The Professional Medical Journal
www.theprofesional.com

ORIGINAL PROF-2656

ARRHYTHMOGENESIS IN MITRAL VALVE PROLAPSE; RISK STRATIFICATION – ROLE OF HIGH RESOLUTION ECG, HOLTER MONITORING AND MITRAL LEAFLET GEOMETRY

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Article received on:
20/09/2014
Accepted for publication:
08/11/2014
Received after proof reading:
21/02/2015

ABSTRACT… Mitral valve prolapse is generally considered a benign condition, however, a subset of patients remains at high risk of arrhythmogenesis which may lead to sudden cardiac death. **Objective:** To stratify risk of arrhythmogenesis in patients with mitral valve prolapse on the basis of high resolution ECG, Holter monitoring, resting heart rate and mitral leaflet geometry. **Study Design:** Cross sectional comparative study. **Place of study:** Armed Forces Institute of Cardiology (AFIC)/National Institute of Heart Diseases, Rawalpindi and Army Medical College, Rawalpindi, Pakistan **Methodology:** Mitral leaflet displacement and thickness were measured on echocardiography in 37 patients with mitral valve prolapse. Resting heart rate and time domain indices of heart rate variability of each patient were recorded from 24 hours Holter monitoring. High resolution ECG of all the patients was carried out to record ventricular late potentials. Statistical analysis was performed using SPSS and the alpha value was set at <0.05 for significance. **Results:** The mean values for resting heart rate, leaflet displacement and leaflet thickness were 77.19 ± 6.29 per minute, 3.64 ± 0.92 mm and 4.96 ± 0.79 mm respectively. Ventricular late potentials were present in 8 (21.62%) whereas heart rate variability was reduced in 5 (13.51%) patients. Leaflet thickness was significantly greater in patients with ventricular late potentials as compared to those without (p-value 0.004). Patients with reduced heart rate variability had significantly higher resting heart rate as compared to those with normal variability (p-value 0.02). One patient (2.7%) had ventricular late potentials, reduced heart rate variability, resting heat rate of 88 beats per minute and leaflet thickness over 5 mm. **Conclusions:** Combined effects of high resolution ECG, holter monitoring and leaflet geometry identified the high risk subset, comprising of 2.7% of the study population.

Key words: Mitral valve prolapse, Ventricular late potentials, heart rate variability, resting heart rate

Article Citation: Khan MA, Shabbir F, Rajput TA. Arrhythmogenesis in mitral valve prolapse; risk stratification – role of high resolution ECG, holter monitoring and mitral leaflet geometry. Professional Med J 2015; 22(2):227-234.

INTRODUCTION

Mitral valve prolapse is generally considered a benign condition, however, a subset of patients remains at high risk of arrhythmogenesis which may lead to sudden cardiac death. Risk stratification of sudden arrhythmogenic cardiac death poses a huge challenge to researchers in the area of cardiac electrophysiology[1]. In majority of the cases the mechanism underlying sudden cardiac death is ventricular fibrillation[2]. 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]. Its prevalence is about 0.6 - 2.4 % in the general population[5]. Mitral valve prolapse refers to the displacement of an abnormally thickened mitral leaflet into the left atrium during systole. On the basis of mitral leaflet thickness, the disorder is divided into classic and non-classic prolapse. Patients with leaflet thickness of 5 mm or more are said to have classic prolapse and those with the lesser thickness have non classic prolapse[6]. There is substantial evidence that mitral leaflet thickness is associated with complications like mitral regurgitation, arrhythmogenesis and bacterial endocarditis[7]. It therefore follows that the patients with classic mitral valve prolapse are at higher risk of complications including sudden cardiac death[8].

There is a large body of evidence that mitral valve prolapse is associated with the development of ventricular tachyarrhythmias[9]. Research evidence suggests that arrhythmogenesis is the basis of sudden cardiac death in these patients[10]. Structural abnormality leading to some mechanoelectrical mechanism or autonomic nervous system imbalance or both are considered to be the underlying mechanisms of arrhythmogenesis[11]. The risk of sudden cardiac death 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[12]. This is a subset of patients in whom risk stratification of sudden arrhythmogenic death is recommended.

High resolution electrocardiography (signal averaged ECG) is recorded by averaging multiple heart beats and amplifying them into a filtered QRS complex by eliminating random noise. Filtered QRS complex is analysed for the presence or absence of ventricular late potentials which are generally present in the terminal part of the complex for the positive signal averaged ECG[13]. Ventricular late potentials represent areas of heterogeneity of electrical activation where speed of cardiac impulse slows down. These areas behave as the substrates for microreentry circuits leading to ventricular fibrillation which may terminate in sudden cardiac death. Presence of ventricular late potentials on signal averaged ECG points towards electrical instability which may lead to ventricular tachyarrhythmias and sudden cardiac death[14].

Holter monitoring is a technique to record ambulatory ECG for prolonged time periods. The digital ECG data is then utilized to analyse various non-invasive markers of arrhythmogenesis. Heart rate variability is one such marker which is simple, cost effective and easy to use. It represents temporal oscillation between consecutive heart beats as represented by variable RR intervals on the surface ECG[15]. Holter ECG recordings of 24 hours duration generally, are used for heart rate variability analysis. 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[16]. Reduced vagal and raised sympathetic activity is reflected by increased resting heart rate and decreased heart rate variability. This kind of autonomic imbalance is characteristic of patients with mitral valve prolapse[17]. 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.

We planned this study with the purpose to stratify risk of arrhythmogenesis in patients with mitral valve prolapse on the basis of high resolution ECG, heart rate variability, resting heart rate and mitral leaflet geometry. We expect that risk stratification would become more reliable if multiple markers are combined together.

MATERIAL AND METHODS

A cross sectional comparative study conducted at Armed Forces Institute of Cardiology (AFIC)/ National Institute of Heart Diseases, Rawalpindi and Army Medical College, Rawalpindi, Pakistan. 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. Patients with acute or old myocardial infarction, diabetes mellitus, ischemic heart disease, systemic hypertension or bundle branch block were excluded. Mitral valve prolapse was diagnosed on 2 dimensional echocardiography using parasternal long axis view, as per the following criteria[18].

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

After the diagnosis of mitral valve prolapse was confirmed, the base line tests like standard ECG, blood sugar profile and arterial blood pressure

measurements were carried out. Signal averaged ECG of the selected patients was recorded using SAECG recording machine '1200 EPX high resolution electrocardiograph'. Ventricular late potentials were considered to be present when at least two out of the following three criteria were fulfilled.[19]

1. Duration of total filtered QRS complex (fQRS) > 114 ms
2. Low amplitude signal under 40 μv (LAS 40) > 38 ms
3. Root mean square voltage of last 40 ms of fQRS (RMS 40) < 20 μv.

Holter monitoring of the included patients was carried out for 24 hours to get digital ECG data for analysis of heart rate variability. We used the holters 'Life Card CF' from Del Mar Reynolds Medical limited in this study. After 24 hours of recording, the digital ECG data were transferred from holter recorder to a computer having 'Pathfinder 700 series' software installed. The whole data were edited manually and all the erroneous beats were identified and discarded. Statistical time domain measures of heart rate variability i.e. SDNN (Standard deviation of all NN intervals), SDANN (Standard deviation of the averages of NN 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 NN intervals) were calculated. Reduced heart rate variability was confirmed when the values of the indices were below the accepted normal limits as described in guidelines by the task force of the European society of Cardiology and the North American society of pacing and electrophysiology[20]. Resting heart rates were determined from Holter recordings, early in the morning before the patients got out of bed. We used the cutoff values of 80 and 84 beats per minute for males and females respectively to declare high resting heat rate[21].

Statistical analysis was performed by using IBM SPSS statistics version 22. Continuous variables were described as means and standard deviations whereas categorical variables as frequencies and percentages. Independent t test was used to compare means of the quantitative variables whereas chi square test of independence was used for the comparison of qualitative variables. Alpha value was set at < 0.05 for significance.

RESULTS

Out of 37 patients, 23 were male and 14 were female with male to female ratio of 1.6 to 1. Mean age of the patients was 26.27±6.19 years and the mean resting heart rate was 77.19±6.29 per minute. On echocardiography (parasternal long axis view), mean displacement of the mitral leaflet into left atrium during systole was 3.64±0.92 mm whereas the mean leaflet thickness during diastole was 4.96±0.79 mm. Signal averaged ECG recording was carried out at a mean noise level of 0.21±0.08μv.

Mean values of fQRS, LAS40 and RMS40, on signal averaged ECG were 100.13 ± 13.77 ms, 32.67 ± 14.20 ms and 40.18 ± 27.38 μv respectively. 4 patients (10.81%) had fQRS over 114 ms, 9 patients (24.32%) had LAS40 over 38 ms and 11 patients (29.72%) had RMS40 below 20μv. Two or more SAECG parameters were deranged in 8 patients (22%) confirming the presence of ventricular late potentials. 29 patients (78%) did not show presence of ventricular late potentials (table I).

SAECG parameter	Mean ± SD	Frequency of patients with deranged parameter	Ventricular late potentials
fQRS (ms)	100.13 ± 13.77	4 (10.81%)	8 (21.62%)
LAS 40 (ms)	32.67 ± 14.20	9 (24.32%)	
RMS 40 (μv)	40.18 ± 27.38	11 (29.72%)	

Table-I. Values of signal averaged ECG parameters and frequency of patients with ventricular late potentials

Mean values of SDNN, SDANN and RMSSD were 141.91±30.94, 125.16±25.58 and 28.40±8.067 respectively. Heart rate variability was reduced in 5 patients(13.51%) in total (13.51%) whereas 32

patients (86.48%) had normal heart rate variability. 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 II). Detailed analysis of HRV parameters revealed that in two patients (5.40%) all the three HRV indices were reduced. 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.

HRV index	Mean ± SD	Frequency of patients with reduced HRV index	Reduced HRV
SDNN (ms)	141.91±30.94	5 (13.51%)	5 (13.51%)
SDANN (ms)	125.16±25.58	3 (8.10%)	
RMSSD (ms)	28.40±8.067	3 (8.10%)	

Table-II. Values of HRV indices and frequency of patients with reduced heart rate variability

Comparison of age, mitral leaflet geometry and resting heart rate was carried out in patients with and without ventricular late potentials with the help of independent samples t test (table III). Age, leaflet displacement and resting heart rate were not significantly different between the two groups whereas thickness of mitral leaflet was significantly greater in the group with ventricular late potentials (p-value 0.004).

Variable	Patients with VLPs	Patients without VLPs	P-value
Age	24.75 ± 7.63	26.69± 5.81	0.44
Leaflet displacement (mm)	3.88 ± 1.08	3.57 ± 0.87	0.39
Leaflet thickness (mm)	5.65 ± 0.64	4.77 ± 0.72	0.004*
Resting heart rate	77.50± 6.56	77.10± 6.33	0.87

Table-III. Comparison of age, leaflet parameters and resting heart rate in patients with and without ventricular late potentials

Age, mitral leaflet geometry and resting heart rate in patients with reduced heart rate variability were also compared with the patients having normal heart rate variability using independent samples t test (table IV).

Variable	Patients with reduced HRV	Patients with normal HRV	P-value
Age	29.80 ± 8.49	25.72 ± 5.726	0.17
Leaflet displacement (mm)	4.02± 1.34	3.51± 0.71	0.20
Leaflet thickness (mm)	4.60± 1.07	5.02± 0.74	0.27
Resting heart rate	82.40 ± 4.159	75.56 ± 6.148	0.02*

Table-IV. Comparison of age, leaflet parameters and resting heart rate in patients with reduced and normal heart rate variability

Age and mitral leaflet geometric parameters were not significantly different between the two groups, however resting heart rate was significantly higher in the group with reduced heart rate variability (p-value 0.02).

There was only one patient (2.7%) who had ventricular late potentials, reduced heart rate variability, high resting heat rate (88 beats per minute) and leaflet thickness over 5 mm. 8 patients (21.62%) had only two risk markers deranged whereas 21 patients (56.75%) were with the derangement of only one risk marker. The rest of the 7 patients had normal results of all the tests (table V).

Cases	Gender	VLPs	ReducedHRV	↑ resting HR	Thickness > 5 mm	Total score
1	F	+	+	+	+	4
2	M	+	-	-	+	2
3	F	+	-	-	+	2
4	F	+	-	-	+	2
5	F	+	-	-	+	2
6	F	+	-	-	+	2
7	M	+	-	-	+	2
8	M	+	-	-	-	1
9	F	-	+	-	-	1
10	F	-	-	-	+	1
11	F	-	-	-	+	1
12	F	-	+	-	-	1
13	M	-	+	-	-	1
14	F	-	-	+	-	1
15	F	-	-	-	+	1
16	M	-	-	+	+	2
17	M	-	-	+	-	1
18	F	-	-	-	+	1
19	M	-	-	-	+	1
20	M	-	-	-	+	1
21	M	-	-	-	+	1
22	M	-	-	-	+	1
23	M	-	+	+	-	2
24	M	-	-	+	-	1
25	M	-	-	+	-	1
26	M	-	-	-	+	1
27	M	-	-	-	+	1
28	M	-	-	-	+	1
29	M	-	-	-	+	1
30	F	-	-	-	+	1

Table-V. Combined results of different risk markers along with total score

DISCUSSION

On the basis of results of all the fours predictive markers which were used in the study, we devised a score system. Patients 'positive' for all the tests had a score of 4 and those negative had 0 score. All other patients fell between these two extremes. We assume the patients having a score of 4 are at high risk of developing ventricular arrhythmias, however those with a score of 3 may also be followed up (though no patients had the score of 3 in the present study). There was only one patient (2.70%) who had a score of 4, which meant he had ventricular late potentials, reduced heart rate variability, high resting heart rate and mitral leaflet thickness over 5 mm. interestingly, this patient also had mitral regurgitation of moderate degree. All these attributes make this patient vulnerable to develop ventricular tachyarrhythmias which may lead to an adverse outcome like sudden cardiac death. We therefore decided to put this particular patient under medical surveillance so as to record the events of ventricular tachyarrhythmias as predicted by the study. This also implies that 2.70% patients with mitral valve prolapse may suffer from sudden cardiac death. The percentage of patients who are likely to develop ventricular arrhythmias drops substantially when signal averaged ECG findings are combined with heart rate variability. Guidelines for risk and prevention of sudden cardiac death published in 2012

recommend to combine multiple risk predictors together to enhance reliability of the assessment.[22] Many studies reported comparatively high risk of arrhythmogenesis when only one risk marker was used as a predicting tool[23]. This 'triangular approach' illustrates the importance of combining more than one risk markers to correctly identify the real subset of patients at high risk of sudden arrhythmogenic cardiac death.

The finding that mitral leaflet thickness was significantly higher in patients with ventricular late potentials whereas resting heart rate was significantly higher in patients with reduced heart rate variability has important implications. This gives a clue for understanding the mechanism underlying ventricular tachyarrhythmias in these patients. The fact that ventricular late potentials are not associated with resting heart rate seems to delink them from autonomic nervous system. Dependence on leaflet thickness and independence from autonomic nervous system points towards the mechanism of development of ventricular late potentials. It entails that 'local' factors might play important role in the genesis of ventricular late potentials. However, factors other than 'local' cannot be excluded altogether. Mitral leaflet thickness is strongly associated with mitral regurgitation and the thick redundant leaflet puts extra stretch on papillary muscles during systole. This may cause some mechanoelectrical changes or modification of cardiac tissue architecture that may lead to development of heterogenous zones in electrical sense[24]. Traction exerted by the thick prolapsed valve on the papillary muscle may lead to the 'buckling' phenomenon[25]. Lee and colleagues reported that such superior traction may affect the mechanical and electrophysiologic function of the left ventricle[26]. There may also be modification of some ion channels taking part in delayed afterdepolarizations. All these processes lead to the genesis of ventricular late potentials and become substrates for the microreentry circuits leading to ventricular tachyarrhythmias.

Association of heart rate variability with resting heart rate and disassociation from mitral leaflet thickness suggests that mechanism of heart rate variability is autonomic nervous system dependent, however, the 'local' factors cannot be totally excluded. Raised resting heart rate signifies suppression of vagal and amplification of sympathetic effects. Heart rate variability which is primarily vagally mediated is reduced with attenuation of parasympathetic nervous system. Many studies have reported heightening of sympathetic nervous system in patients with mitral prolapse as evidenced by raised blood levels of catecholamines and receptor upregulation[27]. Patients having reduced heart rate variability along with ventricular late potentials are at high risk of arrhythmogenesis as they have the arrhythmogenic substrate as well as the 'trigger'. Any irritable but silent ectopic focus may fire in response to enhanced sympathetic drive and 'trigger' the chain reaction of ventricular fibrillation.

Bobkowski et al carried out a study to determine significance of ventricular late potentials in patients with mitral valve prolapse.[28] Their study included 151 children with mitral valve prolapse and 164 healthy controls. They reported that ventricular late potentials were significantly higher in diseased group as compared to the controls ($p<0.0001$). They also carried out follow up for a mean duration of 64 months and found that the frequency of ventricular arrhythmias was significantly higher in patients having ventricular late potentials as compared to those without ($p<0.0001$).

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[29]. 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 prolapse were suggestive of sympathovagal imbalance in favour of sympathetic activity.

Results of our study conclude that there is a subset of patients with mitral valve prolapse which may be at high risk of arrhythmogenesis.Combined effects of high resolution ECG, heart rate variability, resting heart rate and leaflet geometry identified the high risk subset, comprising of 2.7% of the study population. Risk stratification becomes more reliable and purposeful if the results of multiple noninvasive risk markers are combined together. Such a multivariable analysis 'narrows down' the percentage of high risk patients and identifies the actual high risk subset with reasonable reliability.

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"Opportunities multiply as they are seized."

Sun Tzu

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