VENTRICULAR LATE POTENTIALS IN PATIENTS WITH MITRAL VALVE PROLAPSE

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ABSTRACT

Objectives: To determine frequency of ventricular late potentials in healthy individuals and in patients with mitral valve prolapse and to identify patients with Mitral Valve Prolapse at high risk of sudden death based upon ventricular late potentials.

Study Design: Case - Control study.

Place and duration of study: The study was conducted in Army Medical College and Armed Forces Institute of Cardiology, Rawalpindi from March 2005 to February 2006.

Material and Methods: A total of 37 patients with mitral valve prolapse and 37 matching controls were included in the study. Patients with confirm diagnoses of mitral valve prolapse on echocardiography were selected. After recording their conventional ECGs, they underwent exercise tolerance test on treadmill. Signal averaged electrocardiogram of every patient was recorded using computer software for the presence or otherwise of ventricular late potentials. The data was entered into SPSS version 10. Descriptive statistics were used to calculate means and standard deviations while paired sample 't' test at confidence interval of 95 % was used to compare mean values for statistical significance.

Results: Nine (24.32 %) out of 37 cases and only 1 (2.7 %) out of 37 controls had ventricular late potentials on their signal averaged electrocardiogram.

Conclusions: Ventricular late potentials are useful non-invasive predictive markers of sudden cardiac death in patients with mitral valve prolapse.

Keywords: Mitral valve prolapse, ventricular late potentials, ventricular tachyarrhythmias.

INTRODUCTION

Mitral Valve Prolapse (MVP) is a common cardiac valvular abnormality. According to western literature its prevalence is 0.6-2.4%. In this disorder there is superior and posterior displacement of Mitral valve leaflets into the left atrium from their normal position in left ventricle during systole. An enlarged prolapsing Mitral valve may cause abnormal stress on the papillary muscles and stretch induced arrhythmias by mechanoelectrical feedback mechanism.[1]

Mitral Valve Prolapse is generally regarded as a benign condition. However, occasionally it may lead to severe mitral regurgitation, infective endocarditis or cerebral ischemia. It may also produce ventricular arrhythmias which have been associated with sudden cardiac death. It has generated a lot of concern and controversy however, a definitive cause-effect relationship has not been established as yet. Patients with mild billowing and morphologically normal appearing leaflets have risk of complications not different from that in the general population.[2] In contrast, patients with redundant and thickened leaflets caused by pronounced myxomatous infiltration and elongated chordae have a primary form of the disease associated with an increased risk of complications or associated with an increased risk for sudden death.[3]

Mitral Valve Prolapse has been associated with sudden cardiac death, as documented by numerous retrospective reports of cardiac arrest survivors or sudden death victims in whom MVP was the only identifiable cardiac lesion.[4] In the retrospective review by Swartz and colleagues, the incidence of sudden death with MVP was 1.4 % among the 589 patients.[5] Other studies report 0.2 and 0.4%[6,7]. Sudden cardiac death in MVP is presumably caused by ventricular tachyarrhythmias. Several mechanisms have been postulated by which MVP may be arrhythmogenic. MVP may cause stretch-induced arrhythmias by "buckling" of the papillary muscles.[8]

Ventricular late potentials (VLPs) are accepted as non-invasive marker of ventricular

arrhythmias in individuals with and without overt heart disease. Ventricular late potentials are low voltage, high frequency signals present in terminal part of QRS complex that may extend into the ST segment. They cannot be detected by 12 lead standard ECG because these are obscured by high-level background skeletal muscle noise (8-10μv). Signal averaged ECG is a technique that can detect ventricular late potentials by improving signal to noise ratio. The "noise" in orthogonal ECGs ranges from 8 to 10 mv and is generated primarily by the skeletal muscle activity. The temporal and spectral features of ECGs that identify patients with ventricular tachycardia are masked by this level of noise[9]. The purpose of signal averaging is to improve the signal to noise ratio to facilitate the detection of low amplitude bioelectric potentials. Signals may be averaged by temporal or spatial techniques. Available commercial systems use temporal averaging, which reduce random or uncorrelated noise by the square root of the number of waveforms averaged. For effective working following requirements must be met for temporal averaging[10]:-

- First, the signal of interest must be repetitive and invariable.
- Second, the signal of interest must be time-locked to a fiducial point, such as the peak of the QRS complex.
- Third, the signal of interest and the noise must be independent and remain independent during averaging. Current systems reduce noise to >1.0 mV.

In recording signal averaged ECG three orthogonal, bipolar leads XYZ are recorded, averaged, filtered and combined into a vector magnitude called the filtered QRS complex. The filtered QRS complex is then analyzed for the presence or absence of ventricular late potentials according to standard criteria. Ventricular late potentials represent areas of slow conduction velocity, which is characteristic of myocardial ischemia. The ischemic myocardium is a substrate for the development of ventricular arrhythmias.

No local work is available on Ventricular Late Potentials. We have planned to isolate a subgroup of patients with mitral valve prolapse who are at high risk of developing ventricular tachyarrhythmias and sudden cardiac death on the basis of ventricular late potentials. We also determined the frequency of ventricular late potentials in healthy individuals in our own population.

PATIENTS AND METHODS:

This case - control study was conducted in Army Medical College and Armed Forces Institute of Cardiology, Rawalpindi from March 2005 to February 2006. The 37 patients with mitral valve prolapse and 37 matching controls were included in the study. Diagnosis was based on rigorous echo criteria. Classic MVP was defined as superior displacement of the mitral leaflets for more than 2 mm during systole and leaflet thickness for at least 5 mm during diastole. Non-classic prolapse was defined as the displacement of leaflets for more than 2 mm with maximal leaflet thickness less than 5 mm.[11] Recording of SAECG was done by using following three components:

1. The 1200 EPX high resolution electrocardiograph.

2. Arrhythmia Research Technology (ART) software version 4.02 for analysis of Ventricular Late Potentials.

3. The computer and printer

Recording room was made free of all other electrical devices and the extra lights were switched off to avoid electronic noise and 60 Hz interference. In some patients the noise level was very high, so all the lights were switched off and recording was done in total dark. If necessary, torchlight was used. Patients were instructed to lie absolutely calm and quite to avoid electromyographic (EMG) or the physiologic noise. They were told not to speak or move their hands or legs during the recording. Infact EMG is the most common source of noise in this setting. Hairs on the chest were shaved properly to ensure good contact of the electrodes with skin and for greater noise reduction which can be achieved with proper

removal of chest hairs. The sites, on which electrodes were to be placed, were cleaned with spirit swab and then dried properly. Adhesive pregelled electrodes were placed at the above mentioned sites and then connected through leads with 1200 EPX high resolution electrocardiograph. SAECG recordings were obtained for about one thousand heart beats. All the three bipolar leads were recorded, averaged, filtered and combined into a QRS vector magnitude, called filtered QRS complex (fQRS). Infact this is the filtered QRS complex which is analyzed for the presence or otherwise of Ventricular Late Potentials. SAECG is considered to be positive (presence of VLP) when at least two out of the following three criteria are fulfilled.[12]

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.

Statistical analysis

The data was analyzed using "statistical package for social sciences (SPSS)" version 10. Descriptive statistics were used to describe the variables. Independent sample's t-test was used to compare quantitative variables between cases and controls.

RESULTS

Table 1 shows age and male to female ratio of the cases (patients with mitral valve prolapse) and controls. Mean age of cases was 26.27 ± 6.18 while that of controls was 25.72 ± 5.44. The difference between none of these is statistically significant (P = 0.12) as the controls were carefully matched.

Echocardiographic findings i.e. displacement of mitral leaflets in parasternal long axis view during systole, displacement of mitral leaflets in apical four chamber view during systole and thickness of mitral leaflets in parasternal long axis view during diastole, in cases, is presented in Table 2. The values are expressed as mean (± SD). Displacement of mitral valve leaflets into the left atrium during systole, on parasternal long axis view was 3.68 ± 0.98 mm, whereas the displacement on apical four chamber view was 3.95 ± 1.08 mm. Thickness of mitral valve leaflets during diastole on parasternal long axis view was 4.86 ± 0.82 mm. Apical four chamber echocardiogram of case no. 12 is shown in Figure 1, reflecting prolapse of Mitral leaflet equal to 5.0 mm during systole. SAECG of case no. 8 showing ventricular late potentials (fQRS = 122 ms, LAS 40 = 66 ms, RMS 40 = 1.6 μv) is shown in Figure 2.

Comparison of Signal Averaged ECG findings between cases and controls is shown in Table 3. The value of low amplitude signal under 40 μv (LAS 40) in terminal part of filtered QRS complex was significantly more (P<0.05) in MVP cases as compared to the controls. The difference between values of filtered QRS complex, root mean square voltage of signal in last 40 millisecond (RMS 40) of fQRS complex and noise level was statistically insignificant.

Cases at high risk of developing ventricular tachyarrhythmias on the basis of presence of Ventricular Late Potentials on Signal Averaged ECG are shown in Table 4. The duration of filtered QRS complex was greater than 114 milliseconds in 5 cases (13.51 %) whereas only 2 controls (5.40 %) had this abnormality. The value of low amplitude signal under 40 μv was greater than 38 milliseconds in 9 cases (24.32 %) whereas this was present in only 7 controls (18.91 %). The root mean square voltage of signal in last 40 milliseconds of the filtered QRS complex was less than 20 μv in 10 cases (27.02 %) whereas only 4 controls (10.81 %) had this abnormality. Overall, out of 37 cases ventricular late potentials were present in 9 (24.32 %) individuals (fulfilling at least two out of the above mentioned three criteria), whereas these were present in only 1 (2.7 %) out of 37 controls. The difference between subjects at high risk of developing ventricular tachyarrahythmias was statistically significant at P < 0.05.

DISCUSSION

VLPs, as detected by signal averaged electrocardiography, act as non-invasive marker for the development of ventricular

tachyarrhythmias.[13] The criteria for their presence and their co-relation with ventricular tachyarrhythmias are now well established.[10] In our study 9 out of 37 cases (24.32 %) had ventricular late potentials on their signal averaged electrocardiography, whereas only 1 out of 37 controls (2.7 %) had this abnormality. The cut off value for fQRS complex was 114 milliseconds, for LAS 40, 38 milliseconds and for RMS 40, 20 μv. Abnormality in any two out of the three parameters (fQRS > 114 ms, LAS 40 > 38 ms, RMS 40 < 20 μv) of current study indicated the presence of ventricular late potentials. The difference of number of individuals having VLPs between cases and controls was statistically significant at $P < 0.05$. This indicates the presence of some underlying mechanism in patients with Mitral valve prolapse that leads to generation of Ventricular late potentials which is not there in healthy individuals. We determined frequency of ventricular late potentials in healthy individuals of our population. According to our findings 2.7 % of healthy individuals had ventricular late potentials on their signal averaged electrocardiogram. In this study, 15 cases (40.54 %), out of 37 had no mitral regurgitation, 17 (45.94 %) cases had 1+ (trace) and only 2 (5.40 %) cases had 2+ (moderate), mitral regurgitation. Ventricular late potentials did not appear to be associated with mitral regurgitation. Although the complications in mitral valve prolapse are claimed to be associated with mitral regurgitation, ventricular late potentials seemed to be independent of this phenomenon.

The percentage of cases having ventricular late potentials is slightly higher than in our study in the study conducted by Jabi et al[14] . They studied 41 patients with mitral valve prolapse. 29 % of their study population had ventricular late potentials on signal averaged electrocardiogram. This may be because of the difference in criteria used for ventricular late potentials. Jabi and colleagues relied on two parameters of signal averaged electrocardiogram i.e. low amplitude signal under 40 uv (LAS 40) and root mean square voltage of the signal in last 40 millisecond of filtered QRS complex (RMS 40). In their study, either RMS 40 less than 20μv or LAS 40 greater than 39 ms indicated presence of ventricular late potentials. They left the most important criterion of late potentials i.e. duration of filtered QRS complex. This obviously increased the percentage of patients having ventricular late potentials. Whereas in our study we included three parameters i.e. fQRS complex, LAS 40 and RMS 40. Abnormality in any two of the three parameters i.e. fQRS > 114 ms, LAS 40 >38 ms and RMS 40 < 20μv indicated presence of ventricular late potentials.

Maraglino et al[15] studied 200 subjects with mitral valve prolapse and a mean age of 37 ± 17 years. Ventricular late potentials were found to be present in 45 patients (22.5 %). The criteria which they used to establish the presence of ventricular late potentials was fQRS complex > 114 ms, LAS 40 > 38 ms and RMS 40 < 20 μv. Abnormality in any two of the three parameters indicated the presence of ventricular late potentials. This is exactly the same criteria as we used in our study. Therefore the percentage of patients having ventricular late potentials is almost the same with a very slight difference. They found that complex ventricular arrhythmias were more common in subjects, who exhibited late potentials (55.5 %) than in the remaining population (36.7 %); the difference being statistically significant at $P < 0.03$.

Babuty et al[16] reported that complex ventricular arrhythmias and late potentials were frequent in mitral valve prolapse. They studied 58 patients with mitral valve prolapse with a mean age of 46.6 ± 17.8 years. 22.4 % of their study population had ventricular late potentials. The parameters which they used for the presence of ventricular late potentials were same as we used in our study i.e. fQRS complex > 114 ms, LAS 40 > 38 ms and RMS 40 < 20 μv. In our study 24.32 % patients with mitral valve prolapse had ventricular late potentials. The small difference in result may be due to the difference in age and race of the study population.

Bertoni et al[17] studied 29 patients with mitral valve prolapse. They found ventricular

late potentials to be present in 24 % of their study population. The criteria for presence of ventricular late potentials were same as we used in our study. In our study 24.32 % cases had Ventricular late potentials, the result being exactly the same with only a fractional difference. However they found ventricular late potentials to be present in 5 % of their control group. Whereas in our study only 1 % of the control group had shown this abnormality. This difference may be due to the different methodology adopted for selection of controls. We observed very strict criteria for the selection of controls and excluded almost all the possible confounders. But the same strict criteria were not followed by Bertono et al which might have lead to rise in the percentage of individuals with ventricular late potentials.

Bobkowski et al[18] found significantly higher prevalence of ventricular arrhythmias in patients with mitral valve prolapse than without ($P < 0.0001$). Late potentials were more frequently observed in patients with prolapse than those who were healthy ($P < 0.0001$), and also in those with prolapse and suffering from ventricular arrhythmias compared with those without ventricular arrhythmias ($P < 0.02$). During a mean follow up of 64 months, 24 patients with prolapsing mitral valves developed nonsustained ventricular tachycardia. They found that sensitivity of late potentials was low, at 52 %, for the identification of children with mitral valve prolapse who developed ventricular tachycardia, although the specificity was high at 90 %. This gave a positive predictive value of 50 % and a negative predictive value of 91 %. They concluded that prolapse of the mitral valve predisposes to the development of ventricular arrhythmias and ventricular late potentials. They found that an abnormal signal averaged ECG is a very specific predictor for the development of ventricular arrhythmias in such patients.

CONCLUSIONS

It is concluded from this study that ventricular late potentials are useful non-invasive predictors of sudden cardiac death in patients with mitral valve prolapse.

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Table - 1: Age and male to female ratio of MVP cases and controls

(The value of age is given as mean ± SD)

	Cases (n = 37)	Controls (n = 37)
Age in years (Mean ± SD)	26.27 ± 6.18	25.72 ± 5.44
Male : Female	23 : 14	23 : 14

None of the difference is statistically significant

MVP = Mitral valve prolapse, SD = Standard deviation

Table – 2: Echocardiographic findings in MVP cases (n = 37)

Echocardiographic finding	Measurement (mm)
Displacement of mitral leaflets in parasternal long axis view during systole	3.68 ± 0.98
Displacement of mitral leaflets in apical four chamber view during systole	3.94 ± 1.09
Thickness of mitral leaflets in parasternal long axis view during diastole	4.86 ± 0.82

MVP = Mitral valve prolapse, SD = Standard deviation, mm = millimetre

(*The values are given as mean ± SD*)

Table 3: Comparison of Signal Averaged ECG findings in MVP cases and controls

Measures of SAECG	MVP Cases (n =37)	Controls (n =37)
Duration of filtered QRS complex (ms)	100.70 ± 14.55	100.67 ± 9.74
Duration of low amplitude signal under 40 μv (ms)	33.05 ± 14.42*	26.94 ± 10.01
Root mean square voltage of signal in last 40 ms of filtered QRS (μv)	45.13 ± 39.79	33.14 ± 11.79
Noise level (μv)	0.24 ± 0.04	0.26 ± 0.11

*: The difference is statistically significant at ***P < 0.05***

SAECG = signal averaged electrocardiography, ECG = Electrocardiography,
MVP = Mitral valve prolapse, ms = Millisecond, μv = Microvolt
(*The values are given as mean ± SD*)

Table 4: High risk subjects on Signal Averaged ECG

SAECG parameter	MVP Cases (n = 37)	Controls (n = 37)	p-value
fQRS (> 114 ms)	5 (13.51 %)*	2 (5.40 %)	>0.05
LAS 40 (> 38 ms)	9 (24.32 %)	7 (18.91 %)	> 0.05
RMS 40 (< 20 (μv)	10 (27.02 %)*	4 (10.81 %)	>0.05
Cumulative risk (abnormality in 2 or more parameters)	9 (24.32 %)*	1 (2.7 %)	< 0.05

ECG = Electrocardiography, MVP = Mitral valve prolapse, fQRS = Filtered QRS complex, LAS 40 = Low amplitude signal under 40 μv, RMS 40 = Root mean square voltage of signal in last 40 ms of fQRS, ms = Millisecond, μv = Microvolt

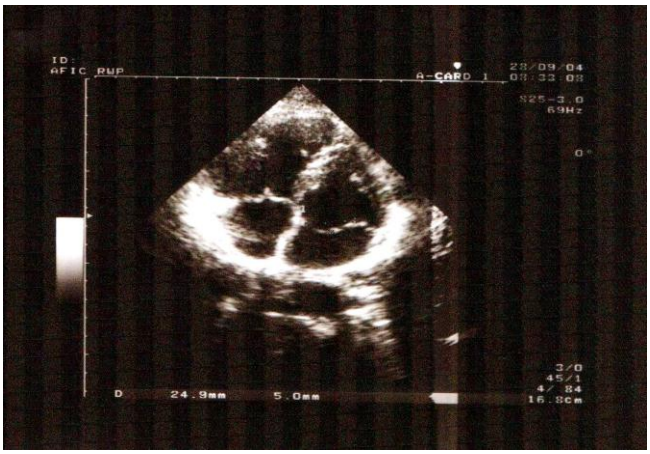

Fig- 1: Apical four chamber echocardiogram of case no. 12 showing prolapse of Mitral leaflet equal to 5.0 mm during systole

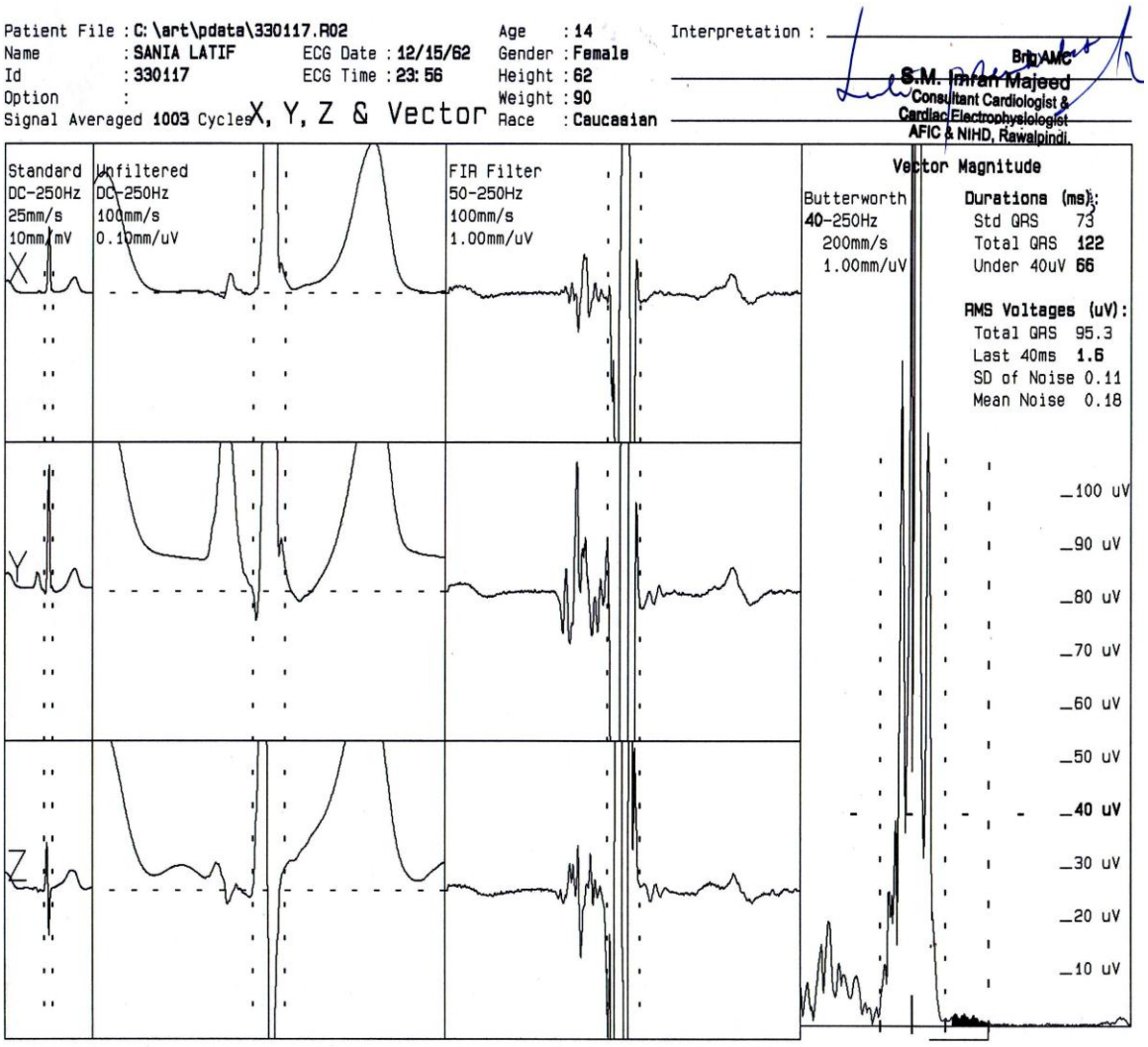

Figure 2: SAECG of case no. 8 showing ventricular late potentials: (fQRS = 122 ms, LAS 40 = 66 ms, RMS 40 = 1.6 μv)