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Original Research Article

Echocardiographic Predictors of Ventricular Arrhythmias in Patients with Non-Ischemic Cardiomyopathy: An Observational Study

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Abstract

Aim: The aim of the present study was to assess the echocardiographic predictors of ventricular arrhythmias in patients with non-ischemic cardiomyopathy.

Methods: In this prospective, observational, multicenter, follow up study the study was conducted at Department of Cardiology. we consecutively included patients admitted with first time diagnosis of heart failure and LVEF <40%. We screened 200 patients in the study. The study patients were included in the heart failure subgroup of the study.

Results: There were 25% females as compared to males in the study. 16% had primary prevention and 4% had secondary prevention. 80% had LVEF <35%. The primary study outcome, life threatening arrhythmia (SCD, appropriate primary prophylactic ICD shock and sustained VT) occurred in 50 patients. These patients were more frequently males, had higher prevalence of atrial fibrillation, wider QRS and larger ventricular and atrial volume. Furthermore, patients with primary outcome had worse LV systolic function by LVEF and GLS and more pronounced MD (all $p < 0.05$). MD was independently associated with the primary outcome when adjusted for age, gender, atrial fibrillation and LV end systolic volume (LVESV) in a multivariate analysis ($p < 0.01$). By including GLS in the model, both MD and GLS were associated with primary outcome, while LVEF was not an independent marker when replacing GLS.

Conclusion: Our study demonstrated that LV GLS has predictive value for VA endpoints in NICM patients, independent and incremental to LVEF. Therefore, the routine use of LV GLS should be considered to noninvasively assess the risk for VA endpoints in NICM patients. Utilising echocardiographic LV GLS may be of particular relevance when cMRI cannot be easily accessed and may provide additional value for patient risk stratification in such instances.

Keywords: echocardiographic predictors, ventricular arrhythmias, non-ischemic cardiomyopathy.

Introduction

Ventricular arrhythmias (VA) pose a substantial risk for the development of sudden cardiac death (SCD). [1,2] While VA may develop because of channelopathies, toxicity, or for idiopathic reasons, structural heart disease is a frequent cause of VA. [3] Assessment of left ventricular (LV) function based on ejection fraction (EF), has traditionally been the most used method to estimate clinical outcome after myocardial infarction. [4]

Cardiac imaging, including echocardiography, may help detect structural and functional heart disease to identify patients at risk of VA. In line with this, the estimation of systolic function by left ventricular ejection fraction (LVEF) is used to guide the indication for the implantation of an implantable cardioverter defibrillator (ICD) in heart failure (HF). [3,5] Myocardial disease with associated ventricular dysfunction in the absence of significant coronary artery disease is broadly referred to as non-ischemic cardiomyopathy (NICM). [6] NICM encompasses a group of heterogenous conditions which can be further categorised as dilated, genetic, inflammatory and infiltrative cardiomyopathies. [7]

NICM can manifest with LV contractile dysfunction with either a dilatated or hypertrophied phenotype. [8] Over time with further tissue injury and development of replacement myocardial fibrosis, a substrate for ventricular arrhythmias (VA) develops, which is a major cause for sudden cardiac death. [9] Death mainly results from heart failure or VA with 3- year mortality rates estimated at 12–20%. [9,10,11] Longitudinal strain by echocardiography can assess both regional and

global (GLS) LV function, and is superior compared to EF in evaluating LV function.[12,13] Importantly, GLS is a better predictor of clinical outcome than EF in patients with relatively preserved systolic function, constituting the majority of patients after myocardial infarction. [14,15,16] Mechanical dispersion (MD) by strain echocardiography, reflecting contraction heterogeneity, is a marker of ventricular arrhythmias with good ability to predict arrhythmic events independently of EF. [17,18]

The aim of the present study was to assess the echocardiographic predictors of ventricular arrhythmias in patients with non-ischemic cardiomyopathy.

Materials and Methods

In this prospective, observational, multicenter, follow up study the study was conducted at Department of Cardiology, NMCH, Sasaram, Rohtas, Bihar, India and we consecutively included patients admitted with first time diagnosis of heart failure and LVEF <40%. We screened 200 patients in the study. The study patients were included in the heart failure subgroup of the study. Time of inclusion was defined as the date of the last echocardiographic examination before discharge, performed when the patient was stabilized from the acute event. We classified patients into ischemic cardiomyopathy (ICM) or non-ischemic dilated cardiomyopathy (NICM) based on the coronary angiogram. Patients defined as non-ischemic dilated cardiomyopathy had no evidence of a stenotic epicardial coronary artery (> 50% diameter in the absence of collateral perfusion), or the extent of coronary artery disease was not considered sufficient to account for the reduced ventricular function. [19] We excluded patients with paced ventricular rhythm, severe stenosis or regurgitation of any valve, poor echocardiographic image quality, ventricular arrhythmia on admission, Takotsubo cardiomyopathy and tachycardia induced/non-ischemic non- dilated cardiomyopathy. Clinical parameters included medical history at inclusion, cardio- vascular risk factors, cardiac symptoms, and physical examination per- formed during the hospital stay and from medical records. The study complied with the Declaration of Helsinki

Echocardiography

All patients underwent a comprehensive transthoracic two- dimensional echocardiographic examination at inclusion using the Vivid E9 or E95 ultrasound systems (GE Vingmed Ultrasound, Horten, Norway). Data were analyzed offline using Echo PAC software (GE Vingmed Ultrasound) blinded to clinical and electrocardiogram (ECG) data. LV ejection fraction (LVEF) was assessed by Simpson's biplane method. [20] LV global longitudinal strain (GLS) was measured by speckle tracking analyses of 2-dimensional (2D) gray scale image loops with >60 frames/s from 3 apical views and calculated as the average peak systolic strain in a 16-segment LV model. [21] LV mechanical dispersion was defined as the standard deviation of time from Q/R on surface ECG to peak negative strain during the entire cardiac cycle in the same 16 LV segments. [22] Color flow Doppler images were obtained of all heart valves to exclude subjects with severe regurgitation or stenosis of any valve. Mitral inflow was assessed in the apical four-chamber view, using pulsed–wave Doppler echocardiography, with the Doppler beam aligned parallel to the direction of flow and the sample volume at the level of the mitral valve leaflet tips. From the mitral inflow profile, the E-wave and A-wave peak velocities were measured. Doppler tissue imaging of the mitral annulus was obtained from the apical four-chamber view, using a sample volume placed in the septal mitral valve annulus for measurement. [23] Tricuspid regurgitant jet velocity was measured during systole at leading edge of spectral waveform. E/A ratio, Left atrial volume index ml/m2 and E deceleration time were assessed. Restrictive filling patterns was defined as E/A > 2. [24] Left atrial volume was measured according to guidelines [20] and indexed for BMI (Left atrial volume index).

Electrocardiography (ECG)

Twelve lead ECG was obtained at inclusion. QRS duration and QT intervals were measured from 12-lead ECG recorded at 25 mm/s. QT intervals were corrected by heart rate using Bazett's formula.

Follow Up

We obtained data regarding all-cause mortality, sudden cardiac death (SCD), ventricular arrhythmia and appropriate shock from the ICD.

Study Outcome

The primary outcome was life threatening ventricular arrhythmias (VA), defined as the combined endpoint of SCD, appropriate shock from a primary preventive ICD and sustained ventricular tachycardia (consecutive ventricular beats at a rate of >100 beats per second lasting for >30 s) documented by 12-lead ECG, Holter monitoring, cardiac device, or aborted cardiac arrest. We calculated annual risk of primary outcome by dividing the total risk during the follow up period by years of follow up. We considered annual risk of primary outcome as “low” when <4%, similar to the general population, “intermediate” when 4–8% annual events and high risk when 8% annual events. The secondary outcome was mortality, defined as all-cause

mortality and appropriate shock from a primary preventive ICD.

Statistical Analysis

Categorical data were presented as numbers and percentage and continuous data as mean SD or as median (interquartile range) as appropriate. Comparisons of means were analyzed using Student's t-test and Mann-Whitney U tests as appropriate. Proportions were compared using Chi-square test. Univariate CoX regression was used to identify markers of VA, and multivariate analysis included significant ($p < 0.05$) variables from the univariate analyses (SPSS version 23.0, SPSS Inc., Chicago, IL, USA). Separate models were created for LVEF and GLS together with MD due to collinearity. Furthermore, separate models were created for LVEDV and QRS due to collinearity with MD. Kaplan–Meier survival analysis with follow up censored at 36 months was performed for patients stratified by etiology and with mechanical dispersion above and below 70 ms and tested by log-rank tests. Reproducibility and repeatability of MD and GLS was tested in 50 randomly selected patients and expressed as intraclass correlation coefficients (ICC). A p-value <0.05 was considered statistically significant.

Results

Table 1: Baseline characteristics

Parameters	N, Mean±SD	P Value
Age, years	67 ± 13	<0.01
Female, n (%)	50 (25)	0.07
Heart rate, bpm	76 ± 14	0.21
Systolic BP, mmHg	124 ± 21	0.12
Diastolic BP, mmHg	76 ± 12	0.04
NYHA class	2.2 ± 0.9	0.15
ECG parameters		
Atrial fibrillation, n (%)	20 (10)	0.16
QRS duration, ms QTc interval, ms Primary prevention ICD, n (%)	110 ± 26 462 ± 43 32 (16)	<0.001 0.40 <0.001
Secondary prevention ICD, n	8 (4)	0.55
Sudden cardiac death, n (%)	16 (8)	0.01
Sustained VT, n (%)	4 (2)	0.90
Shock from primary ICD, n	20 (10)	0.04
Shock from primary ICD, n	20 (10)	0.04
All-cause mortality, n (%)	18 (9)	<0.01
Primary outcome, n (%)	22 (11)	0.11
Primay outcome annual event rate, n (%)		
Secondary outcome, n (%)	22 (11)	0.04
Secondary outcome annual	12 (6)	
Echocardiographic parameters		
LVEDV, ml	176 ± 60	<0.001
LVESV, ml	123 ± 49	<0.001
LVEF, %	31 ± 6	<0.001
LVEF <35%, n (%)	160 (80)	0.05

There were 25% females as compared to males in the study. 16% had primary prevention and 4% had secondary prevention. 80% had LVEF <35%.

Table 2: Characteristics of patients with LVEF <40%, comparing patients with and without life threatening ventricular arrhythmia

	No life-threatening VA n = 150	Life threatening VA n = 50	P-value	Multivariate HR (95% CI)	P-value
Age, years	66 ± 13	70 ± 14	0.11	1.03 (0.99–1.06)	0.12
Female, n	45	3	<0.01	0.23(0.05–1.00)	0.07
ICM, n	105	40	0.17		
Heart rate, bpm	76 ± 15	76 ± 13	0.90		
Systolic BP, mmHg	125 ± 22	122 ± 18	0.46		
Diastolic BP, mmHg	76 ± 15	74 ± 10	0.36		
NYHA class	2.2 ± 0.9	2.4 ± 0.9	0.14		
ICD, n (%)	30	15	0.09		

ECG parameters					
Atrial fibrillation, n	15	10	0.001	1.70 (0.66–4.40)	0.25
QTc interval, ms	462 ± 41	460 ± 58	0.83		
QRS duration, ms	109 ± 26	120 ± 25	0.05		
Echocardiographic parameters					
LVEDV, ml	173 ± 60	198 ± 61	0.02		
LVESV, ml	121 ± 48	145 ± 53	<0.01	1.00 (1.00–1.30)	0.32
LVEF, %	31 ± 6	28 ± 7	<0.01	0.88 (0.90–1.02)	0.16
GLS, %	—10.7 ± 3.1	—9.3 ± 3.8	<0.01	1.14 (1.00–1.30)	0.05
MD, ms	62 ± 17	75 ± 30	0.01	1.02 (1.00–1.03)	0.01
E/e´	18.0 ± 10.9	18.7 ± 8.4	0.75		
Mitral E/A ratio	1.4 ± 0.9	1.9 ± 1.2	0.03	1.56 (1.08–2,25)	0.03

The primary study outcome, life threatening arrhythmia (SCD, appropriate primary prophylactic ICD shock and sustained VT) occurred in 50 patients. These patients were more frequently males, had higher prevalence of atrial fibrillation, wider QRS and larger ventricular and atrial volume. Furthermore, patients with primary outcome had worse LV systolic function by LVEF and GLS and more pronounced MD (all $p < 0.05$). MD was independently associated with the primary outcome when adjusted for age, gender, atrial fibrillation and LV end systolic volume (LVESV) in a multivariate analysis ($p < 0.01$). By including GLS in the model, both MD and GLS were associated with primary outcome, while LVEF was not an independent marker when replacing GLS.

Discussion

Cardiomyopathy is a disease of the heart muscle characterised by cardiac enlargement and impaired systolic function of one or both ventricles. [25] The incidence of dilated cardiomyopathy (DCM) is reported as 5 to 8 cases per 100 000 population per year and appears to be increasing. [26] The natural history of DCM has not been well established. [27] Sudden deaths due to rapid ventricular arrhythmias account for approximately 50-80% of all deaths in patients with idiopathic DCM. [28,29] The overall long-term prognosis in DCM has improved due to evolving advances in diagnosis and therapy. However, there are still many incidences of sudden cardiac death (SCD) in DCM, which is a first disease manifestation in 4% of all patients with DCM. [28]

There were 25% females as compared to males in the study. 16% had primary prevention and 4% had secondary prevention. 80% had LVEF <35%. The primary study outcome, life threatening arrhythmia (SCD, appropriate primary prophylactic ICD shock and sustained VT) occurred in 50 patients. The primary cardiomyopathies can be further subdivided into genetic, mixed and nongenetic acquired disorders. It has been demonstrated that the mechanism for VA is re-entrant circuits caused by myocardial fibrosis, irrespective of the specific NICM etiology. [30] The pathophysiology between NICM and ICM are quite different. The distribution of myocardial fibrosis can be vastly different in these groups, with ischemia resulting in endocardial or transmural scar, while in NICM fibrosis is usually isolated to the epicardium or midwall. [31-33] These patients were more frequently males, had higher prevalence of atrial fibrillation, wider QRS and larger ventricular and atrial volume. Furthermore, patients with primary outcome had worse LV systolic function by LVEF and GLS and more pronounced MD (all $p < 0.05$). MD has been associated to arrhythmic risk in NICM [34] and to cardiac arrhythmic risk and fibrosis by cardiac magnetic resonance (CMR) in patients with hypertrophic cardiomyopathy. [35] Importantly, we were able to identify a subgroup of NICM patients with MD > 70 ms with increased risk of events, and possible benefit from primary preventive ICD. Importantly, these patients should not be evaluated as low risk individuals, but remain in ICD evaluation according to previous guidelines.

MD was independently associated with the primary outcome when adjusted for age, gender, atrial fibrillation and LV end systolic volume (LVESV) in a multivariate analysis ($p < 0.01$). By including GLS in the model, both MD and GLS were associated with primary outcome, while LVEF was not an independent marker when replacing GLS. However, LVEF remains a 'blunt' measure with limited ability in risk stratification, as some NICM patients with preserved LVEF still experience VA endpoints. [36] Despite LVEF having some prognostic value in NICM patients, it was demonstrated that myocardial scar has a strong incremental prognostic value for sudden cardiac death. [37] More recently it was demonstrated that echocardiographic LV GLS has good correlation with myocardial scar with improved prognostic value compared to LVEF. [38] Thus, LV GLS could be utilised for patient risk stratification in predicting VA endpoints, as demonstrated in this meta-analysis than LVEF. Future studies could evaluate the additive value of combining cMRI scar with LV GLS in risk stratification of NICM patients.

Conclusion

Our study demonstrated that LV GLS has predictive value for VA endpoints in NICM patients, independent and incremental to LVEF. Therefore, the routine use of LV GLS should be considered to noninvasively assess the risk for VA endpoints in NICM patients. Utilising echocardiographic LV GLS may be of particular relevance when cMRI cannot be easily accessed and may provide additional value for patient risk stratification in such instances. Further prospective studies are required to validate our findings and integrate LV GLS into decision making and guidelines for ICD implantation in NICM patients.

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