

Assessment of Myocardial Fibrosis by Myocardial Deformation Analysis via Echocardiography

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Abstract

Myocardial fibrosis (MF) is a pathological condition common to several primary and secondary heart diseases. Diffuse MF is a common feature in nearly all heart diseases, playing a crucial role in the progression of heart failure (HF). Several studies have indicated that the existence of MF serves as a prognostic factor for adverse outcomes across a range of heart conditions, underscoring the significance of this factor in clinical settings. Consequently, diagnostic approaches for MF, whether in subclinical phases or within established heart diseases, emerge as valuable instruments for early detection, risk stratification, and/or ongoing monitoring of disease developments. Despite being the most accurate non-invasive test for MF research, cardiovascular magnetic resonance (CMR) imaging is a test that is not widely available and is expensive. An alternative method with increased accessibility and cost-effectiveness for assessing heart diseases and researching MF involves echocardiography with the Speckle Tracking (STE) technique to evaluate myocardial deformation ("strain"). Studies show that diminished strain values (both global and segmental) in various heart conditions are associated with the presence and extent of MF, as determined by CMR or histological analysis. MF research using echocardiographic myocardial deformation analysis with STE has gained more space in clinical and research routines as it is an easy-to-perform and low-cost test. The results found by this technique can have a relevant diagnostic, therapeutic, and prognostic impact on clinical practice.

MF is a pathological condition common to several chronic heart diseases, whether primary ones or secondary to systemic diseases with cardiac involvement. Diffuse MF is a common feature in nearly all heart diseases, playing a crucial role in the progression of HF.¹ MF is commonly found after an ischemic insult, but other causes, such as pathologies leading to volume or pressure overload, diabetes mellitus, hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy, non-compacted myocardium, arrhythmogenic right ventricular dysplasia, and systemic diseases such as sarcoidosis, can also contribute to MF.² Several studies have demonstrated that MF serves as a prognostic factor for adverse outcomes across a

range of heart conditions and HF, underscoring the significance of this factor in clinical settings.¹⁻³

MF occurs from the deposition of extracellular matrix (ECM) in the myocardial tissue, leading to excess collagen in relation to cardiomyocytes.² Following an aggressive event, the activation of inflammatory cells and cytokines triggers the proliferation of cardiac fibroblasts, which is a pivotal process in enhancing the production of collagen and other ECM proteins. The disproportionate ECM increase prompts an adaptive response within the myocardium, progressively distorting the architecture of muscle fibers, affecting the physiology of cardiomyocytes, and ultimately resulting in the gradual dysfunction of the heart muscle, characterized by the loss of compliance and/or myocardial contractility.^{1,3-4} The MF process is the final stage of cardiomyopathies, resulting in irreversible damage to myocardium structure and to cellular and electrical functions, with consequent remodeling of the cavities. The degree of MF is related to the severity of ventricular dysfunction.⁵

The diagnosis of MF is increasingly important in the context of cardiomyopathies, as it reflects the pathological structural evolution related to HF in heart diseases and corroborates the need to integrate its diagnosis into the clinical management of patients.³ Consequently, diagnostic approaches for MF, whether in subclinical phases or within established heart diseases, emerge as valuable instruments for early detection, risk stratification, and/or ongoing monitoring of disease developments.

The gold standard for diagnosing MF is endomyocardial biopsy.³ Nevertheless, due to its invasive nature and the potential for complications, the use of this test is limited to situations where there is recent-onset HF with unsatisfactory evolution, evolving with progressive hemodynamic instability and/or ventricular arrhythmias or second-degree atrioventricular blocks Mobitz II or third degree that do not respond adequately to conventional measures.⁴ Therefore, alternative non-invasive MF diagnostic methods are necessary for daily clinical practice.³

Non-invasive diagnostic techniques for MF include CMR with gadolinium for late enhancement investigation, heart tomography with iodinated contrast, PET CT, cardiac SPECT, and echocardiography with the assessment of myocardial deformation using the STE technique.^{2,4}

Among non-invasive MF diagnosis methods, CMR is considered the most accurate as it better characterizes the myocardial tissue.⁴ By using gadolinium-based contrast and late enhancement investigation, it is possible to define areas of focal scar/fibrosis in the different segments of the heart. Still through T1 sequence mapping, the method can detect signs of increased extracellular volume compatible with diffuse fibrosis of the myocardium.^{2,3} However, due to its lower availability in peripheral centers and high cost, it has been limited to selected cases.

Keywords

Endomyocardial Fibrosis; Global Longitudinal Strain; Echocardiography; Cardiomyopathies.

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Echocardiography presents itself as a cost-effective and widely available alternative for assessing heart diseases. The integration of two-dimensional echocardiography with the evaluation of myocardial deformation using STE has become increasingly significant in clinical applications as both a diagnostic and prognostic tool across various heart diseases.⁶

STE uses dedicated software to identify Speckles in the two-dimensional image of the heart muscle. Speckles are a group of points in the two-dimensional image that occur due to the interaction of ultrasound waves with the myocardial tissue. These grouped points are selected by the software and monitored during the myocardial contraction and relaxation process. Through displacement and speed, it is possible to estimate the strain values and strain rate of the myocardial segments. Myocardial deformation analysis can be performed in the longitudinal, circumferential, and radial axes.⁶⁻⁸

STE has become a valuable tool for both the diagnosis and management of various myocardial diseases, including primary or systemic conditions, valvular heart disease, ischemic heart disease, HF, myocardial dyssynchrony, and those associated with diabetes mellitus and arterial hypertension. Additionally, STE is instrumental in diagnosing and monitoring cardiotoxicity resulting from chemotherapy, which is a prevalent application of this technique.⁶

Several studies have demonstrated that reduced strain values (both global and segmental) in different heart conditions are related to the presence and degree of MF, as determined by CMR or histological analysis. The assessment of myocardial deformation through STE allows for a comprehensive understanding of how the underlying disease impacts myocardial function.⁹

In HCM, studies demonstrate that the reduced global and regional strain value is related to the detection of MF on CMR. Popovic et al.¹⁰ demonstrated that individuals with HCM and fibrosis detected on CMR exhibit reduced longitudinal strain values. Their findings also revealed that fibrosis and end-diastolic thickness of the myocardial wall are predictors of lower values of segmental longitudinal strain. Kobayashi et al.¹¹ compared the strain rate values of the septal segment of patients with HCM undergoing myectomy due to dynamic obstruction of the left ventricular outflow tract with histopathological analysis and identified that lower strain rate values were correlated with the magnitude of myocyte hypertrophy, degree of fibrosis, dysplasia of intramural coronary arterioles, and disarray of myocardial fibers.

Gjesdal et al.¹² compared the post-infarction scar tissue mass in chronic ischemic heart disease assessed by CMR with the values found in the analysis of myocardial deformation by STE. In this study, reduced global longitudinal strain (GLS) values showed a significant inverse correlation with the amount of scar tissue detected on CMR. The GLS was even superior to the measurement of left ventricular ejection fraction in identifying smaller infarcts.

Recently, Nagata et al.¹³ published a study evaluating the association between abnormal myocardial mechanics related to mitral valve prolapse (MVP), the presence of MF, and the association with arrhythmias. The study revealed that individuals with MVP and MF predominantly located in the basal and middle segments of the inferolateral wall, as observed through CMR, exhibited reduced strain values in the inferoposterior basal

segment. Moreover, these patients demonstrated an abnormal strain pattern in the lower lateral wall, characterized by two distinct peaks—pre- and post-systolic—which occurred less frequently in the group without MF. Notably, the presence of MF and the abnormal double-peak strain pattern assessed through STE showed an association with ventricular arrhythmia.

In a separate study by Slimani et al.,¹⁴ investigating the relation between post-load, MF, and left ventricular strain in the pre- and postoperative phases of patients with aortic stenosis undergoing valve replacement, it was revealed that reduced values of GLS and global circumferential strain (GCS) were linked to higher values of end-systolic stress in the left ventricular wall. Histopathological analysis of MF indicated that individuals with increased end-systolic stress in the left ventricular wall bore a greater burden of MF, leading to a more adverse outcome after aortic valve replacement. Fabiani et al.¹⁵ also demonstrated the association between reduced GLS and ventricular septum longitudinal strain values and the presence of MF in patients undergoing aortic valve replacement for aortic stenosis and myocardial biopsy.

In patients with HF undergoing heart transplantation, analysis of GLS by STE of the recipient's heart before the procedure showed a correlation with the degree of MF, as assessed by histopathological evaluation of the diseased heart, showing lower GLS values in hearts with MF greater than 50%. Analysis of the GCS and left ventricular torsion also showed a correlation with the presence of MF, but to a lesser extent.¹⁶

Kostakou et al.¹⁷ and Leitman et al.,¹⁸ when evaluating patients diagnosed with myocarditis, observed that these individuals had reduced GLS values despite preserved ejection fraction on conventional echocardiography, in addition to reduced myocardial deformation values in segments that showed fibrosis or edema on CMR.

Reduced strain values by STE of the left atrium and right ventricle are also associated with the histopathological finding of MF with prognostic impacts. In their review on MF detection using STE, Lisi et al.⁵ highlight their study revealing a correlation between the GLS of the right ventricular free wall and the presence of MF, as observed in histological analyses. The review also discusses research indicating an association between reduced right ventricle GLS and a poorer prognosis in conditions such as pulmonary hypertension and left HF. Furthermore, this review mentions their group's work on left atrium analysis using STE, demonstrating a connection between reduced values of peak GLS (PGLS) in the left atrium and the presence of MF in patients with significant mitral insufficiency undergoing valve repair due to MVP. They also mention that reduced PGLS values in the left atrium were predictors of a worse prognosis (HF and mortality) in two years.

Although uncommon in the literature, some studies have also shown a correlation between reduced strain values using the STE technique and the presence of fibrosis on CMR in chagasic patients. Gomes et al.¹⁹ demonstrated that, in patients with stage A chagasic heart disease (asymptomatic, with positive serology, without changes on the electrocardiogram and chest x-ray) with MF on CMR, the analysis of deformation using STE detected reduced global, longitudinal, circumferential, and radial strain values when compared with patients who did not have fibrosis. A recently published meta-analysis found that

patients with indeterminate-form Chagas disease (CD) did not show different GLS values when compared to healthy controls. However, in the segmental analysis, CD patients presented reduced myocardial deformation values in the basal and middle segments of the lower septal wall.²⁰ STE application could perhaps be an additional tool for early diagnosis of myocardial changes not detected by conventional methods, possibly with clinical and prognostic implications.

The Cardiomyopathy Unit at Instituto do Coração/HC-MFUSP has initiated a study involving chagasic patients lacking ventricular dysfunction but exhibiting fibrosis or edema on

CMR, who underwent a one-year treatment with colchicine. Before and after the treatment, all participants underwent transthoracic echocardiography with an analysis of myocardial deformation through STE. The results of this analysis hold the potential for STE to identify segments affected by fibrosis/edema as observed on CMR.

MF research using echocardiographic myocardial deformation analysis with STE has gained more space in clinical and research routines as it is an easy-to-perform and low-cost test. The results found by this technique can have a relevant diagnostic, therapeutic, and prognostic impact on clinical practice.

References

- López B, Ravassa S, Moreno MU, José GS, Beaumont J, González A, et al. Diffuse Myocardial Fibrosis: Mechanisms, Diagnosis and Therapeutic Approaches. *Nat Rev Cardiol*. 2021;18(7):479-98. doi: 10.1038/s41569-020-00504-1.
- Gupta S, Ge Y, Singh A, Gräni C, Kwong RY. Multimodality Imaging Assessment of Myocardial Fibrosis. *JACC Cardiovasc Imaging*. 2021;14(12):2457-69. doi: 10.1016/j.jcmg.2021.01.027.
- González A, Schelbert EB, Díez J, Butler J. Myocardial Interstitial Fibrosis in Heart Failure: Biological and Translational Perspectives. *J Am Coll Cardiol*. 2018;71(15):1696-706. doi: 10.1016/j.jacc.2018.02.021.
- Mandoli GE, D'Ascenzi F, Vinco G, Benfari G, Ricci F, Focardi M, et al. Novel Approaches in Cardiac Imaging for Non-invasive Assessment of Left Heart Myocardial Fibrosis. *Front Cardiovasc Med*. 2021;8:614235. doi: 10.3389/fcvm.2021.614235.
- Lisi M, Cameli M, Mandoli GE, Pastore MC, Righini FM, D'Ascenzi F, et al. Detection of Myocardial Fibrosis by Speckle-Tracking Echocardiography: from Prediction to Clinical Applications. *Heart Fail Rev*. 2022;27(5):1857-67. doi: 10.1007/s10741-022-10214-0.
- Mondillo S, Galderisi M, Mele D, Cameli M, Lomoriello VS, Zacà V, et al. Speckle-Tracking Echocardiography: a New Technique for Assessing Myocardial Function. *J Ultrasound Med*. 2011;30(1):71-83. doi: 10.7863/jum.2011.30.1.71.
- Collier P, Phelan D, Klein A. A Test in Context: Myocardial Strain Measured by Speckle-Tracking Echocardiography. *J Am Coll Cardiol*. 2017;69(8):1043-56. doi: 10.1016/j.jacc.2016.12.022.
- Almeida ALC, Gjesdal O, Mewton N, Choi E, Teixido-Tura G, Yoneyama K, et al. Speckle Tracking by Bidimensional Echocardiography - Clinical Applications. *Rev Bras Ecocardiogr Imagem Cardiovasc*. 2013;26(1):38-49.
- Moharram MA, Lamberts RR, Whalley G, Williams MJA, Coffey S. Myocardial Tissue Characterisation Using Echocardiographic Deformation Imaging. *Cardiovasc Ultrasound*. 2019;17(1):27. doi: 10.1186/s12947-019-0176-9.
- Popović ZB, Kwon DH, Mishra M, Buakhamsri A, Greenberg NL, Thamilasan M, et al. Association Between Regional Ventricular Function and Myocardial Fibrosis in Hypertrophic Cardiomyopathy Assessed by Speckle Tracking Echocardiography and Delayed Hyperenhancement Magnetic Resonance Imaging. *J Am Soc Echocardiogr*. 2008;21(12):1299-305. doi: 10.1016/j.echo.2008.09.011.
- Kobayashi T, Popovic Z, Bhonsale A, Smedira NG, Tan C, Rodriguez ER, et al. Association Between Septal Strain Rate and Histopathology in Symptomatic Hypertrophic Cardiomyopathy Patients Undergoing Septal Myectomy. *Am Heart J*. 2013;166(3):503-11. doi: 10.1016/j.ahj.2013.06.011.
- Gjesdal O, Vartdal T, Hopp E, Lunde K, Brunvand H, Smith HJ, et al. Left Ventricle Longitudinal Deformation Assessment by Mitral Annulus Displacement or Global Longitudinal Strain in Chronic Ischemic Heart Disease: are They Interchangeable? *J Am Soc Echocardiogr*. 2009;22(7):823-30. doi: 10.1016/j.echo.2009.04.023.
- Nagata Y, Bertrand PB, Baliyan V, Kochav J, Kagan RD, Ujka K, et al. Abnormal Mechanics Relate to Myocardial Fibrosis and Ventricular Arrhythmias in Patients with Mitral Valve Prolapse. *Circ Cardiovasc Imaging*. 2023;16(4):e014963. doi: 10.1161/CIRCIMAGING.122.014963.
- Slimani A, Melchior J, Meester C, Pierard S, Roy C, Amzulescu M, et al. Relative Contribution of Afterload and Interstitial Fibrosis to Myocardial Function in Severe Aortic Stenosis. *JACC Cardiovasc Imaging*. 2020;13(2 Pt 2):589-600. doi: 10.1016/j.jcmg.2019.05.020.
- Fabiani I, Scatena C, Mazzanti CM, Conte L, Pugliese NR, Franceschi S, et al. Micro-RNA-21 (Biomarker) and Global Longitudinal Strain (Functional Marker) in Detection of Myocardial Fibrotic Burden in Severe Aortic Valve Stenosis: a Pilot Study. *J Transl Med*. 2016;14(1):248. doi: 10.1186/s12967-016-1011-9.
- Cameli M, Mondillo S, Righini FM, Lisi M, Dokollari A, Lindqvist P, et al. Left Ventricular Deformation and Myocardial Fibrosis in Patients with Advanced Heart Failure Requiring Transplantation. *J Card Fail*. 2016;22(11):901-7. doi: 10.1016/j.cardfail.2016.02.012.
- Kostakou PM, Kostopoulos VS, Tryfou ES, Giannaris VD, Rodis IE, Olympios CD, et al. Subclinical Left Ventricular Dysfunction and Correlation with Regional Strain Analysis in Myocarditis with Normal Ejection Fraction. A New Diagnostic Criterion. *Int J Cardiol*. 2018;259:116-21. doi: 10.1016/j.ijcard.2018.01.058.
- Leitman M, Vered Z, Tyomkin V, Macogon B, Moravsky G, Peleg E, et al. Speckle Tracking Imaging in Inflammatory Heart Diseases. *Int J Cardiovasc Imaging*. 2018;34(5):787-92. doi: 10.1007/s10554-017-1284-y.
- Gomes VA, Alves GF, Hadlich M, Azevedo CF, Pereira IM, Santos CR, et al. Analysis of Regional Left Ventricular Strain in Patients with Chagas Disease and Normal Left Ventricular Systolic Function. *J Am Soc Echocardiogr*. 2016;29(7):679-88. doi: 10.1016/j.echo.2016.03.007.
- Gómez-Ochoa SA, Rojas LZ, Hernández-Vargas JA, Largo J, Muka T, Echeverría LE. Longitudinal Speckle Tracking Strain Abnormalities in Chagas Disease: a Systematic Review and Meta-Analysis. *J Clin Med*. 2022;11(3):769. doi: 10.3390/jcm11030769.



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