ORIGINAL ARTICLE

Screening of High Risk Patients with Mitral Valve Prolapse – Role of Heart Rate Variability

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ABSTRACT

Objective: To screen out patients with Mitral Valve Prolapse at high risk of ventricular arrhythmogenesis, based upon Heart Rate Variability.

Place and Duration of Study: Department of Cardiac Electrophysiology Armed Forces Institute of Cardiology/National Institute of Heart Diseases, Rawalpindi from May 2007 to March 2008.

Materials and Methods: This cross sectional study included 37 patients with mitral valve prolapse. Patients with acute or old myocardial infarction, diabetes mellitus, ischemic heart disease and systemic hypertension were excluded. Patients were holtered for 24 hours and time domain analysis of heart rate variability was carried out. Statistical time domain measures of heart rate variability i.e. SDNN, SDANN and RMSSD were calculated. Descriptive statistics were used to calculate frequencies and percentages of categorical variables using SPSS version 22.

Results: Mean values of SDNN, SDANN and RMSSD were 141.62 ± 30.80, 125.16 ± 25.58 and 28.40 ± 8.06 milliseconds respectively. Two patients (5.40%) had reduced HRV in all the three indices. In one patient (2.70%) values of SDNN and SDANN were reduced whereas in another one patient (2.70%) the values of SDNN and RMSSD were reduced. In remaining one patient only SDNN was found to be reduced.

Conclusion: There is a subset of patients with mitral valve prolapse with reduced heart rate variability which may be at risk of ventricular arrhythmogenesis.

Keywords: *Heart rate variability, Mitral valve prolapse, Arrhythmogenesis, Holter monitorin.*

Introduction

Screening of patients at high risk of sudden cardiac death poses a huge challenge to researchers in the area of cardiovascular medicine.[1] Sudden cardiac death is defined as natural death from cardiac causes, heralded by abrupt loss of consciousness within one hour of the onset of acute symptoms.[2] In majority of the cases the mechanism underlying sudden cardiac death is ventricular fibrillation.[3] As the patient expires shortly after the onset of acute symptoms, there is no much time for treatment. Hence, the best way to prevent sudden cardiac death is its prediction and putting the patient under medial surveillance.[3] Mitral valve prolapse is a common valvular heart disease in which sudden cardiac death has been reported.[4]It refers to the displacement of an abnormally thickened mitral leaflet into the left atrium during systole.[5] Its prevalence is about 0.6 - 2.4 % in the general population.[6] Mitral valve prolapsehas been associated with ventricular arrhythmias along with other complications like mitral regurgitation, heart failure and bacterial endocarditis.[7] Although, the disorder generally takes a benign course, nevertheless, a few unfortunate patients remain at high risk of ventricular arrhythmias and sudden cardiac death. The risk of sudden cardiac death in these patients is 0.1% per year, not much different from the rest of the general population (0.2%), however, the risk may increase to 0.9 to 2% in cases with associated complication especially mitral regurgitation.[8] This is a subset of patients in whom risk stratification of sudden arrhythmogenic death is recommended.[9]Heart rhythm is under the control of autonomic nervous system. Sympathetic and parasympathetic (vagal) are the two divisions of autonomic nervous system having reciprocal effect on heart rate. Sympathetic system activation leads to positive chronotropism whereas parasympathetic activation leads to negative chronotropism.[10] Sympathetic overactivity is the basis of autonomic imbalance in these patients as indicated byraised blood levels of catecholamines, and enhanced β receptoraffinity.[11] In a healthy individual, at rest, vagal effect prevails leading to reciprocal suppression of sympathetic nervous system.[12]Evidence suggests that autonomic imbalance in patients suffering from mitral valve prolapse leads to ventricular arrhythmias which may terminate into sudden cardiac death.[13] A recent

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study has indicated that sympathetic preponderance not only affects cardiac rhythm but also promotes myxomatous degeneration in mitral valve leaflets and worsens the disease.[11]This has led researchers to work on quantification of autonomic nervous system. In past few years, various ECG based quantitative markers of autonomic activity have been developed for risk stratification, like heart rate variability, baroreflex sensitivity, QT dispersion and heart rate turbulence.[14]Among these, heart rate variability has emerged as a simpleand easy tool to quantify the autonomic nervous system.[15]Heart rate variability is the temporal oscillation between consecutive heart beats as represented by variable RR intervals on the surface ECG.[16] It is a noninvasive and cost effective marker of autonomic imbalance that can be used in patients with mitral valve prolapse to screen out the high risk group.[17]Holter ECG recordings of 24 hours duration generally, are used for the analysis of heart rate variability. Heart rate variability represents respiratory sinus arrhythmia and is primarily mediated by vagus nerve. Its value within normal range signifies sympathovagal balance with vagal dominance.[18] Reduced vagal and raised sympathetic activity is reflected by decreased heart rate variability. This kind of autonomic imbalance is characteristic of patients with mitral valve prolapse.[19] It therefore, follows that reduced heart rate variability representative of sympathetic dominance can isolate the patients with mitral valve prolapse who are at risk of sudden arrhythmogenic death.

The present study was carried out to determine patients with mitral valve prolapse at high risk of sudden arrhythmogenic death, based upon heart rate variability.

Materials and Methods

It was a cross-sectional descriptive study, conducted at Armed Forces Institute of Cardiology/National Institute of Heart Diseases, Rawalpindi from May 2007 to March 2008. Before starting the study, formal approval from medical ethics committee was obtained. Written and informed consent was also taken from all the patients. 37 patients with mitral valve prolapse, from 15 to 38 years of age were included in the study through convenience non-probability sampling. Mitral valve prolapse was diagnosed on 2 dimensional echocardiography using parasternal long axis view, as per the following criteria.[20]

- Systolic displacement of mitral leaflet greater than 2 mm
- Leaflet thickness of 5 mm or more for classic prolapse and less than 5 mm for non-classic prolapse

Patients with acute or old myocardial infarction, diabetes mellitus, ischemic heart disease and systemic hypertension were excluded. Patients fulfilling the inclusion criteria were Holter monitored for 24 hours using 'Life Card CF' Holters from Del Mar Reynolds Medical Company limited. After 24 hours of recording, the digital ECG data were transferred from holter recorder to a computer having Pathfinder 700 series software installed. Out of three channels, the one which displayed best ECG recording and with least artifacts was selected. The whole data were edited manually with extreme care using visual checks and manual correction of all QRS complexes. All the erroneous beats were identified and edited from data. After editing, the time domain analysis of heart rate variability was carried out. Statistical time domain measures of heart rate variability i.e. SDNN (Standard deviation of all normal to normal intervals), SDANN (Standard deviation of the averages of normal to normal intervals in all 5 minutes segments of the entire recording) and RMSSD (The square root of the mean of the sum of the squares of differences between adjacent normal to normal intervals) were calculated. Statistical analysis was done by using IBM SPSS Statistics version 22. Descriptive statistics were used to calculate frequencies and percentages of categorical variables.

Results

There were 37 patients with mean age of 26.27 ± 6.18 years and male to female ratio of1.6:1.

Displacement of mitral leaflets on echocardiography was 3.68±0.98 mm whereas the leaflet thickness was 4.86±0.82 mm (Table I).

Values of SDNN, SDANN and RMSSD were 141.62 ± 30.80, 125.16 ± 25.58 and 28.40 ± 8.06 respectively (Table II). Five patients (13.51%) were found to have reduced SDNN values whereas three patients (8.10%) had reduced SDANN and another three (8.10%) had reduced RMSSD values (Table III).

Out of 37, HRV was reduced in 5 patients in total

(13.51%).Detailed analysis of HRV parameters revealed that in two patients (5.40%) all the three HRV indices were reduced (group 1). In one patient (2.70%) values of SDNN and SDANN were reduced (group 2) whereas in another one patient (2.70%) the values of SDNN and RMSSD were reduced (group 3). In remaining one patient only SDNN was found to be reduced (Table IV).

Table I: Echocardiographic findings in patients with mitral valve prolapsed (N=37)

Echocardiographic finding (parasternal long axis view)	**Measurement (mm) Mean ± SD**
Displacement of mitral leaflets	3.68 ± 0.98
Thickness of mitral leaflets	4.86 ± 0.82

Table II: Values of heart rate variability indices (N=37)

HRV indices	**Value (ms) Mean ± SD**
SDNN	141.62 ± 30.80
SDANN	125.16 ± 25.58
RMSSD	28.40 ± 8.06

Table III: Frequency of patients according to reduction in single HRV index (N=37)

HRV indices	**Patients with reduced HRV**
SDNN	5 (13.51%)
SDANN	3 (8.10%)
RMSSD	3 (8.10%)

Table IV: Frequency of patients according to cumulative reduction in HRV indices (N=37)

Patients	**Reduced HRV**			
	All the three indices (group 1)	SDNN+SDANN (group 2)	SDNN+RMSSD (group 3)	SDNN
Frequency	2	1	1	1
Percentage	5.40%	2.70 %	2.70 %	2.70 %

Discussion

According to the results of our study, 5 patients (13.50%) out of 37 had reduced heart rate variability. Combined analysis of all the HRV indices divided the patients in three groups. In first group, two patients (5.40%) had reduced heart rate variability in all the three parameters (SDNN, SDANN and RMSSD). In second group, two patients had reduced HRV in two parameters (SDNN plus SDANN or RMSSD) and in third group the remaining one patient showed reduced HRV inonly one parameter (SDNN). Although all the three groups had reduced HRV and are at risk of sudden arrhythmogenic death, the risk is comparatively higher for group one (5.40%) as compared to the other two groups. It is reported in literature that prediction of sudden cardiac death on the basis of single predictive tool is not reliable. Hence judicious combination of different predictive markers is recommended. This goes in accordance with the high risk group of our study in which HRV was reduced in all the three parameters. Han et al studied heart rate variability in sixty seven children with mitral valve prolapse. Their study included thirty seven healthy and age-matched children as controls.[17] Time and frequency domain indices of heart rate variability were calculated from 24 hours holter ECG recordings. They found that all the time and frequency domain indices were significantly lower in children with mitral valve prolapse than in controls (p-value < 0.05).They also reported that frequency of individuals with reduced heart rate variability was significantly higher in the diseased group as compared to the control group (p-value < 0.05).Lower values of heart rate variability indices in children with mitral valve prolapsewere suggestive of sympathovagal imbalance in favor of sympathetic activity. Anders, et al carried out a study to evaluate mitral valve prolapse as a cause of sudden cardiac death in young adults.[9]They conducted series of autopsies of the patients who died of sudden cardiac death. They found the incidence of mitral valve prolapse among autopsies of sudden cardiac death cases, to be about 4 to 5%. They presented six such cases of unexpected death in young female adults and concluded that even clinically benign cases of mitral valve prolapse, in young adults, might result in sudden unexpected death. Rosenthal et al studied 20 patients with mitral valve prolapse and 12 controls without the disease.[21]During programmed ventricular stimulation, 9 patients and ventricular arrhythmias as compared to the healthy subjects where only one subject showed arrhythmogenesis (p < 0.05). On high intensity stimulation, five more

patients showed ventricular arrhythmias. They concluded that frequency of patients with mitral leaflet prolapse who had inducible ventricular tachyarrhythmias during programmed ventricular stimulation was significantly higher than the healthy controls.

Tsuji et al, in Framingham Heart Study, analysed association of heart rate variability with mortality.[22] Their study included 736patients with an average age of 72 ± 6 years. They studied various frequency and time domain measures of heart rate variability. During follow up, 74 subjects of their study died. They found significant association between reduction of heart rate variability measures and all-cause mortality (p=0.009). They concluded that estimation of heart rate variability by ambulatory monitoring offers predictive value that goes beyond the information provided by the traditional risk markers. Results of the studies mentioned above including those of our study conclude that there is a subset of patients with mitral valve prolapse which may be at high risk of sudden arrhythmogenic cardiac death. This high risk group can be screened out on the basis of heart rate variability. Studies mentioned above also indicate that heart rate variability is a significant predictive marker of sudden arrhythmogenic death and can be used for risk stratification in patients with mitral valve prolapse. However, the predictive value of heart rate variability can be enhanced if combined with other ECG based markers of arrhythmogenesis like Signal Averaged ECG, T wave alternans and QT dispersion. Within the domain of mitral valve prolapse, leaflet thickness greater than 5 mm and association with mitral regurgitation increase the effectiveness of heart rate variability as a predictive marker of sudden cardiac death.

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