PREDICTIVE PARAMETERS OF VENTRICULAR ARRHYTHMIAS IN ACUTE MYOCARDITIS WITH PRESERVED LVEF

Authors: G. Novo1, D. Di Lisi1 , D. Bellavia2,E. La Franca2, MG. Carmina3, S. Novo 1 , G. Di Bella4, F. Clemenza2.

Affiliations:

1. Department of Health Promotion Sciences, Maternal-Infant Care, Internal Medicine and Specialties of Excellence "G. D'Alessandro ", University of Palermo, Cardiology Unit, University Hospital P. Giaccone, Palermo, Italy

2. Department for the Treatment and Study of Cardiothoracic Diseases and Cardiothoracic Transplantation IRCCS ⁻ ISMETT (Mediterranean Institute for Transplantation and Advanced Specialized Therapies), Palermo, Italy.

3. Division of Cardiology, Hospital V. Cervello, Palermo, Italy

4. Clinical and Experimental Department of Medicine, University of Messina, Italy

All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

Corresponding author:

**Dr. Daniela Di Lisi**

**email danydilis@hotmail.it**

No conflicts of interest to declare.

Abstract:

Background: Myocarditis have variable clinical presentation, evolution and prognosis. Aim of our study was to evaluate the value of speckle tracking echocardiography and cardiac magnetic resonance (CMR) in the prediction of ventricular arrhythmias and other cardiovascular adverse events in patients with acute myocarditis, at hospital admission. Methods: 70 patients (62 M, 8 F; mean age 31,3±13,2) with myocarditis and preserved left ventricle ejection fraction (LVEF) were enrolled. Electrocardiogram (ECG), continuous ECG

monitoring, echocardiography with measurement of global longitudinal strain of the left ventricle (GLS), mechanical dispersion (MD) and CMR with quantitative measurement of delayed enhancement (DE) were performed. Adverse events were assessed (arrhythmias, heart

failure, cardiogenic shock, syncope) during in-hospital stay. Results: We found a significant greater amount of DE mass in patients with cardiac arrhythmias (p = 0,01), but not of edema (p = 0,57). GLS was significantly impaired in patients with ventricular arrhythmias (p = 0,04), conversely MD was not significantly prolonged in this setting (p = 0,16). GLS > - 19.2% (sens 100%, specif 55,7%) and a DE mass >9,9 gr (sens 100%; specif. 58,6%)

had the best sensitivity and specificity to identify patients with cardiac arrhythmias. Compared

to GLS, DE mass showed a stronger association with ventricular arrhythmias (p < 0,001).

Conclusions: in our study DE mass and GLS were associated with ventricular arrhythmias in patients with acute myocarditis and preserved LVEF. DE showed the stronger association with the occurrence of ventricular arrhythmias.

**Introduction:**

Myocarditis is an inflammatory disease of the myocardium with various etiology: infectious, immune-mediated and toxic. The suspicion is based on clinical symptoms, electrocardiographic modifications, troponin elevation and possible structural and functional abnormalities at echocardiography. However, diagnosis is challenging and conventional echocardiography has limited diagnostic value especially in patients with preserved left ventricular function. Endomyocardial biopsy is the gold standard diagnostic technique, however being an invasive procedure it is not indicated for every patient. Cardiac magnetic resonance (CMR) became a first line noninvasive diagnostic tool in patients with acute myocarditis without hemodynamic instability. The presence and extent of late gadolinium enhancement (DE) at CMR seems to correlate with prognosis.[[1]](#endnote-1) Particularly the presence of antero-septal mid-wall DE at CMR is a strong prognostic independent predictor of long-term outcomes in patients with acute myocarditis and preserved Left Ventricular (LV) function.[[2]](#endnote-2)

A discrete number of studies demonstrated a reduction of global longitudinal strain (GLS) in patients with acute myocarditis and preserved ejection fraction compared to healthy controls. Some studies also demonstrated an impairment of circumferential strain, and correlation between longitudinal and circumferential strain measures and event-free survival.[[3]](#endnote-3)-[[4]](#endnote-4)

Adding GLS to the Lake-Louise criteria improve significantly the diagnostic performance of CMR to detect myocarditis with preserved ejection fraction: sensitivity (96%), specificity (55%), and accuracy(75).[[5]](#endnote-5)

Aim of our study was to evaluate the role of both functional (LV GLS and mechanical dispersion ) and tissue substrate (fibrosis and edema) to predict ventricular arrhythmias in patients with acute myocarditis and preserved LV ejection fraction (EF ≥50%):

**Methods:**

Seventy patients admitted to three Italian hospitals in Palermo (Policlinico P. Giaccone, Hospital V. Cervello,ISMETT) with clinically suspected acute myocarditis and left ventricular (LV) ejection fraction (EF) >50% were evaluated between January 2012 and May 2018.

Diagnosis of myocarditis was suspected in the presence of typical symptoms (chest pain pericarditis like or ischemic like pain, heart failure symptoms, arrhythmias) if patients fulfilled one or more of the following diagnostic criteria (new electrocardiographic modifications, elevated [troponin](https://www.sciencedirect.com/topics/medicine-and-dentistry/troponin), functional or structural abnormalities at echocardiography) or in asymptomatic patients with two or more diagnostic criteria. Diagnosis of myocarditis was confirmed in the presence of two or more Lake Louise criteria (myocardial [edema](https://www.sciencedirect.com/topics/nursing-and-health-professions/edema), [hyperemia](https://www.sciencedirect.com/topics/medicine-and-dentistry/hyperaemia) and DE) at CMR.

At hospital admission and during the first day of hospitalization, patients underwent clinical/instrumental evaluation (electrocardiogram, ECG continuous monitoring, echocardiogram, CMR, coronary angiography) and laboratory tests ([leukocytes](https://www.sciencedirect.com/topics/medicine-and-dentistry/leukocyte), [C-reactive protein](https://www.sciencedirect.com/topics/medicine-and-dentistry/c-reactive-protein) (CRP), creatine kinase -CK-MB and troponin I).

Exclusion of coronary artery disease with coronary angiography was performed in patients older than 30 years and at high risk of coronary artery disease (36,84% of patients).

Occurrence of the following cardiovascular events was reported during hospitalization: heart failure, cardiogenic shock, arrhythmias (supraventricular arrhythmias, ventricular not sustained or sustained tachycardia, arrhythmic cardiac arrest).

**Echocardiography**

Echocardiographic analysis included assessment of conventional parameters (left ventricular ejection fraction LVEF- by biplane Simpson method, right ventricular function, diastolic function and quantification of cardiac chambers), and myocardial deformation indices. Particularly the evaluation of left ventricular global longitudinal strain, and mechanical dispersion (MD, which is the standard deviation of times to peak systolic strain in a 16 segments model) measurement were carried out (AFI, GE Vivid 9).[[6]](#endnote-6)

**Cardiac Magnetic Resonance**

Using a 1,5 T CMR machine, we acquired in all patients cine [steady-state](https://www.sciencedirect.com/topics/medicine-and-dentistry/steady-state) free precession (cine-SSFP) images, T2-weighted imaging, and DE at 10 min after gadolinium injection in the short-axis (9 to 13 images covering the entire LV), 2-chamber, and 4-chamber planes.

Short-axis cine-SSFP images were acquired immediately after gadolinium injection for hyperemia assessment. In addition, at CMR we assessed not only the presence and the location of edema and DE but we also quantified the extent of DE and edema, using automatic methods.[[7]](#endnote-7) In particular endocardial and epicardial contours in each image were manually traced to identify left ventricular tissue. Mean signal intensity (SI) and SD measured in the myocardial-ROI were used: higher enhancement was defined as myocardium with SI >mean of myocardial-ROI plus 6 SD, higher edema was defined as myocardium with SI >mean of myocardial-ROI plus 2 SD. Using the different thresholds of signal intensity were created original DE image depicting with different colors areas of normal myocardium and enhanced myocardium. The extent of DE and edema was expressed in grams such as absolute value and in percentage respect to the ventricular mass.

**Statistical Analysis**

Continuous variables were expressed as mean and standard deviation (SD) or as median and interquartile range (IR), as appropriate according to data distribution. Categorical variables were reported as absolute number and frequency. The Mann-Whitney non-parametric test was used to compare continuous variables in patients with or without events. Logistic regression analysis (backward method) was used to explore the impact of significant variable to predict the occurrence of ventricular arrhythmic events. The corresponding ROC curves were considered significant with an area under the curve > 0.7 (discrete quality of the index).

Differences were considered statistically significant when *p*<0.05

All analyses were performed using MedCalc Statistical Software version 19.2.1 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2020)

**Results**

Age at presentation was 31,3 ± 13,2 years old, 62 patients were male and 8 females. Median duration of hospitalization was 6 days (IR 4 - 9 days). The most frequent symptom at presentation was chest pain (95.7% of patients), other symptoms were: syncope (4.2%), palpitations (5,26%), fatigue (17,11%), dyspnea (12.8%). 72,8% of patients had prodromal symptoms 1 month before (fever) and 30% of patients had fever at hospital admission. Demographic and clinical characteristics of patients are reported in Table 1.

The number of patients who suffered arrhythmias during in hospital stay was 13 (1,42% of patients had sustained ventricular tachycardia, 14,28% not sustained ventricular tachycardia, 5,71% frequent ventricular extrasystoles (>500/24), 1,42% supraventricular arrhythmias).

At echocardiographic evaluation median left ventricular ejection fraction was 59.9 ± 4.3%; GLS was of -18,7 ± 2,1%, (Table 2). Mechanical dispersion (MD) was 33 ms (IR 31-38,7).

At CRM, 7 % of patients had edema (EDE); subepicardial edema was found in 45 patients, intra-myocardial edema in 12 patients. Hyperemia was found only in one patient. 92% of patients had DE (it was located in subepicardium in 80%, midwall in 23%).

Quantitative analysis showed mean DE mass of 10,5 gr (IR 6,5 ; 18,6), percentage compared to whole myocardial mass 8,5% (IR 3,8 ; 14.9) ; mean EDE-mass was of 15,8 gr (IR 8.1 ; 23), percentage 13.9 % (IR 7.2 ; 22.2) (Table 2).

GLS values were lower in patients with ventricular arrhythmias compared to those without (-16,5% IR -18,2, -15.4; vs -19,1% IQ -20,4, -17,1; p 0,04), conversely mechanical dispersion was not significantly prolonged in patients with cardiac arrhythmias (42 ms IR 31-52; vs 33 ms IR 31-37,7; p 0,16).

At CMR significantly higher values of DE mass were found in patients with arrhythmias compared to patients without (18,9 gr IQ 14,5-21,2; vs 9,2 IQ 6,16-15,66; p 0,01). A significant difference in edema mass was not detected between patients with or without arrhythmias (18,6 IQ 4,6-38; VS 14,6 IQ 5,9-21; p 0,57)

At ROC analysis a GLS value of > - 18,57% ( sens 85,7%; specif 60%; AUC 0,743; p 0,03) and a DE mass > 9,9 gr (sens 100%; specif. 58,6%; AUC 0,788; p < 0,001)) had the best sensitivity and specificity to identify patients with cardiac arrhythmias (Figure 1 and 2).

Compared to GLS, DE mass showed a stronger association with cardiac arrhythmias (OR 1,13 95% IC 1,007 to 1,2783, p 0,038).

**Discussion:**

Myocarditis is a challenging diagnosis due to the heterogeneity of clinical presentation, and conventional echocardiography has diagnostic limited value especially in patients with preserved ejection fraction. Cardiac magnetic resonance is nowadays considered the first line tool to confirm a suspicion of myocarditis in patients without hemodynamic instability, moreover it demonstrated prognostic power. However it is not always feasible due to patients’ contraindications (metallic part, claustrophobia) and it is not widely available. Therefore it is very important to identify diagnostic tool that can improve the diagnostic accuracy of conventional echocardiography, that has the advantage of wide availability, portability to patient’s bed-side and doesn’t employ ionizing radiation. It has been demonstrated that global longitudinal strain is reduced in patients with acute myocarditis and preserved ejection fraction compared to healthy controls and that adding GLS measurement to the Lake-Louise criteria improve significantly the diagnostic performance of CMR to detect myocarditis with preserved ejection fraction.3

Another crucial issue in patients with myocarditis is prognostication. In fact natural history is highly variable, ranging from quick resolution, to relapse, to the development of dilated cardiomyopathy and heart failure or unexpected sudden cardiac death.[[8]](#endnote-8)

The main determinant of prognosis is left ventricular function. Patients with severe LV dysfunction and refractory heart failure are generally characterized by poor prognosis, with a 60% heart transplant free survival at 10-year follow-up.[[9]](#endnote-9) On the contrary patients with preserved ejection fraction are considered at low risk. However they can also experience adverse events, therefore, it is important to identify clinical and instrumental signs able to early predict the evolution and prognosis. Several studies were performed to correlate cardiac imaging parameters and prognosis. Aquaro et al. demonstrated that DE presence and site correlates with the prognosis in myocarditis; especially antero-septal mid-wall DE at CRM is a strong independent predictor of long-term outcomes compared to other patterns of presentation.2

Also GLS demonstrated to add prognostic information in patients with myocarditis.3

In our study we aimed to evaluate the usefulness of measuring GLS, MD by echocardiography and DE mass and edema by cardiac magnetic resonance to predict arrhythmic risk in patients with acute myocarditis and preserved ejection fraction.

Mechanical dispersion is a novel parameter derived by speckle tracking that is expression of the inhomogeneity of mechanical contraction and could be a surrogate of electrical instability. It has been demonstrated that prolonged MD is associated with increased risk of ventricular arrhythmias in several clinical scenario such as hypertrophic cardiomyopathy, dilated cardiomyopathy and ischemic cardiomyopathy.[[10]](#endnote-10)-[[11]](#endnote-11)--[[12]](#endnote-12)[[13]](#endnote-13)

To the best of our knowledge no previous studies in the literature assessed the value of MD in myocarditis.

In our study delayed enhancement mass was significantly associated with arrhythmias while edema was not. Moreover, we found significantly lower values of GLS in patients with arrhythmias, compared to those without, during in-hospital stay.

Mechanical dispersion was prolonged in patients with arrhythmias compared to patients without, but significance was not reached. Probably the negativity of our results is related to the finding that MD was within normal range in the whole population and value above the reference proposed to be predictive of arrhythmias in other clinical scenarios were generally not found in our population.

Cardiac magnetic resonance remains the best tool not only to confirm the clinical suspicion of acute myocarditis, as already demonstrated in the literature, but also for prognostication. Particularly in our population of patients’ measurement of DE mass was helpful to identify patients with ventricular arrhythmias. However, this technique is not always available in the clinical practice, especially in the acute phase.

In light of our finding measurement of global longitudinal strain in patients with acute myocarditis and preserved ejection fraction not only improve the diagnostic accuracy of conventional echocardiography to suspect this challenging diagnosis but can also aid to identify patients at risk of ventricular arrhythmias in the acute setting and therefore to plan tailored therapeutic strategy.

The main limitation of our study is that we do not have a long term follow up to evaluate the relationship between the MRI and strain parameters and prognosis, including occurrence of arrhythmias; we aim to continue follow up in the future. Moreover, we did not perform endomyocardial biopsy in our population to confirm diagnosis of myocarditis, however there are increasing evidences that in the setting of patients at low risk it is not indicated.

In conclusion, higher value of DE mass, measured by quantitative methods and GLS by speckle tracking, showed in our study to be associated with ventricular arrhythmias in patients with myocarditis and preserved ejection fraction. Measurement of edema mass and MD do not seem to add predictive information in terms of arrhythmic risk in our population of patients. DE showed the strongest association with the occurrence of arrhythmias, however due to its wide availability also at patients bed-side, measurement of GLS by echocardiography could be the first line tool, during the acute phase, to identify patients at risk of arrhythmias and could be an option when MRI is not available or not feasible.

**Statement of Ethics**

Ethics approval was not necessary because patients have been subjected to routine clinical and instrumental evaluation (diagnostic and therapeutic assessment on the basis of current ESC Guidelines).

All patients enrolled signed informed consent to participate in the study. All data about patients are anonymous.

**Disclosure Statement**

All authors have not Conflict of Interest to declare.

**Funding Source:**

We have not support and financial involvement. All authors didn’t get money beyond their normal salary.

**Text tables**

Tab 1. Demographic and clinical variables in the study population

Tab 2. Echocardiographic and CMR data in the study population

Tab 3. Comparison between of variables between patients with or without ventricular arrhythmias (Mann Whitney test).

**Figure legends**

Fig. 1 ROC curve DE

Fig. 2 ROC curve GLS

References

1. Aquaro GD, Positano V, Pingitore A, et al.Quantitative analysis of late gadolinium enhancement in hypertrophic cardiomyopathy. J Cardiovasc Magn Reson 2010; 12:21. [↑](#endnote-ref-1)
2. [Aquaro GD](https://www.ncbi.nlm.nih.gov/pubmed/?term=aquaro%252525252525252525252525252520gd%25252525252525252525252525255bauthor%25252525252525252525252525255d&cauthor=true&cauthor_uid=29025554),[Perfetti M](https://www.ncbi.nlm.nih.gov/pubmed/?term=perfetti%252525252525252525252525252520m%25252525252525252525252525255bauthor%25252525252525252525252525255d&cauthor=true&cauthor_uid=29025554), [Camastra G](https://www.ncbi.nlm.nih.gov/pubmed/?term=camastra%252525252525252525252525252520g%25252525252525252525252525255bauthor%25252525252525252525252525255d&cauthor=true&cauthor_uid=29025554), et al. Cardiac MR With Late Gadolinium Enhancement in Acute Myocarditis With Preserved Systolic Function: ITAMY Study. J Am Coll Cardiol 2017; 70:1977-1987. [↑](#endnote-ref-2)
3. Hsiao JF, Koshino Y, Bonnichsen CR et al. Speckle tracking echocardiography in acute myocarditis. Int J Cardiovasc Imaging 2013; 29: 275 – 284 [↑](#endnote-ref-3)
4. [Di Bella G](https://www.ncbi.nlm.nih.gov/pubmed/?term=di%2525252525252525252525252520bella%2525252525252525252525252520g%252525252525252525252525255bauthor%252525252525252525252525255d&cauthor=true&cauthor_uid=30315606), [Carerj S](https://www.ncbi.nlm.nih.gov/pubmed/?term=carerj%2525252525252525252525252520s%252525252525252525252525255bauthor%252525252525252525252525255d&cauthor=true&cauthor_uid=30315606), [Recupero A](https://www.ncbi.nlm.nih.gov/pubmed/?term=recupero%2525252525252525252525252520a%252525252525252525252525255bauthor%252525252525252525252525255d&cauthor=true&cauthor_uid=30315606), et al. Left ventricular endocardial longitudinal dysfunction persists after acute myocarditis with preserved ejection fraction. Echocardiography 2018; 35:1966-1973. [↑](#endnote-ref-4)
5. Kasner M, Aleksandrov A, Escher F, et al. [Multimodality imaging approach in the diagnosis of chronic myocarditis with preserved left ventricular ejection fraction (MCpEF): The role of 2D speckle-tracking echocardiography.](https://www.ncbi.nlm.nih.gov/pubmed/28536004) Int J Cardiol 2017;243:374-378. [↑](#endnote-ref-5)
6. Lang R.M, Badano L.P, Mor-Avi V, et al.Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2015; 28:1-39. [↑](#endnote-ref-6)
7. Harrigan CJ, Peters DC, Gibson CM, et al. Hypertrophic cardiomyopathy: quantification of late gadolinium enhancement with contrast-enhanced cardiovascular MR imaging. Radiology 2011; 258:128–133 [↑](#endnote-ref-7)
8. Sinagra G, Anzini M, Naveen L. Myocarditis in Clinical Practice. Mayo Clin Proc 2016; 9:1256-1266 [↑](#endnote-ref-8)
9. Anzini M, Merlo M, Sabbadini G, et al. Long-term evolution and prognostic stratification of biopsy-proven active myocarditis. Circulation 2013;128:2384-2394 [↑](#endnote-ref-9)
10. Donal E, Delgado V, Bucciarelli-Ducci C, et al. Multimodality imaging in the diagnosis, risk stratification, and management of patients with dilated cardiomyopathies: an expert consensus document from the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2019; 20: 1075-1093. [↑](#endnote-ref-10)
11. Schnell F, Matelot D, Daudin M, et al. Mechanical Dispersion by Strain Echocardiography: A Novel Tool to Diagnose Hypertrophic Cardiomyopathy in Athletes. J Am Soc Echocardiogr. 2017; 30:251-261. [↑](#endnote-ref-11)
12. Haugaa KH, Goebel B, Dahlslett T, et al. Risk assessment of ventricular arrhythmias in patients with nonischemic dilated cardiomyopathy by strain echocardiography. J Am Soc Echocardiogr. 2012;25:667-73. [↑](#endnote-ref-12)
13. Haugaa KH, Smedsrud MK, Steen T, et al. Mechanical dispersion assessed by myocardial strain in patients after myocardial infarction for risk prediction of ventricular arrhythmia. JACC Cardiovasc Imaging 2010;3:247-56. [↑](#endnote-ref-13)