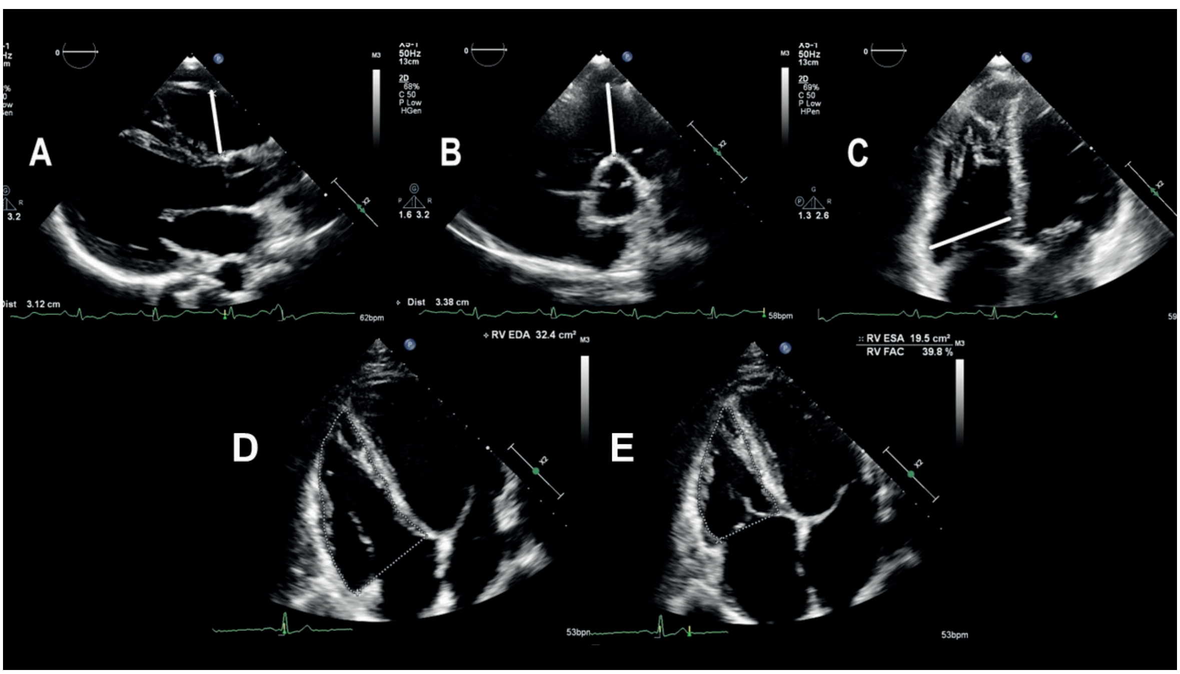
Review Article

My Approach To Echocardiographic Evaluation in Arrhythmogenic Cardiomyopathy

Danilo Bora Moleta,[1] Cassio Carvalho Soeiro Machado,[2] Lucas Arraes de França,[3] Marcelo Luiz Campos Vieira[3,4]
Hospital viValle,[1] São José dos Campos, SP – Brazil
Hospital do Coração do Brasil,[2] Brasília, DF – Brazil
Hospital Israelita Albert Einstein,[3] São Paulo, SP – Brazil
Universidade de São Paulo, Instituto do Coração,[4] São Paulo, SP – Brazil

Central Illustration: My Approach To Echocardiographic Evaluation in Arrhythmogenic Cardiomyopathy



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Representation of measurements of RV diameters and their functional assessment on a two-dimensional echocardiography. Diameters of the proximal outflow tract evaluated in the parasternal window on the long axis (A) and on the short axis (B). Basal diameter in the apical 4-chamber window (C). Fractional variation in area, with assessment in diastole (D) and systole (E).

Keywords

Cardiomyopathies; Arrhythmogenic Right Ventricular Dysplasia; Ventricular Tachycardia; Sudden Cardiac Death; Right Ventricular Dysfunction

Mailing Address: Danilo Bora Moleta •
Hospital viValle. Av. Linneu de Moura, 995. Postal Code: 12244-380. São José dos Campos, SP – Brazil
E-mail: dbmoleta@gmail.com
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Abstract

Careful echocardiographic evaluation of the right ventricle, although challenging and sometimes neglected, is of utmost importance in the diagnosis of certain pathologies, such as arrhythmogenic cardiomyopathy (ACM) — a hereditary myocardial disease associated with the development of ventricular arrhythmias, heart failure, and sudden death. This article aims to review the diagnostic criteria proposed in the 2010 Task Force and the modifications suggested by the 2020 Padua criteria, as well as illustrate the potential use of advanced echocardiography techniques for earlier detection and prognostic definition.

Introduction

Arrhythmogenic cardiomyopathy (ACM) is one of the main causes of sudden death among young people and athletes.[1] It is a genetically transmitted disease, characterized by the progressive replacement of the univentricular or biventricular myocardium by fibrofatty tissue that is predisposed to systolic dysfunction and potentially fatal ventricular arrhythmias.[2] Today we recognize that CMA actually corresponds to a group of diseases with different genotypes and phenotypic presentations.[3]

Initially, the pathology was described as a cardiac condition that involved ventricular arrhythmias, sudden death, and fibrofatty replacement of the right ventricular (RV) myocardium, and was then called arrhythmogenic RV dysplasia.[4] With the advancement of the understanding of pathophysiology and the involved genetics, mainly with the recognition of the genetically determined defect in intercellular adherence by desmosomes, the disease was classified as cardiomyopathy.[1] From carrying out magnetic resonance imaging (MRI) exams in patients with the diagnosis and evaluating the pathological anatomy of victims of sudden death, the involvement of the left ventricle (LV) was also recognized, and the term ACM was proposed.[5]

The process of fibrofatty replacement begins in the epicardial or mesocardial layer, extending to transmural involvement, with wall thinning and the formation of aneurysms, typically located at the apex and in the inferior and infundibular walls of the RV ("classic triangle of dysplasia").[1] However, it was recognized that the apex of the RV is only impacted in the most severe forms of the disease and that another point of the triangle would be the lateral wall of the LV.[6] Generally, LV involvement provides more nonspecific findings on the echocardiogram, and there is an overlap with manifestations of other cardiomyopathies. The ventricular septum is normally spared in the disease.

The current CMA classification includes the following phenotypic variants: right dominant, classic RV arrhythmogenic cardiomyopathy (RVAC), with minimal or no LV involvement; the biventricular variant, characterized by parallel involvement of the RV and LV; and LV arrhythmogenic cardiomyopathy (LVAC), with minimal or no RV involvement.[7]

In this article, our objective will be to review the diagnostic criteria proposed in the 2010 Task Force (TFC) and the modifications suggested by the 2020 Padua criteria, as well as illustrate the potential use of advanced echocardiography techniques for early detection and prognostic definition.[8]

Diagnosis

The diagnosis is currently based on TFC 2010, involving a combination of data from different categories: imaging, electrocardiography, family history, genetics and histology. Imaging modalities include ventriculography, echocardiography, and MRI, with a qualitative assessment of RV contractility, in addition to few quantitative measurements of dimensions and systolic function (Table 1). The 2010 TFC does not involve structural findings related to the LV. The image category has a sensitivity of around 70% and a specificity of around 95%. The presence of segmental contractile alteration is mandatory in order to fulfill diagnostic criteria using imaging methods, with the degree of dilation and global dysfunction determining the definition of greater or lesser criteria. Isolated findings on imaging tests, without electrocardiographic changes, should be considered suspicious and do not enable a diagnosis of the disease. Patients with initial structural changes, which are difficult to detect using imaging methods, may present arrhythmias and sudden death. Therefore, it is important to refine diagnostic tools for early detection and prognostic stratification. Updated criteria, known as the "Padua criteria", including involvement of the LV, have been proposed, but further validation is still necessary (Table 2).[2, 8, 9]

Table 1 – Modified diagnostic criteria – 2010 Task Force

Imaging criteria for ACM	
Overall or regional dysfunction and structural changes	
	Major
Echocardiogram	RV with akinesia, dyskinesia or aneurysm AND one of the following parameters, measured at end-diastole: – RVOT in the long axis ≥ 32 mm – RVOT in the short axis ≥ 36 mm – FAC ≤ 33%
Resonance	RV with akinesia or dyskinesia or asynchronous contraction AND one of the following: – Indexed RV end-diastolic volume ≥ 110 ml/m² (man) or ≥ 100 ml/m² (woman) – RVEF ≤ 40%
Ventriculography	RV with akinesia, dyskinesia, or aneurysm
	Minor
Echocardiogram	RV with akinesia, dyskinesia, or aneurysm AND one of the following parameters, measured at end-diastole: – RVOT in the long axis ≥ 29 to < 32 mm – RVOT in the short axis ≥ 32 to < 36 mm – FAC > 33% to ≤ 40%
Resonance	RV with akinesia or dyskinesia or asynchronous contraction AND one of the following: – Indexed RV end-diastolic volume ≥ 100 to < 110 ml/m² (men) or ≥ 90 to < 100 ml/m² (women) – RVEF > 40% to ≤ 45%

RV: right ventricle; RVOT: right ventricular outflow tract; FAC: fractional area variation; RVEF: right ventricular ejection fraction; ACM: arrhythmogenic cardiomyopathy.

Initial echocardiographic evaluation

Echocardiography is the imaging modality initially used for screening, in conjunction with an MRI, and mainly for sequential evaluation, due to its low cost, availability, patient tolerance, and non-invasiveness. It is essential in the long-term follow-up of patients with an established diagnosis and the use of an implantable cardioverter defibrillator (ICD) of a model that is not compatible with the MRI. However, diagnosing AMC by echocardiography is challenging and requires experience. The identification of segmental contractile changes requires evaluation in multiple views, some of which are unusual in routine examinations. The peculiar anatomy of the right ventricle and the retrosternal position make it difficult to visualize its complex geometry.[9]

Although some of the parameters presented below are not part of the 2010 TFC, additional data demonstrating dysfunction may help identify cases that require surveillance or close follow-up.

The 2010 TFC includes the following criteria, using two-dimensional echocardiography: akinesia, dyskinesia, or aneurysms, associated with increased diameters in the proximal RV outflow tract (RVOT) or reduced fractional variation in the RV area (FAC).[2, 8, 9]

The search for changes in RV segmental contractility should be carried out in parasternal long-axis views, parasternal views of the RV inlet, parasternal short-axis views from the basal level to the apex, apical 4-chamber views focused on the RV, and subcostal views, for a more complete assessment of the RV myocardial segments (Figure 1). In patients with advanced disease, the detection of aneurysms is more frequent, and it is possible to detect intracavitary thrombi (Figure 2).

Table 2 – International diagnostic criteria 2020 (Padua Criteria) – category of morphofunctional alterations

	International criteria for AMC 2020 (Padua) – Morphofunctional Changes	
	RV	**LV**
	Major	**Major**
Echocardiogram, resonance, or ventriculography	RV with akinesia, dyskinesia or aneurysm AND one of the following parameters: – Global RV dilation (according to references for each method for sex, age, and body surface); – Global systolic dysfunction (according to RVEF references for each method per sex and age)	There are no criteria with sufficient specificity in this category.
	Minor	**Minor**
Echocardiogram, resonance, or ventriculography	RV with akinesia, dyskinesia, or aneurysm, with no characterization of dilatation or global systolic dysfunction	Global systolic dysfunction (reduction in LVEF or GLS), with or without dilation; Hypokinesia or akinesia of segments of the free wall, septum, or both

Adapted from Corrado D et al. There is no major criterion for LV involvement in this imaging category, but there is a separate category of structural changes with a description of specific late enhancement patterns on MRIs. RV: right ventricle; LV: left ventricle; EF: ejection fraction; GLS: global longitudinal strain; AMC: arrhythmogenic cardiomyopathy; RVEF: right ventricular ejection fraction; LVEF: left ventricular ejection fraction.

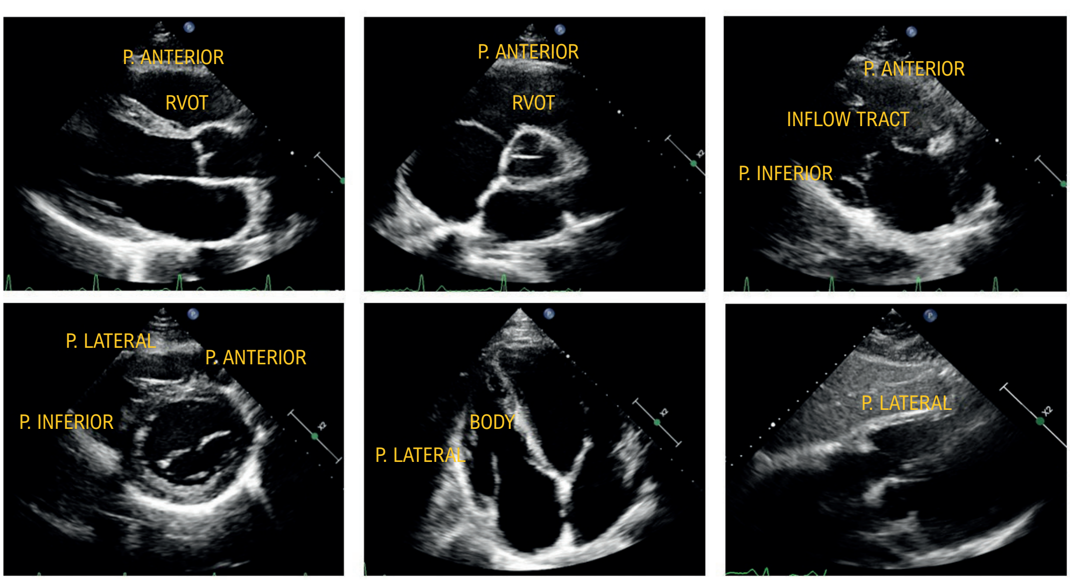

Figure 1 – *View of the RV and its walls in the parasternal, apical 4-chamber windows focused on the RV and subcostal. RV: right ventricle; RVOT: right ventricular outflow tract; P: wall.*

The diameter of the RVOT can be measured in the parasternal long axis or short axis view (Central Illustration – A and B). The short axis measurement is considered more robust and reproducible. In addition to the RVOT measurement recommendation from TFC 2010, it is also suggested to measure the basal, medium and longitudinal diameters in the apical 4-chamber view focused on the RV (Central Illustration – C).[10] Since the latest guidelines for quantification of cardiac chambers published by the main echocardiography societies, the basal diameter has gained greater relevance and is currently the most commonly described in reports. However, when evaluating patients with suspected RVAC, for diagnostic definition, it is essential to also provide the diameter measurements obtained through the parasternal window in the report. Dilation of the RV, whether in the body or in the outflow tract, is associated with a worse prognosis, with a greater occurrence of serious arrhythmias.[11]

Regarding the functional assessment of the right ventricle, the most important measurement to be obtained for classification is the fractional variation of its area (FAC), which must be calculated from images obtained in the apical 4-chamber window focused on the RV, in diastole and in systole, with great attention paid to obtaining the complete edge of the cavity (including apex) and with the greatest possible definition of the free wall endocardium (Central Illustration D and E). In addition to its diagnostic value, reduced FAC is associated with the occurrence of serious cardiovascular outcomes.[12]

It is also recommended to evaluate other functional parameters on a conventional echocardiography, such as systolic excursion of the tricuspid annulus plane (TAPSE) and peak systolic velocity of the lateral tricuspid annulus (s′ wave). There are no specific cut-off values for basal diameter, TAPSE and s′ wave peak velocity in CMA, with the lower limits of normality to evaluate RV longitudinal function considered to be 17 mm and 9.5 cm/s, respectively. Both are usually reduced in RVAC with a definitive diagnosis, especially in advanced forms. The reduction in TAPSE is correlated with a worse prognosis in patients with an established diagnosis of RVAC.[13] It should be remembered that these measurements are more representative of the basal longitudinal contraction of the RV. Thus, due to the characteristic segmental and focal involvement in RVAC, they can remain unchanged during the initial phases of the disease and even in more advanced forms that spare the base of the RV.

In addition to the quantitative assessment of the RV, some findings from the subjective visual assessment are also relevant. The main ones are the presence of a hyperrefringent moderator band, an increase and disorganization of endocardial trabeculations at the apex of the RV and the appearance of saccules in the free wall (Figure 3).

As for the LV, using conventional two-dimensional echocardiography, the presence of reduced ejection fraction and segmental contractile changes should be monitored, especially in the basal lateral wall. However, any myocardial segment can be affected, without regard to coronary territories.[2]

Advanced echocardiographic evaluation

The assessment of RV systolic function using speckle tracking echocardiography is gaining importance, especially in the early detection of dysfunction and the prognosis of various diseases. The possibility of evaluating longitudinal strain immediately after image acquisition on the echocardiography equipment itself and with automated software dedicated to the study of RV myocardial deformation contributes substantially to the potential use of this technique in daily practice.

RV longitudinal strain is studied in the apical 4-chamber view focused on the RV. Currently, the role of the RV free wall strain (RVFWLS) is better defined, with its value calculated from the average of the systolic peak strain of the 3 segments of this wall. RV global longitudinal strain (RV GLS), obtained by averaging the systolic peak strain of the 6 segments evaluated in the apical 4-chamber view focused on the RV, is less used, especially in RVAC, in which there is no septal involvement (Figure 4). There is a description of a reduction in longitudinal strain in the early stages of ACM, mainly in the subtricuspid region (basal segment of the free wall). There are no specific strain reference values for diagnosing ACM, and the same normality reference values defined for the assessment of the RV systolic function in the guidelines are suggested. There are authors who recommend a higher cutoff value for ACM screening, with an absolute value of 23% proposed for the RVFWLS. However, the absolute value for the most commonly used lower limit of normality is 20%.[9, 10]

In a cohort of patients being monitored at a reference Arrhythmology service, we obtained excellent sensitivity of the RVFWLS when identifying patients with RVAC, which was altered in 92% of them. In this same population, the major TF 2010 criteria were met in only 37% of patients using conventional echocardiography and 67% using MRI. In the same group of patients, absolute RVFWLS values below 14.35% were associated with a worse prognosis, with a greater occurrence of serious arrhythmic events.[11]

In addition to the deformation amplitude, the mechanical dispersion can be obtained from the systolic strain, calculated by the standard deviation of the time to peak of the strain, in the model of 3 or 6 segments of the RV, with cutoff values being > 25 ms and > 30 ms, respectively. Increased mechanical dispersion is associated with the presence of structural involvement typical of ACM and the occurrence of arrhythmias.[9]

The assessment of LV systolic function using speckle tracking is also relevant in ACM, especially considering the possibility of earlier diagnosis of LV involvement. The most commonly used parameter, due to practicality and availability, has been the LV global longitudinal strain (LV GLS), with the same normal values suggested in guidelines for quantifying cardiac chambers, with no specific cut-off values for ACM. The reduction in longitudinal deformation can be localized or diffuse, with no correlation to the coronary territory (Figure 5).[9, 10]

LV involvement, with fibrofatty replacement of the myocardium, is also associated with the presence of low voltage on the electrocardiogram. In a cohort of 111 patients

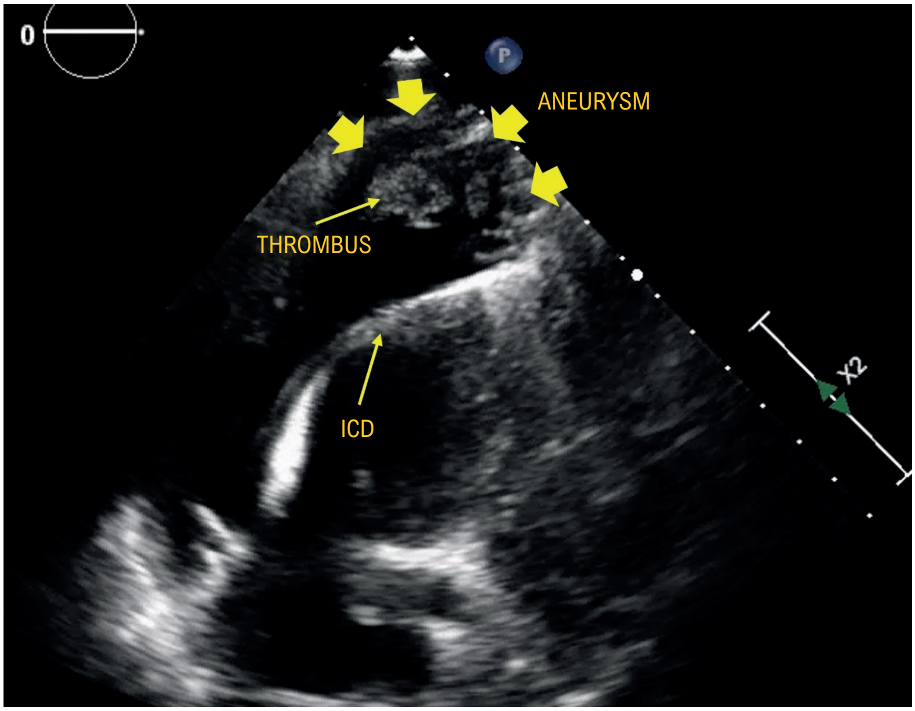

Figure 2 – *Image compatible with intracavitary thrombus in an aneurysm at the apex of the RV in a patient with RVAC using an ICD. RV: right ventricle; RVAC: right ventricular arrhythmogenic cardiomyopathy; ICD: implantable cardioverter defibrillator*

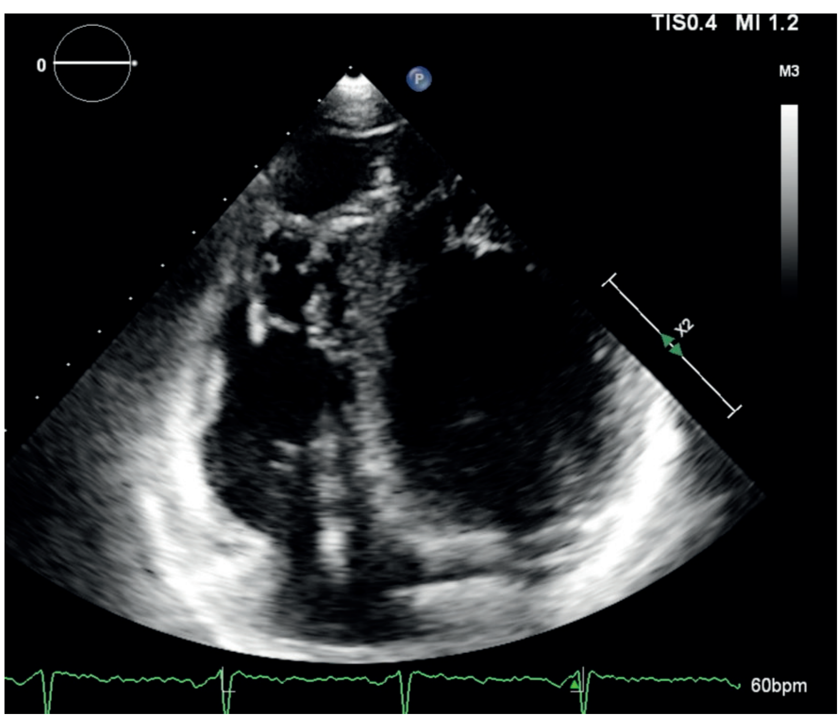

Figure 3 – *Hyperrefringence and increased trabeculation at the apex of the right ventricle in a patient with ACM.*

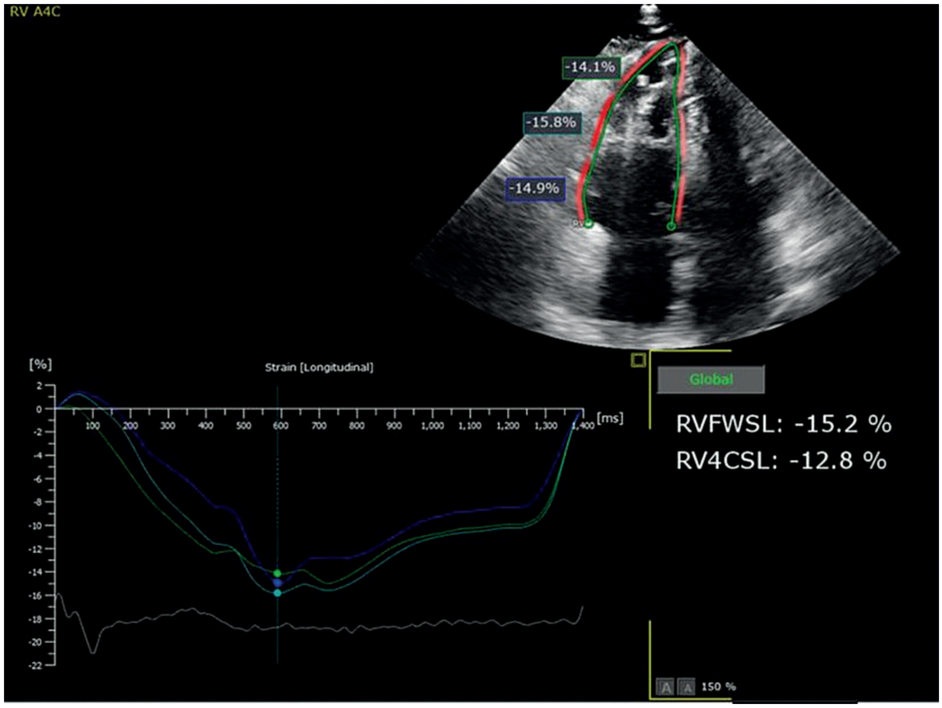

Figure 4 – *Assessment of the longitudinal strain of the right ventricle (RV), in the apical 4-chamber view focused on the RV, showing the results of the reduced longitudinal strain of the RV free wall and GLS of the RV: -15.2% and - 12.8%, respectively.*

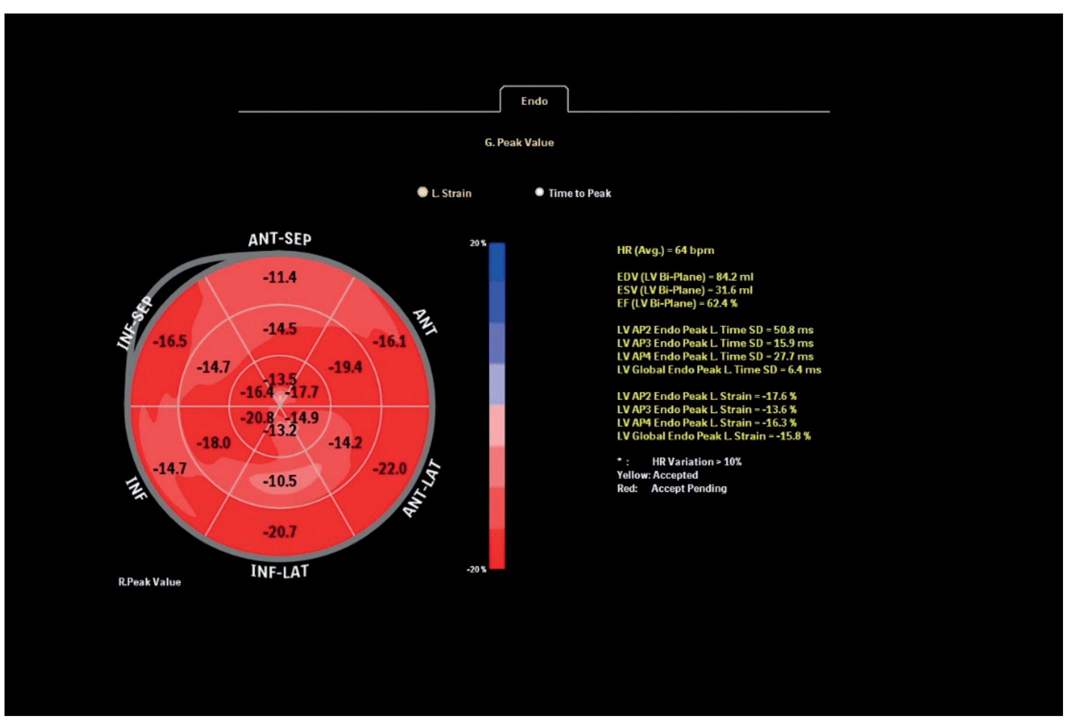

Figure 5 – *Final result with polar map (bull's eye) of the evaluation of GLS of the LV in a patient diagnosed with ACM and biventricular involvement.*

with ACM, the presence of a low-voltage electrocardiogram was an independent predictor of mortality due to heart failure and the need for transplantation.[14]

The study of LV mechanical dispersion, obtained at the end of the LV GLS assessment, has also been gaining ground, with a prognostic value being suggested in several situations, including ACM. In this condition, a dispersion above 45 ms indicates a worse prognosis.[15]

Three-dimensional echocardiography (3D ECHO) is also promising in the assessment of ACM, as it provides volumetric assessment of the RV and LV, with the possibility of calculating the three-dimensional ejection fraction (EF) for both ventricles, in a manner closer to an MRI of the heart (RMC) (Figure 6). Three-dimensional imaging can facilitate the detection of segmental contractile changes due to the possibility of evaluating the three portions of the RV almost completely in a single acquisition. However, the role of 3D ECHO is greater in already established ACM, for the sequential assessment of biventricular systolic dysfunction. In the initial stages, there is normally no significant volumetric increase or reduction in ejection fraction, even when assessed by CMR.

Regarding the *r*ight ventricular ejection fraction (RVEF) by 3D ECHO, many cases have limited assessment due to an inadequate acoustic window for image acquisition or a very significant increase in the RV. Even so, its use for evaluating systolic function in diseases that affect the RV in general has already been recommended in the main guidelines, in places with availability and experience. RVEF > 45% is considered normal. There are still no defined cutoff values for ACM.[9, 10]

Conclusion

Echocardiography is extremely important in the initial and serial evaluation of patients with ACM. Imaging exams do not allow for a diagnosis to be made in isolation. The role of imaging exams is mainly to detect the changes necessary for diagnosis according to current criteria and provide prognostic information that can assist in clinical decisions in this complex scenario.

The advancement of echocardiography and MRIs, combined with clinical, electrocardiographic, and genetic data in new algorithms, eventually associated with artificial intelligence to reduce interobserver variability, could contribute to earlier and more accurate diagnoses and produce better prognostic stratification with an impact on reducing mortality.

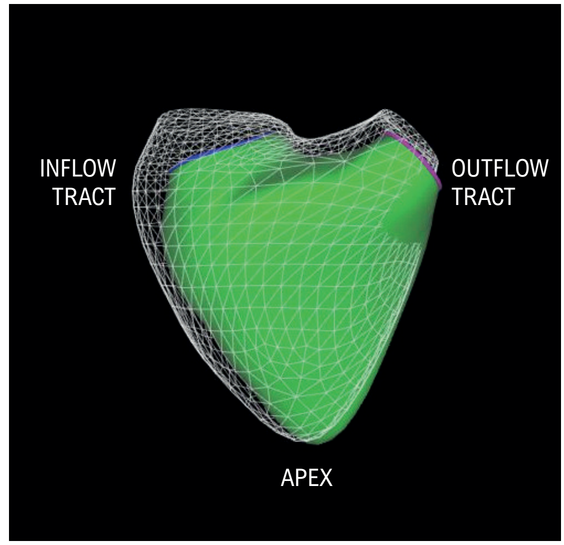

Figure 6 – *Reconstrução tridimensional do VD de paciente com CMA. Em uma única aquisição é possível avaliar volumes, FE e contração segmentar das diferentes porções do VD.*

Author Contributions

Conception and design of the research: Moleta DB; writing of the manuscript: Moleta DB, Machado CCS; critical revision of the manuscript for intellectual content: Moleta DB, Machado CCS, França LA, Vieira MLC.

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

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