ASSOCIATION OF VIABILITY OF MYOCARDIUM WITH PARAMETERS OF HEART RATE VARIABILITY IN PATIENTS OF FIRST ANTERIOR MYOCARDIAL INFARCTION

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Abstract: Background & Objective: Heart rate variability (HRV) is depressed after acute myocardial infarction (MI) and has been considered as a powerful predictor of mortality and arrhythmic complications in patients of MI. The present study was done to evaluate whether presence of viable tissue within the akinetic myocardium in MI patients, as assessed by dobutamine stress echocardiography (DSE), has any influence on the parameters of HRV. **Methods**: 51 patients with anterior wall ST elevation myocardial infarction (STEMI) treated conservatively underwent DSE two weeks after the index event of MI for assessment of myocardial viability. HRV recording was done for 20 minutes in these patients. **Results**: Out of 51 patients, 26 were DSE positive and 25 were DSE negative for viable myocardium. Among DSE positive group, the first 25 patients were taken for comparative analysis. Only the time domain parameters of HRV were significantly high in patients in the DSE positive group as compared to that observed in DSE negative group. On logistic regression analysis, only pNN50 (with p value = 0.021) could make a significant contribution for prediction of myocardial viability in the patients of MI. When pNN50 value increased by one unit, it was 1.43 times more likely to predict viable myocardium. **Conclusion**: The presence of viable myocardial tissue in akinetic segments among patients of first anterior wall STEMI influences the time domain as well as frequency domain HRV measures. HRV could be used as a potential screening tool to detect myocardial viability in patients of MI.

Keywords: DSE, HRV, Myocardial viability, Myocardial infarction.

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Introduction:

HRV is a physiological phenomenon where there is beat to beat variation in the time interval between heart beats under resting conditions. These beat to beat variations occur due to continuous changes in the sympathetic and parasympathetic outflow and interplay to the heart, and the inherent nature of the sinoatrial (SA) node. HRV is widely recognized as an important inexpensive, non-invasive technique to assess autonomic flow in normal individuals and in many diseases including cardiovascular diseases. Reduced HRV after acute MI has been shown to be a highly significant risk factor for adverse outcomes including all cause mortality[1], arrhythmic[2] and sudden death[3, 4, 5].

After coronary occlusion, five types of myocardial outcomes are possible – normal structure and function, myocardial ischemia, stunned myocardium, myocardial hibernation, and infarction[6]. Stunned myocardium (depressed function at rest but preserved perfusion) is observed after a transient ischemia followed by reperfusion. It improves spontaneously in days to weeks. Hibernating myocardium (depressed function and perfusion at rest) [7] is chronic, adaptive reversible contractile dysfunction secondary to significant coronary artery disease. This results in wall abnormalities (hypokinetic, akinetic, dyskinetic segments) which are potentially reversible after revascularization.

Viable myocardium may be present in the infarcted, akinetic zone in patients having persistent left ventricle (LV) dysfunction weeks to months after myocardial infarction. Identifying viable tissue may permit improvement in LV function and prognosis after revascularisation in this patient group.

Several non-invasive techniques are available to identify dysfunctional but viable tissue: DSE, single photon emission computed tomography (SPECT) imaging, positron emission tomography (PET) metabolic imaging with F18-fluorodeoxyglucose (FDG), cardiac magnetic resonance (CMR) and myocardial contrast echocardiography (MCE).

In a study[8], PET revealed residual metabolic activity (metabolism – perfusion mismatch) in a high proportion (54%) of chronic electrocardiographic Q wave regions in patients with clinical history of one or more myocardial infarctions, implying persistence of substantial amounts of viable tissue and significant probability of functional improvement after revascularization.

DSE is a valuable and the most frequently used tool for detection of myocardial viability. Hibernating and stunned myocardium (viable myocardium) have a characteristic feature of positive inotropic reserve, which is absent in irreversibly damaged infarcted myocardium, i.e. necrosis or scar (non – viable myocardium) [9]. Recovery of contractility of akinetic myocardium after revascularization is better predicted by contractile reserve demonstrated by DSE than by SPECT or PET.

HRV is decreased in patients with infarcted myocardium but it is not clear whether the presence of viable segments in the infarction area affects the parameters of HRV. A few studies have been done to find out the differences between viable and non – viable myocardium in post MI patients.

In the present study it was hypothesized that parameters of HRV are more deranged in non – viable infarcted myocardium (detected by DSE) as compared to that observed in the viable myocardium and the various measures of HRV were evaluated in this background.

Material and Methods:

The present observational descriptive analytical study was carried out in the departments of Cardiology and Physiology at S.M.S. Medical College and Attached Hospitals, Jaipur, India from April 2013 to October 2013. The study cohort consisted of patients diagnosed with the first episode of anterior wall ST segment elevation myocardial infarction (STEMI) treated conservatively with or without thrombolytics, had an uneventful hospital stay and were discharged on secondary prophylaxis. They underwent DSE 2 weeks post myocardial infarction for risk stratification and assessment of myocardial viability and also underwent HRV testing. Based on DSE results they were classified into DSE positive (improvement of contractility of at least one grade in two or more segments) and DSE negative group (no improvement or improvement in less than two segments) for viable and nonviable myocardium respectively.

The sample size required at 95% confidence and 80% power was calculated at the scale of 11 patients in each group that was rounded off to 25 patients in each group. 25 consecutive patients with viable and 25 consecutive patients with non viable myocardium were included on first come first basis after beginning of the study. For obtaining this sample size a total of 64 patients were evaluated out of which 13 patients were excluded wherein 26 patients were DSE positive and 25 patients were DSE negative. First 25 cases in DSE positive group were included in the study.

Patients with atrial fibrillation, acute coronary syndrome in the past, contraindication for DSE, in whom good quality echocardiograms and HRV recordings could not be obtained, on drugs like diuretics, anticholinergics (including antidepressants, antihistamines, and over-the-counter cough and cold medications), sympathomimetic (α and β agonist), parasympathomimetic agents, fludrocortisones and patients who were not willing to participate in the study were excluded from the study.

Echocardiogram and DSE:

Echocardiograms was obtained using the Philips iE33 x matrix Echocardiography System. 2 D – and M – Mode echocardiography measurements were obtained to assess systolic and diastolic dimensions, left ventricular ejection fraction (LVEF), and regional wall motion abnormalities. LVEF was calculated as per Simpson method.

DSE were assessed in parasternal (long axis and short axis) and apical views (four – chamber and two – chamber views) in loop format. The images are digitised and stored during low dose, peak dose and after peak dose. The images were compared in a quad screen format. Dobutamine was administered intravenously by an infusion pump. A graded dobutamine infusion starting at 2.5 mcg/kg/min and increasing at 3 – minute intervals to 5, 7.5, 10, 20, 30, and 40 mcg/kg/min was used for DSE. End points were achievement of target heart rate (defined as 85% of the age-predicted maximum heart rate), new or worsening wall – motion abnormalities, significant arrhythmias, hypotension, severe hypertension, and intolerable symptoms. Atropine, in divided doses of 0.3 to 0.6 mg to a total of 2.0 mg, was used as needed to achieve target heart rate[10].

Throughout dobutamine infusion ECG was monitored and blood pressure and heart rate were measured. Echocardiograms were obtained by the end of each infusion stage. Images were recorded and reviewed by two independent observers unaware of the patient's clinical state. In cases of disagreement a consensus was reached.

Regional contractility was analyzed according to 17 – segment model. A score was given to each segment: 1 – normo or hyperkinesis; 2 – hypokinesis; 3 – akinesis; 4 – dyskinesis. Images from low dose of dobutamine infusion were compared with peak stress images to maximize the sensitivity and interpreted as per the Table 1. Presences of viability were defined as improvement by at least one score in two or more segments. For example, akinesis improving to hypokinesis or normal in two or more segments was considered as viable myocardium. Improvement from dyskinesia to akinesis was not considered as viable.

RWMA, regional wall motion abnormalit; Category 2 and 3 were considered for DSE positive group and category 3 for DSE negative group.

HRV Recording:

Short – term analysis of HRV was carried out in the Department of Physiology, SMS Medical College and Attached Hospitals, Jaipur, India as per international protocol [11]. ECG signal was continuously amplified, digitized and stored in for offline analysis and was assessed in time domain, frequency domain and non – linear methods using the HRV soft version 1.1. Full revision of ECG and editing of beats was done when indicated. HRV was measured in both the groups for comparison amongst its different parameters. All the recordings were done between 10 am and 1 pm.

Nature of tissue	Resting function	Low Dose	Peak dose
1. Normal	Normal	Normal	Hyperkinetic
2. Viable, ischemic	RWMA	Improvement	Worsening (Biphasic response)
3. Viable, non ischemic	RWMA	Improvement	Sustained improvement
4. Infarction	RWMA	No change	No change

Table 1. Interpretation by Regional Wall Motion Analysis in DSE

Though HRV can be measured over any length of recorded ECG, as per the guidelines of Task Force (1996) at least 5 minutes of ECG must be recorded to quantify Sympathetic and Parasympathetic tone and at least 20 minutes must be recorded to ensure the correct performance of the geometric methods[11]. So, in this study we used 20 minutes of ECG recording for HRV analysis.

Time domain HRV variables by statistical methods included SDNN, SDANN, rMSSD,

pNN50, Mean R-R interval. Time domain HRV variables by geometric methods included HRV triangular index, TINN. Frequency domain HRV variables included Total power, LF (ms^2), HF (ms^2), LF (ms^2)/HF (ms^2) ratio, LF (n.u.), HF (n.u.). Non – linear methods HRV variables included SD1, SD2 and SD1/SD2.

Statistical Analysis

Continuous data were summarized in form of mean and standard deviation. Differences in mean were analyzed using student's t test. Logistic regression was applied to find the predictors of myocardial viability. Count data were summarized in forms of proportions. The differences in proportions were analyzed using chi square test. The level of significance was kept at 95% for all statistical analysis. Clearance from ethical committee was taken.

Results

From April 2013 through October 2013, a total of 64 patients were enrolled from cardiology outpatient department, SMS Hospital for DSE as part of risk stratification and subsequently underwent ECG recording for HRV analysis. Two patients were ineligible for DSE due to LV apical clot, six patients did not give consent

Table 2. Baseline Clinical Characteristics of the Patients.

Variables	DSE Positive mean (SD)	DSE Negative mean (SD)	P value (student 's t test)
Mean RR interval (ms)	952.19(136.78)	792.16(121.06)	<0.001
pNN50 (%)	15.81 (14.42)	2.43 (3.11)	<0.001
SDSD (ms)	70.31 (57.74)	36.80 (31.31)	0.013
RMSSD (ms)	70.28 (57.71)	36.79 (31.30)	0.013
SDANN (ms)	18.10 (12.27)	11.61 (7.75)	0.03
SDNN (ms)	66.99 (34.54)	39.63 (21.26)	0.0014
HRV INDEX	0.14 (0.06)	0.12 (0.07)	0.27
TINN (ms)	667.77 (685.03)	483.53 (535.20)	0.294

for HRV recording and five patients had poor ECG recording for HRV. Out of remaining 51 eligible patients, 26 were DSE positive and 25 were DSE negative. First 25 cases in DSE positive group were included in the study.

The baseline characteristics (presence of diabetes mellitus, hypertension, smoking, thrombolysis, age, sex and LVEF) of both the group was comparable (p value > 0.05). (Table 2)

PARAMETERS	DSE POS (n=25)	DSE NEG (n=25)
AGE (YRS)	55.52±(11.23)	55.76±(11.33)
AGE>60 YRS (%)	9(36%)	9(36%)
MALE (%)	21(84%)	20(80%)
DM (%)	3(12%)	3(12%)
HTN (%)	3(12%)	4(16%)
SMOKING (%)	13(52%)	12(48%)
THROMBOLYSIS (%)	17(68%)	17(68%)
LVEF (%)	34.88%	32.77%
BETA BLOCKER USE (%)	23(92%)	24(96%)

Table 3. Time Domain HRV Parameters in Both Groups.

DM, diabetes mellitus; HTN, hypertension; LVEF, left ventricle ejection fraction.

Time domain variables of HRV:

The mean R-R interval was significantly greater in the DSE positive than in the DSE negative group indicating that mean heart rate was more in patients with non viable myocardium than in viable myocardium. All HRV parameters by statistical method were significantly higher in DSE positive group than in DSE negative group (Table 3).

The geometric HRV parameters were numerically higher in DSE positive group than in DSE negative group but it was not statistically significant (Table 3).

Frequency domain variables of HRV:

Differences in the frequency – domain measures of HRV could be appreciated between DSE positive and DSE negative

groups, though the differences were not statistically significant (Table 4).

Table 4. Frequency Domain HRV Parameters in Both Groups.

Variables	DSE Positive mean (SD)	DSE Negative mean (SD)	P value (student's t test)
LF %	28.41 (13.20)	23.50 (10.74)	0.155
HF %	31.39 (15.81)	23.31 (15.50)	0.074
TOTAL POWER	6136.95 (8012)	2524 (5592)	0.070
LF (n.u.)	48.36 (13.26)	52.75 (19.94)	0.36
HF (n.u.)	51.63 (13.26)	47.24 (19.94)	0.36
LF/HF	1.12 (0.81)	1.63 (1.36)	0.115

Non – Linear variables of HRV:

There were significantly higher values of SD1 and SD2 in DSE positive group as compared to DSE negative group but the difference in ratio of SD1/SD2 among the groups were non-significant (Table 5).

Table 5. Non Linear HRV Parameters in Both Groups.

Variables	DSE Positive mean (SD)	DSE Negative mean (SD)	P value (student's t test)
SD1	49.71 (40.83)	26.03 (22.15)	0.014
SD2	96.16 (55.86)	55.90 (32.07)	0.0003
SD1/ SD2	0.47 (0.15)	0.42 (0.17)	0.264

A logistic regression analysis was conducted to find predictors of myocardial viability (detected by DSE) for 50 patients using pNN50, Mean R-R interval, SDANN, RMSSD, SDNN, SD1, SD2, SD1/SD2 ratio and TINN as predictors. (Table 6)

Table 6. Logistic regression analysis to predict myocardial viability for 50 patients.

		B	S.E.	Wald	df	Sig.	Exp(B)	95.0% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	pNN50	.361	.157	5.309	1	.021	1.435	1.055	1.951
	Mean RR	.009	.005	2.929	1	.087	1.009	.999	1.019
	RMSSD	36.709	50.237	.534	1	.465	8.760E15	.000	5.063E58
	SDANN	.122	.063	3.788	1	.052	1.129	.999	1.277
	SDNN	.105	.132	.635	1	.425	1.111	.858	1.439
	TINN	.000	.002	.000	1	.991	1.000	.997	1.003
	SD1	-51.642	70.930	.530	1	.467	.000	.000	8.861E37
	SD2	-.217	.158	1.877	1	.171	.805	.591	1.098

	sd1/sd2	-10.934	9.701	1.270	1	.260	.000	.000	3.231E3
	Constant	-4.559	4.734	.928	1	.335	.010		

A test of the full model was statistically significant, indicating that the predictors as a set reliably distinguished between viable and non-viable myocardium (chi square = 32.494, p < .0001 with df = 9). Also Hosmer and Lemeshow Test show a good fit by high p value (0.486) and low chi square value (7.481).

Nagelkerke R^2 of 0.637 indicated a moderate relationship between predictions and grouping. Prediction success overall was 86% (84% for viable myocardium and 88% for non viable myocardium). The Wald criterion demonstrated that only pNN50 (with p value=.021) made a significant contribution to prediction. Other predictors were not significant predictors.

For pNN50: - EXP (B) value indicates that when pNN50 value changes with one unit, the odds ratio is 1.43 times as large and therefore 1.43 times more likely to have viable myocardium.

Discussion:

The present study was carried out in patients who suffered from first episode of anterior wall STEMI and got treated conservatively with or without thrombolytics depending on the window period and chest pain at presentation. They underwent DSE as part of risk stratification at least 2 weeks after index event. The presence of viable and ischemic myocardial segments in the infarction zone is a class I indication for coronary angiography and revascularisation[12].

Several non invasive diagnostic tests are available to identify myocardial viability. PET, SPECT, and DSE are considered the traditional techniques to evaluate myocardial viability. Recently, newer techniques have been introduced including cardiac magnetic resonance, myocardial contrast echocardiography and electromechanical mapping. The gold standard for assessing myocardial viability is PET[13]. However, PET imaging is expensive and requires equipment and radiotracer that may not be readily available at all places. DSE is an inexpensive, most frequently used tool to assess myocardial viability and ischemia. According to a study of sensitivity, specificity, and predictive accuracies of various non-invasive techniques for detecting viable myocardium by Bax et al, [14] it was found that FDG PET had the maximum sensitivity and specificity of 93% and 58% respectively whereas DSE had the maximum sensitivity and specificity of 81% and 80% respectively. So, PET is the most sensitive whereas DSE is the most specific method to assess myocardial viability.

Recovery of contractility of akinetic myocardium after revascularization is better predicted by contractile reserve demonstrated by DSE than by SPECT or PET. It has been demonstrated that a substantial number of segments that are nonviable on DSE (i.e., lack of contractile reserve) are viable by nuclear imaging that suggest that these segments were plausibly more damaged. Recent data have indeed shown that segments with viability on FDG PET without contractile reserve have more severe ultra structural damage when compared with “FDG PET – viable segments” with contractile reserve[14]. In this backdrop DSE was used for detection of viable myocardium in the present study.

Both the groups of DSE positive and DSE negative patients did not differ with respect to morbidities and factors that might have an influence on HRV parameters like diabetes mellitus, systemic arterial hypertension, smoking, fibrinolysis and left ventricular ejection fraction.

In the present study all time – domain HRV parameters evaluated through statistical methods were significantly higher in patients

with DSE positive for myocardial viability as compared to that observed in DSE negative patients. Among time domain HRV parameters, SDNN has an established prognostic value in patients after AMI. Kleiger et al[1] used cycle length variability (CLV; standard deviation of normal RR intervals within one 24 – hour period) as a measure of HRV in 808 patients at 11 ± 3 days after AMI and documented that the relative mortality risk was 5.3 times as high in patients with SDNN < 50 ms than in patients with SDNN > 100 ms at a mean follow-up time of 31 months. In patients with moderately decreased SDNN (50-100 ms) the relative risk of mortality was 1.6 times higher. In the present study SDNN was 67 ms (i.e. between 50 – 100 ms) in DSE positive group and 39 ms (i.e. < 50 ms) in DSE negative group in spite of similar LVEF. Kleiger showed that even in group with an ejection fraction below 30%, low CLV more than doubles the risk. This suggest that our patients with non – viable myocardium are at higher risk compared to patients with viable myocardium in spite of similar LVEF.

Another HRV parameter, pNN50 represents the vagal influence. Algra et al.[15] studied a total of 6,693 consecutive patients who underwent 24 – hour ambulatory ECG for various reasons and were followed up for 2 years; of these, 245 patients died suddenly. Patients with low parasympathetic activity as expressed by 50 – ms interval differences < 3% had a risk for sudden death approximately double (crude relative risk = 1.8) than of those with high parasympathetic activity (50 ms interval differences ≥ 3%). In a study by Bryniarski et al[16] in post myocardial infarction patient, the value of pNN50 in viable myocardium versus non – viable myocardium in infarcted zone was 8.6 ± 5.5 versus 1.3 ± 0.9, respectively. In the present study this value was 15.81 (± 14.42) in DSE positive versus 2.43 (± 3.11) in DSE negative group, respectively suggesting that patients with viable myocardium has higher parasympathetic tone compared to patients with non – viable myocardium.

When logistic regression analysis was applied to predict myocardial viability (by DSE) for 50 patients using pNN50, Mean R – R interval, SDANN, RMSSD, SDNN, SD1, SD2, SD1/SD2 ratio and TINN as predictors, it was found that the prediction success was 86% overall (84% for viable myocardium and 88% for non viable myocardium). However, only pNN50 (with p value = 0.021) made a significant contribution to prediction. When pNN50 value changes with one unit, the odds ratio is 1.43 times as large and therefore 1.43 times more likely to have viable myocardium. Other parameters of HRV could not contribute significantly as an independent predictor for myocardial viability in logistic regression.

The frequency domain measures differed between the study groups indicating higher parasympathetic tone in patients with viable myocardium in the infarcted zone, although it was not statistically significant.

The mechanisms for depressed HRV in acute MI are not completely understood but it is hypothesized that it could be due to the deranged interplay of the autonomic neural outflow to the heart.

a) The first hypothesis suggest that the changes in the geometry of a beating heart secondary to necrotic and non – contracting segments may reflexly enhance beyond and above normal the firing of sympathetic afferent fibers by mechanistic distortion of the sensory endings[17,18]. This sympathetic excitation effectively attenuates the influences of vagal fibres directed to the sinus node

b) The second hypothesis suggests the reduced responsiveness of sinus nodal cells to neural modulations following MI[19].

The differences in HRV parameters between the study groups could be explained by the presence of viable segments in DSE positive patients. Casolo et al[20] studied 54 consecutive patients with evidence of AMI by collecting the 24 – hour SDNN from Holter tapes recorded on day 2 or 3. They also measured HRV in 15 patients with unstable angina and in 35 age-matched normal subjects. They found that HRV was significantly higher in non-Q-wave AMI than in Q-wave AMI and

HRV was lower in AMI than in unstable angina patients and controls, suggesting the inverse relation of degree of HRV reduction with clinical severity and infarct size. In our study, in spite of similar LVEF, patients with stunned or hibernating myocardium had significantly higher HRV than in patients with only infarcted myocardium.

So, the time domain HRV measurement used in this study to identify high risk patients may provide initial information about myocardial viability with pNN50 being the most important predictor.

Conclusion

In the present study from the behavior of the data so evaluated in terms of the various parameters of HRV in relation to the presence of viable myocardium as exemplified by DSE, it could be concluded that the presence of viable myocardial tissue in infarcted zone among patients of first anterior wall STEMI influences changes in the time domain as well as frequency domain HRV measures. However, only the time domain HRV variables changes (pNN50 being the significant predictor of myocardial viability in the infarction zone) were observed to be statistically significant in patients who were DSE positive as compared to that observed in DSE negative patients.

Heart Rate Variability, a reflection of the autonomic interplay of the sympathovagal measures and local influences, has the potential to prognosticate the time – course of myocardial infarction and in conjunction with DSE can plausibly assess the myocardial viability and subsequently help in the management of MI. If the present findings is confirmed in larger group of patients,then HRV has the potential to become an important screening tool to assess myocardial viability prior to DSE.

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