracic echocardiogram showing ascending aortic dilation (arrow), with a maximum diameter of 46 mm, consistent with aortopathy associated with a UAV. PAT: Patient Temperature; TEE: Transesophageal Echocardiography.

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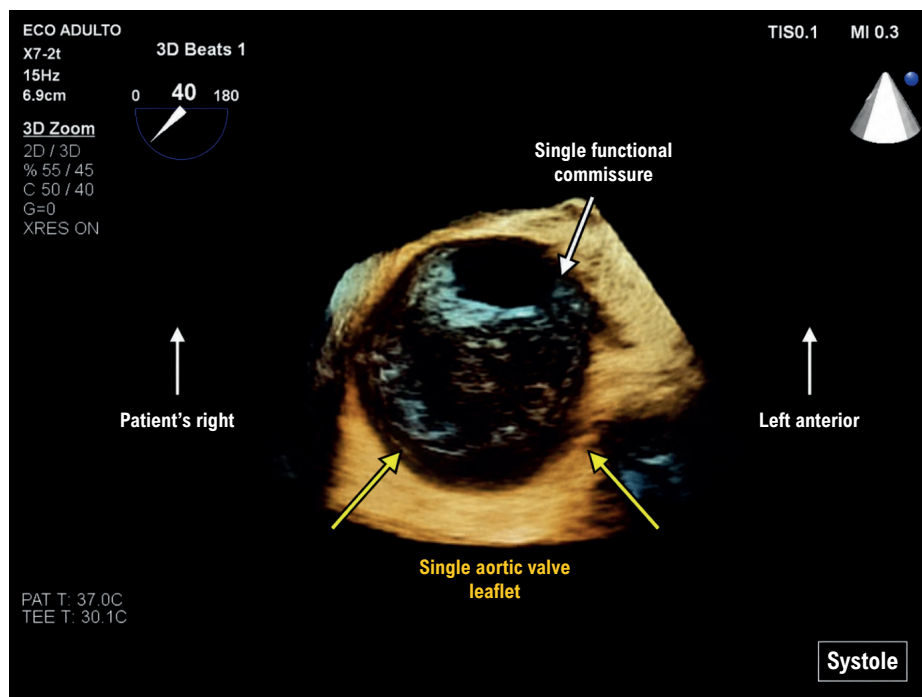


Figure 3 – Three-dimensional transesophageal echocardiography (en face view) of the aortic valve, acquired during systole, showing a unicommissural UAV. The white arrow indicates a single functional commissure, allowing for differentiation from a calcified bicuspid aortic valve. PAT: Patient Temperature; TEE: Transesophageal Echocardiography.

Furthermore, reduced global longitudinal strain (13%),⁸ even with a preserved ejection fraction, indicates subclinical myocardial dysfunction, as described by Delgado et al.,⁹ representing an early marker of ventricular impairment and greater hemodynamic severity. The association of UAV, aortopathy, and atrial septal defect is uncommon in clinical practice, particularly in patients who reach adulthood without a prior diagnosis. This finding suggests a broader spectrum of cardiac developmental abnormalities. The severity of aortic stenosis warrants a surgical approach, as recommended by current guidelines.^{1,4,10} The choice of a bioprosthetic valve, although less durable, is acceptable given the patient's preference and the risks associated with chronic anticoagulation.^{1,4} Postoperative complications, including conduction disturbances, have been documented in the literature and should be taken into account during preoperative management and counseling. The reported case reinforces the importance of diagnostic suspicion in young patients with significant aortic stenosis, as well as the key role of advanced echocardiography in anatomical definition, prognostic stratification, and therapeutic planning.

Author Contributions

Conception and design of the research and writing of the manuscript: Santos KQ; acquisition of data, analysis and interpretation of the data and critical revision of the manuscript for intellectual content: Santos KQ, Melo MBL.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any thesis or dissertation work.

Ethics Approval and Consent to Participate

The authors declare that this clinical case report does not constitute research involving human subjects. Informed consent was obtained from all participants included in the study.

Use of Artificial Intelligence

The authors did not use any artificial intelligence tools in the development of this work.

Availability of Research Data

The underlying content of the research text is contained within the manuscript.

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Beyond the Appendage: Left Atrial Wall Thrombosis in Rheumatic Mitral Stenosis

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A 61-year-old woman with a history of rheumatic valvular heart disease and permanent atrial fibrillation (AF), chronically anticoagulated with rivaroxaban, presented with acute ischemic stroke and bilateral upper-limb ischemia. Neuroimaging revealed an acute infarction in the right middle cerebral artery territory and a subacute infarction in the left posterior cerebral artery territory (Figure 1A). Doppler ultrasound confirmed arterial occlusion in both upper limbs (Figure 1B).

Transesophageal echocardiography demonstrated marked left atrial (LA) enlargement, dense spontaneous echocardiographic contrast within the left atrial appendage (LAA), and reduced appendage flow velocities, without evidence of an organized thrombus (Figure 1C). The mitral valve exhibited features consistent with chronic rheumatic disease, with an estimated valve area of 1.0 cm² (Figure 1D). Notably, two- and three-dimensional imaging identified a large mural thrombus adherent to the LA wall, extending along the lateral and posterior walls and measuring approximately 4 × 0.8 cm (Figure 1E-F; Supplementary Videos 1-3).

Three months after hospital discharge, the patient remains enrolled in a rehabilitation program, with persistent severe motor and cognitive deficits.

LA mural thrombus is an uncommon finding, reported in approximately 2.7% of anticoagulated patients with AF.^{1,2} Although oral anticoagulation reduces thromboembolic risk, the INVICTUS trial demonstrated superior outcomes with vitamin K antagonists (VKAs) compared with rivaroxaban in patients with rheumatic heart disease–associated AF.^{3,4}

This case highlights a rare but clinically significant presentation of LA mural thrombus and reinforces current recommendations favoring VKA therapy in rheumatic AF. Importantly, it underscores that cardioembolic sources may extend beyond the LAA.

Author Contributions

Conception and design of the research: Resende B, Carlos T, Teixeira R; Acquisition of data, analysis and interpretation of the data e writing of the manuscript: Resende B, Carlos T; critical revision of the manuscript for intellectual content: Teixeira R, Gonçalves L.

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The authors did not use any artificial intelligence tools in the development of this work.

Availability of Research Data

The underlying content of the research text is contained within the manuscript.

Keywords

Echocardiography; Mitral Valve Stenosis; Atrial Fibrillation

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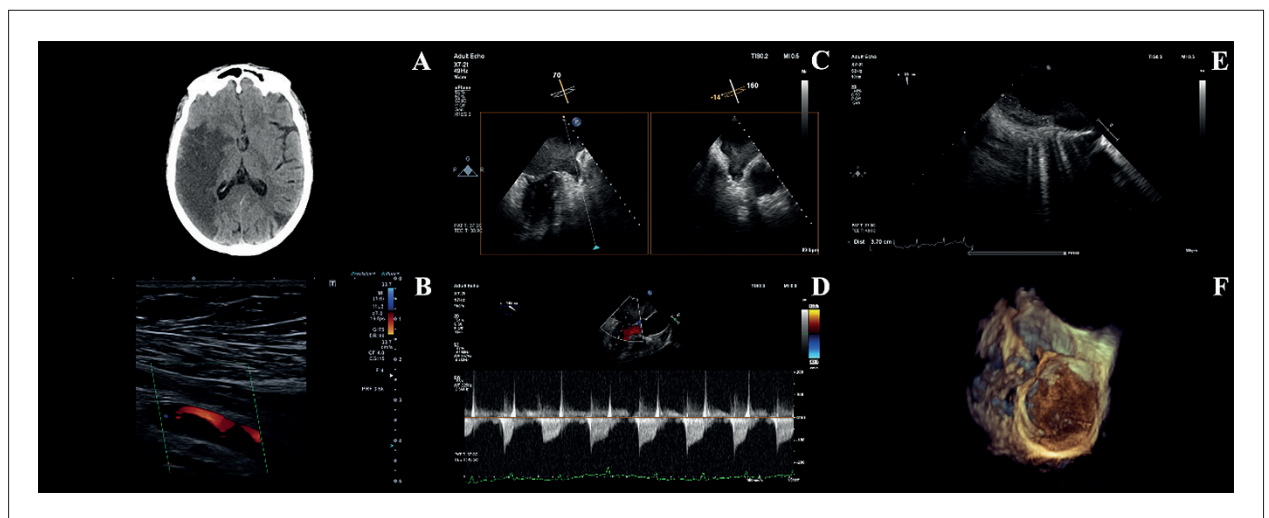


Figure 1 – Multimodality imaging findings; A) Brain computed tomography performed three days after admission showing an evolved cortico-subcortical ischemic lesion in the right temporoparietal region; B) Upper-limb arterial Doppler ultrasound of the right subclavian artery demonstrating arterial occlusion; C) Transesophageal echocardiography showing the LA appendage with marked spontaneous echocardiographic contrast and no organized thrombus; D) Transesophageal echocardiographic assessment of the mitral valve demonstrating features of rheumatic mitral stenosis, with spectral Doppler findings consistent with significant valvular obstruction; E) Two-dimensional transesophageal echocardiographic image demonstrating a large mural thrombus adherent to the lateral and posterior walls of the left atrium, measuring up to 37 mm in its longest axis; F) Live three-dimensional transesophageal echocardiographic imaging of the LA mural thrombus

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Left Ventricular Strain: Guideline Update and New Analysis Software

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Introduction

Myocardial strain analysis is a sensitive method for the early assessment of alterations in left ventricular (LV) mechanics; it is capable of detecting incipient changes and is less influenced by ventricular geometry or loading conditions.¹ Echocardiography is a reproducible and cost-effective method for this assessment, given the ongoing development and widespread integration of new technologies into ultrasound systems. Various studies have demonstrated the importance of measuring global longitudinal strain (GLS), in addition to conventional parameters, for assessment of structural and functional changes in diverse clinical scenarios,¹ including the following:

- Athletes
- Systemic arterial hypertension
- Cardiomyopathies (dilated, ischemic, Chagas, cardiotoxicity, amyloidosis, Fabry, hypertrophic, takotsubo)
- Active ischemic heart disease
- Arrhythmias
- Dyssynchrony
- Valvular heart diseases

Myocardial segment for strain analysis and standardization of echocardiographic reporting

Ultrasound software vendors currently vary regarding the optimal myocardial segment (endocardium, myocardium, or epicardium) for strain analysis.² Although endocardial tracking, combined endocardial and epicardial analysis, and midwall/full-wall tracking are equally feasible and reproducible, there is growing evidence that midwall strain measurements based on full-wall tracking are less susceptible to variations in imaging geometry that are considered suboptimal.^{1,3} There is also more robust evidence in the literature regarding reference values and clinical applicability for this approach, which also appears to be the most accurate, as the region of interest (ROI) includes a larger number of myocardial points (speckles) that can be tracked^{1,2} (Figure 1).

Keywords

Sprains and Strains; Heart Ventricles; Echocardiography

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Regarding standardization of echocardiographic reporting, the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI), in their latest consensus statement,¹ recommend the following:

1. When presenting segmental strain values, the negative sign should be retained for differentiating dyskinetic from normal myocardial contractility.
2. If the negative sign is omitted, then the term global longitudinal shortening should be used to correctly refer to the values presented.
3. The current recommendation is to report the myocardial strain value determined at the end of ventricular systole, rather than the peak systolic value^{1,2} (maximum negative systolic strain within the systolic interval or peak strain), as illustrated in Figure 2.
4. Reference values for LV GLS are as follows^{1,5}:
Normal: More negative than –18%
Borderline: –16% to –18%
Abnormal: Less negative than –16%.*

* Morris et al. conducted the most comprehensive meta-analysis on LV GLS, involving a total of 47 studies and 23,208 healthy adults.⁵ This study identified 16% (absolute value) as the lower limit of normal across major software packages.

5. Normal values of GLS may vary between software versions. Comparisons of GLS should ideally be made using the same software vendor and version.¹
6. The optimal use of LV GLS is in sequential follow-up, by comparison with baseline. A relative change of 10% to 15% is likely significant.¹
7. The use of three-dimensional strain is still in development due to variations in software and inconsistent results, and it is not recommended for clinical use.¹
8. Regional strain values have shown too much variability between tests and between vendors to be used clinically.¹

Determining the timing of the systolic period

Accurate determination of the effective systolic period is fundamental for myocardial strain quantification.^{1,4} Echocardiographic assessment, as validated in ultrasound systems, commonly employs the following time markers:

- **End-diastole:** Peak of the R wave on the electrocardiogram.
- **End-systole:** End of the T wave on the electrocardiogram or aortic valve closure in the apical three-chamber view.

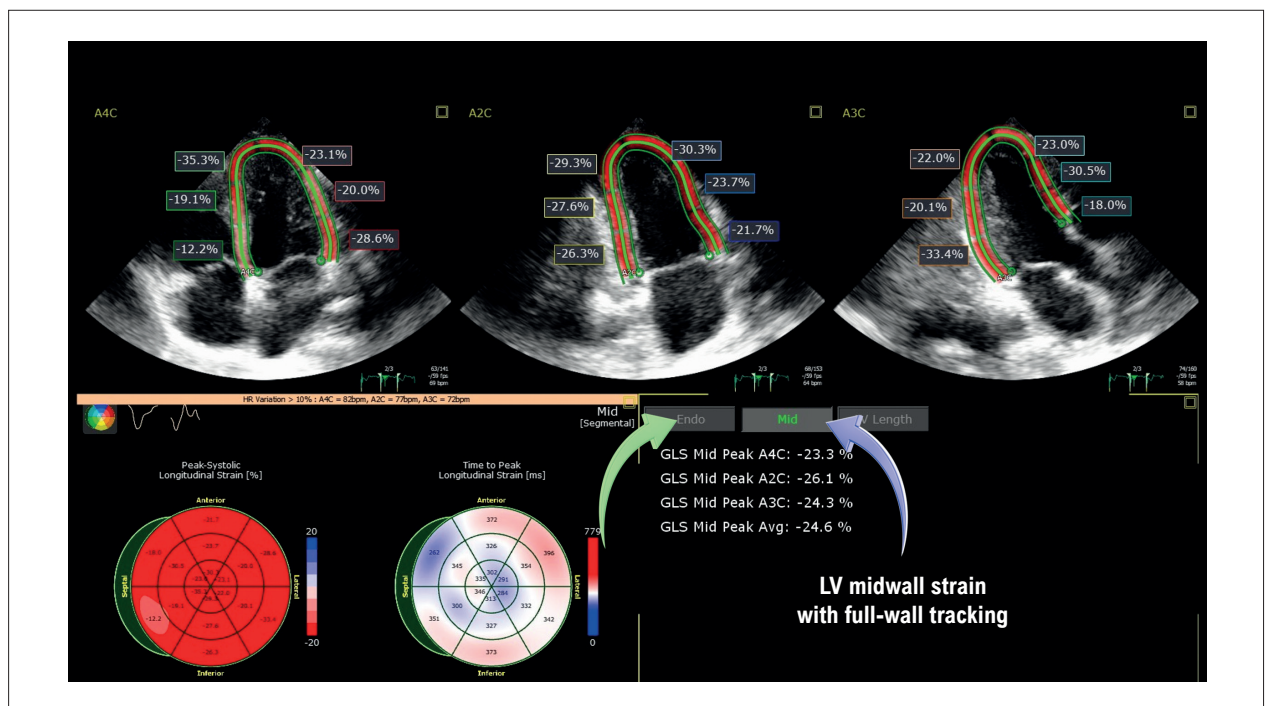


Figure 1 – Assessment recommended by the ASE and the EACVI¹ regarding the myocardial segment tracked for the analysis of LV GLS, as well as the description of the final value (blue arrow). Despite the recommendation to use the midwall segment of the left ventricle, echocardiography software still allows assessment of other segments, such as, in this case, the endocardial segment (green arrow). LV: left ventricular.

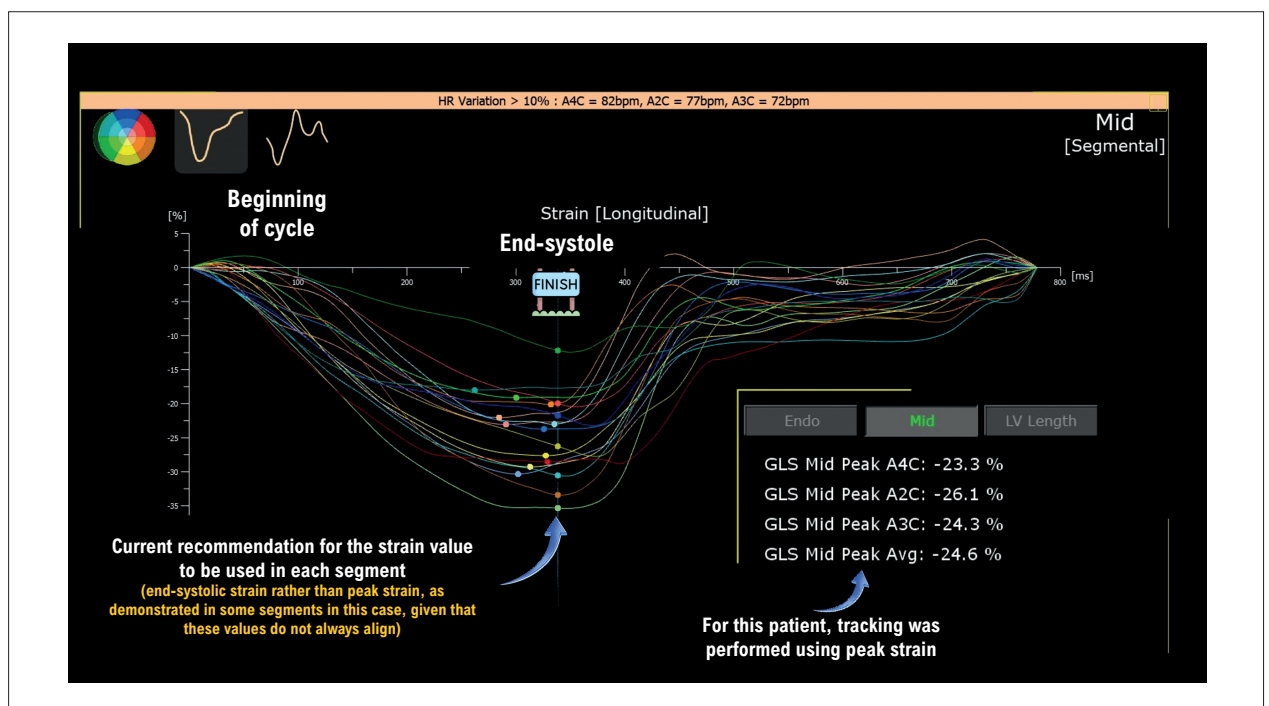


Figure 2 – Assessment of strain curves and description of the values to be used. According to the Clinical Applications of Strain Echocardiography: A Clinical Consensus Statement from the ASE Developed in Collaboration with the EACVI of the European Society of Cardiology, the final value used should be the one shown at the end of ventricular systole, which does not always align with peak strain.^{1,4}

Viewpoint

This assessment can be replaced by event markers guided exclusively by two-dimensional echocardiography:

- **End-diastole:** Mitral valve closure or the onset of a new cardiac cycle.^{1,4}
- **End-systole:** Aortic valve closure.^{1,4}

Precautions and implications of errors during analysis

Image analysis for strain estimation is based on the following assumptions:

- The image was adequately acquired and is of sufficient quality to allow for effective speckle tracking.
- The region under analysis was correctly defined.
- Systolic and diastolic timings were accurately identified.

Inaccuracy in any of these factors can lead to errors in the strain results. Listed below are the main factors that can increase or decrease strain values:¹

- Parameters that may overestimate strain values:
 - Image acquisition with LV foreshortening³
 - Narrow ROI
 - Inaccurate definition of end-diastolic and end-systolic timing⁴
 - Using only a single cardiac cycle in cases of arrhythmia, for example, atrial fibrillation
- Parameters that may underestimate strain values:
 - Inadequate image quality (incorrect speckle tracking)
 - Wide ROI
 - Inaccurate definition of end-diastolic and end-systolic timing
 - Using only a single cardiac cycle in cases of arrhythmia, for example, atrial fibrillation

Limitations and new technological solutions

Despite the validated standardization for myocardial strain assessment, the significant volume of echocardiographic exams in outpatient settings often means that electrocardiography is not routinely used; this hinders the retrospective analysis of cardiac strain and the determination of global strain values.

Considering these data, some companies have incorporated features into their software that allow for strain assessment without electrocardiographic gating, as well as using data from a single cardiac cycle, thereby facilitating assessment of results either during the exam or afterward. For this analysis, it is necessary to determine the end-diastolic point between two cardiac cycles, as shown in Figure 3.

In previous software for analysis, it was important to mark the timing of both mitral valve closure and aortic valve

closure. However, in current analysis methods, these data points are replaced by a cardiac cycle gated exclusively by mitral valve opening and closure using M-mode (superior temporal resolution). Figure 4 outlines the step-by-step process for acquiring data and analyzing GLS without requiring an electrocardiogram.

Conclusion

Gating images for strain analysis using the mitral valve leaflet is a viable, reliable, and easily reproducible alternative that is increasingly being incorporated into the software embedded in echocardiography systems. Given the impact of this analysis across various clinical scenarios, this alternative should always be considered; it greatly facilitates the reporting of this echocardiographic parameter, which has validated prognostic value superior to that of ejection fraction alone. As with any new analysis technique, this approach requires comparative studies to determine the accuracy of the measurement in relation to established, validated markers of clinical events.

Author Contributions

Conception and design of the research and writing of the manuscript: Gomes HM; Silva HAGP.

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Availability of Research Data

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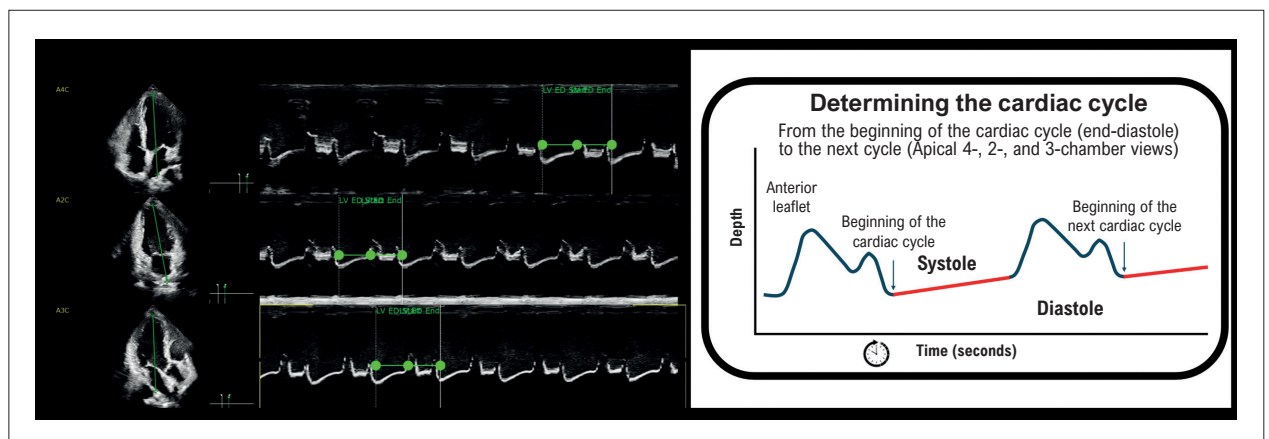


Figure 3 – M-mode assessment of the mitral valve (anterior leaflet) to accurately establish cardiac cycle timing. Markers must first identify end-diastole, which guides the speckle-tracking software in determining the beginning and end of the cardiac cycle (in this case, tracking a single complete cardiac cycle).

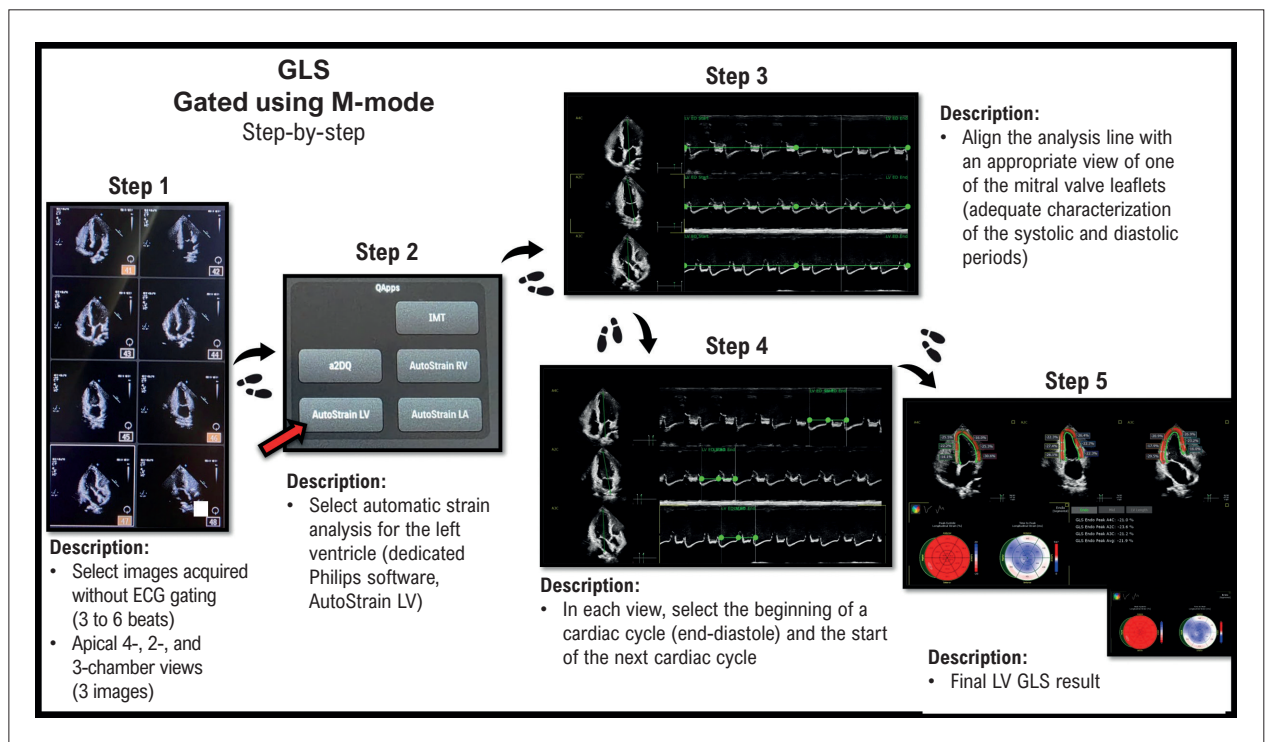


Figure 4 – Step 1: Acquisition of echocardiographic images in the 4-chamber, 2-chamber, and 3-chamber views (3 to 6 cycles whenever possible). Step 2: Select the images and initiate automatic strain analysis using dedicated software, in this case, AutoStrain LV. Step 3: Using M-mode, select a view through the mitral valve (anterior or posterior leaflet) to allow for correct tracking of the cardiac cycle. Generally, the anterior leaflet allows for better tracking due to its length. Step 4: Manually determine the end-diastolic period (start of the cycle) by marking this parameter in two cardiac cycles (Note: If necessary, adjust ROI thickness, depending on myocardial thickness, and use moving two-dimensional imaging to better identify end-diastole). Step 5: Accept the tracking and longitudinal strain result, and record the global value in the report. GLS: global longitudinal strain; LV: left ventricular.

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