Original Article

Effect Of Reperfusion On Time Domain Parameters Of Heart Rate Variability

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Abstract

Objective: To compare the effect of reperfusion by measuring time domain parameters of heart rate variability before and after percutaneous transluminal coronary angioplasty.
Study design: Quasi-experimental study design
Place and Duration: Department of Clinical Cardiac Electrophysiology, Armed Forces Institute of Cardiology/National Institute of Heart Diseases (AFIC/NIHD), Rawalpindi in 2018.
Patients and Methods: 40 patients with coronary artery disease having a mean age of 55.20 ± 8.03 years were recruited by non-probability convenience sampling. DMS 300-4A Holter monitors were used to obtain 24 hours of ambulatory ECG recording before and within 24 hours after percutaneous transluminal coronary angioplasty. Digital ECG data were transferred to the computer and edited with the help of DMS Cardio scan software. Heart rate variability was analyzed in time domain measures. For time domain analysis normal heart rate, SDNN, SDNNi, SDANN, RMSSD, and pNN50 were recorded from 12 lead digital ECG data.
Results: The results of our study demonstrated significantly decreased heart rate variability in coronary artery disease patients on comparison of pre and post-angioplasty values only SDNNi was significantly reduced (p-value = 0.035) whereas the reduction in SDNN and pNN50 was statistically insignificant (p-value > 0.05). On the contrary, SDANN and RMSSD displayed a slight rise after angioplasty, but it was not significant (p-value > 0.05).
Conclusion: Reperfusion after percutaneous transluminal coronary angioplasty decreases heart rate variability within 24 hours after the procedure. Whereas heart rate during the same period after angioplasty increases. This reflects autonomic balance shifts towards sympathetic predominance as indicated by reduced heart rate variability and a rise in heart rate. This makes the susceptible patients vulnerable to the development of ventricular arrhythmias, especially during 24 hours after angioplasty. Therefore, patients with decreased heart rate variability are at risk of ventricular arrhythmogenesis so they may be kept under medical surveillance for at least 24 hours after percutaneous transluminal coronary angioplasty.
Keywords: Ischemia, Holter monitoring, coronary artery disease, Heart Rate Variability

Introduction

According to the world health organization, ischemic heart disease due to coronary artery occlusion is the chief cause of death globally.[1] Severe ischemia can alter electrical potentials which can quicken fatal ventricular arrhythmias which may lead to sudden cardiac arrest.[2] Mostly fatal arrhythmia in ischemic heart disease patients results due to a disparity of the autonomic nervous system with the sympathetic multitude.[3] Various noninvasive methods have been established to forecast these events in patients and diversify the high-risk patients of sudden cardiac arrest.[4] These include signal-averaged electrocardiogram, Heart rate variability, Q-T dispersion, heart rate turbulence, and T-wave alternan.[5]

Heart rate variability (HRV) is a biological phenomenon defined as the chronological difference of heartbeat-to-beat variation in normal sinus rhythm.[6] HRV is represented as variations in heart rate around the mean value. Heart rate variability is also known as RR length variability or cardiac cycle variability. Heart rate variability is regulated by the autonomic nervous system through the antagonistic activity of sympathetic and parasympathetic branches which results in oscillation of heart rate. On surface electrocardiogram, this oscillation is represented as recurring fluctuations in RR intervals.[7] Heart rate variability can be used as a non-invasive marker of the autonomic nervous system. Different factors like respiration, baroreflex sensitivity, and genetic and environmental factors can affect heart rate variability by altering autonomic regulation. [8]

Heart rate variability is measured by time and frequency domain methods. Frequency domain parameters are VLF (very low frequency), LF (low frequency), HF (high frequency), and LF/HF ratio. Whereas time domain indices are SDNN (standard deviation of all normal to normal intervals in 24 hours), SDANN (standard deviation of the 5-minute mean of normal to normal intervals), RMSSD (root mean squared successive differences between adjacent normal to normal intervals over the entire recording) and pNN50 (percentage of differences between successive normal to normal intervals over 24 hours that are greater than 50 milliseconds).[9] The time domain parameters of HRV are actually arithmetical derivations demonstrating the dispersion of normal oscillation of heartbeat.[10] To do statistical analysis of time domain analysis in ECG recordings, we need a total of 24 hours to be edited and their mathematical derivatives are developed through statistical formulations.[11]

Heart rate variability has been found to be reduced in patients with ischemic heart disease.[12] Chronic myocardial ischemia is the basis of redistribution of autonomic nerve endings, increased catecholamines, hypersensitivity for sympathetic stimulation, accumulation of metabolites, and electrolyte imbalance leading to structural and functional alterations in ventricles.[13] These changes can cause heterogeneity of impulse propagation in ischemic tissues and decreased ventricular refractoriness which results in the onset of lethal arrhythmias.[14]

The current study was designed to determine the effect of reperfusion achieved by percutaneous transluminal coronary angioplasty on time domain parameters of heart rate variability in coronary artery disease patients. We planned to investigate the changes in heart rate variability using 24 hours of Holter monitoring before and within 24 hours after percutaneous transluminal coronary angioplasty. The results of the study would provide insight into the early effects of reperfusion on autonomic imbalance within 24 hours. This would certainly help in improving the health care facilities provided to the susceptible patients who are at risk of ventricular arrhythmogenesis.

Materials and Methods

The study was a cross-sectional comparative study that was carried out at the Cardiac Electrophysiology Department of the Armed Forces Institute of Cardiology (AFIC) in collaboration with Army Medical College, Rawalpindi. The study was started after the official approval of the Ethical Review Board of Army Medical College, Rawalpindi. Written informed consent was taken from all the patients undergoing the study. 50 coronary artery disease patients of either sex was encompassed in our study. The patients were diagnosed on the basis of angiography and those included had more than 70% occlusion of the vessel's lumen. The diabetic, hypertensive, bundle block, and structural heart disease patients were not included in the study. We used DMS 300-4A Holters from "Diagnostic

Monitoring Software (DMS)" US limited. We obtained 12-lead ECG recording pre and post-angioplasty. After effective pre-angioplasty monitoring in 53 patients the post angioplasty data in 6 patients could not be done because there was unsuccessful catheterization of occluded vessels which hampered our results as there was no successful reperfusion of the cardiac muscle. We discarded data of 7 patients due to distortions in more than two leads of the recordings. Final data was of 40 patients with successful angioplasty and interpretable pre and post ECG recordings.

Inferential statistics were used for the comparison of continuous variables as the time field indices of HRV like SDNN, SDNNi, SDANN, pNN50 and RMSSD. The data were also explored for the presence of outliers. Parametric 'one sample t test' and 'paired samples t test' were used to compare pre-angioplasty time domain heart rate variability with normal reference values and post-angioplasty values respectively. The alpha value was set at < 0.05 for significance at confidence level of 95%.

Results

We analyzed the data of 40 patients with mean age in years of 55.2 ± 8. There were 39 male and one female patients with male to female ratio of 39:1. Pre and post-angioplasty mean heart rates were 75.95 ±5.88 and 78.55 ± 7.62 beats per minute respectively. Shapiro Wilk test showed that heart rate data followed normal distribution (p-value > 0.05). Therefore 'parametric, paired samples t test' was applied to compare pre and post angioplasty heart rates. The result showed that post-angioplasty heart rate was significantly higher when compared to pre-angioplasty heart rate (p-value = 0.044) as shown in table 1.

Pre-angioplasty, time domain indices of heart rate variability were compared with the post-angioplasty indices as illustrated in table 3. Values of SDNN, SDNNi and pNN50 showed reduction after angioplasty as compared to the values before the procedure. However, only SDNNi was significantly reduced (p-value = 0.035) whereas the reduction in SDNN and pNN50 was statistically insignificant (p-value > 0.05). On the contrary, SDANN and RMSSD displayed slight rise after angioplasty, but it was not significant (p-value > 0.05).

Table-1 Comparison of pre and post-angioplasty mean heart rates (N=40)

Heart rate	*Values (mean ± SD)*	*Paired samples t-test*	
		t-value	**p-value**
Pre-angioplasty	75.95 ± 5.88	-2.08	0.044*
Post-angioplasty	78.55 ± 7.62		

*p-value significant (< 0.05), SD = standard deviation

Table-2 Comparison of pre and post-angioplasty time domain indices of heart rate variability (N=40)

Time domain variables	*Values (mean ± SD)*		*One sample t-test*	
	Pre-angioplasty	**Post-angioplasty**	**t-value**	**p-value**
SDNN (ms)	102.15 ± 23.66	99.83 ± 34.416	0.425	0.673
SDNNi (ms)	45.83 ± 11.09	41.60 ± 11.67	2.18	0.035*
SDANN (ms)	90.45 ± 24.66	92.00 ± 37.72	-0.267	0.791
RMSSD (ms)	24.98 ± 7.26	25.50 ± 9.632	-0.320	0.751
pNN50 (%)	6.88 ± 6.12	6.10 ± 7.01	0.671	0.506

*p-value significant (< 0.05)

Discussion

Patients with coronary artery disease have significantly decreased heart rate as compared to the normal values in healthy people. On comparison of pre and post-angioplasty heart rate variability in patients with coronary artery disease, it was found that values of almost all the post-angioplasty heart rate variability time domain indices were decreased, however only SDNNi was significantly decreased.

The disequilibrium of autonomic nerves in the form of boosted sympathetic and diminished vagal activity

causes reduction in heartrate variability in the coronary occlusion patients.[15] There are various articles suggesting that increased release of norepinephrine and enhanced disturbance in vagal nerve endings causes alteration of normal autonomic balance in patients with chronic ischemia.[16] Ischemia due to constant occlusion also causes redistribution of autonomic nerve endings. [17] This enhancement in inhomogeneity of autonomic innervation augments sympathetic response and causes reduction in vagal inflection in the ischemic patients which leads to reduction in heart rate variability.[18]

Ischemia related changes are the underlying cause of reduced heart rate variability in coronary artery disease patients [19]. Therefore, it follows that removal of ischemia after reperfusion should enhance heart rate variability by restoring the balance of autonomic nervous system. However, effects of reperfusion on heart rate variability are complex, multifaceted and depend upon time after reperfusion at which heart rate variability is recorded. The effects of reperfusion can be divided into early i.e. within 24 hours of angioplasty and late i.e. after 24 hours especially after 3 to 5 days. Early after angioplasty reperfusion decreases heart rate variability whereas late after angioplasty it increases the variability.[20] Time after angioplasty at which heart rate variability is recorded is therefore, an important factor in determining the final status of heart rate variability.

On comparison of pre and post-angioplasty heart rate variability, we found that heart rate variability was reduced after the angioplasty. Reduced heart rate variability denotes sympathetic predominance over the vagal activity. We analysed the post-angioplasty heart rate variability 'early' that is within 24 hours after angioplasty when the patients were retained in post-catheterization ward. As the patients were kept in hospital for a day after angioplasty, the anxiety level of the patients must be raised as they had undergone an invasive procedure of percutaneous transluminal coronary angioplasty. Anxiety and stress is the outcome of sympathetic stimulation which reciprocally suppresses parasympathetic activity. This state of autonomic imbalance with sympathetic preponderance leads to reduction in heart rate variability. According to studies done by Verkuil *et al* and Pieper *et al*, anxiety can decrease heart rate variability and increase heart rate due to increased sympathetic drive during stress [21, 22]. The logic of increased sympathetic inflection in our patients after angioplasty is also supported by a significant increase in average heart rate after angioplasty. The mean heart rate before angioplasty was 75.95 beats per minute whereas after the angioplasty it was 78.55 beats per minute. The post-angioplasty heart rate was significantly higher as compared to the initial value before the procedure (p=0.044). Increased heart rate in our study population, after the procedure, indicates heightened sympathetic response which led to reduced heart rate variability in these patients.

A certain amount of time is required for reperfusion to increase heart rate variability by restoring normal autonomic balance. However, the immediate effect of reperfusion is to decrease heart rate variability by inducing the 'reperfusional injury'. Transluminal ballooning pressure and sheer effect of blood flow cause intravascular muscular filament strain which can lead to transient oedema and denervation of myocardial nerve endings. This reperfusional injury involves especially the subendocardial layer where the vagal nerve endings are in abundance.[13] Local damage to vagal nerve endings in re-perfused myocardium may be another reason for reduced heart rate variability.[23] A subcellular paradigm of reperfusional injury was explored by Jennings who conducted a study to examine the effects of reperfusion on mitochondria.[24] According to her, the mitochondria of injured myocardial cells swell extensively on reflow of calcium rich plasma. Swollen mitochondria absorb calcium and calcium accumulation occurs inside them in the form of hydroxyapatite making amorphous matrix densities (AMDs).[25] After 24 hours normal myocardium and injured myocardial cells are indistinguishable. The only signs left after a day is presence of amorphous matrix densities in the ischemic region. She concluded that cellular injury after reperfusion of ischemic myocardium persisted for at least 24 hours. We conducted our study within 24 hours of reperfusion when the acute cellular injury was there which might have affected the heart rate variability.[24] The cumulative effect of anxiety and reperfusional injury along with damage to vagal nerve endings and mitochondria appear to be the logical basis for reduced heart rate variability in our study.

Erdogan *et al* evaluated heart rate variability in 139 patients with coronary artery disease and compared pre and post-angioplasty values.[26] They analysed heart rate variability in both time and frequency domains within 24 hours after angioplasty. They reported that heart rate variability was reduced after the procedure but none of the parameters showed statistically significant reduction. Erdogan *et al* concluded that revascularization did not affect heart rate variability

within 24 hours which supported the results of our study.

In a follow up study conducted by Sedziwy *et al*, heart rate variability was measured in time domain at three different occasions after the angioplasty.[27] They recruited 65 patients with coronary artery disease and analysed heart rate variability after 14 days, 3 months, 6 months and finally one year of reperfusion. They reported that heart rate variability was significantly higher when recorded 14 days after the procedure as compared to the pre-angioplasty value. Their results are opposite to those of our study where we found decreased heart rate variability after angioplasty. The opposing results seem to be due to the different timings of heart rate variability recording after the procedure. We recorded heart rate variability within 24 hours after angioplasty whereas Sedziwy et al had their first recording after 14 days of the procedure. Sedziwy *et al* further reported that heart rate variability kept increasing significantly till three months after the procedure. After three months heart rate variability did not show any significant increase when measured at 6 months and one year after the procedure. The results imply that more the time elapses after angioplasty the better would-be autonomic balance but up till about three months. By three months, maximum optimization of the autonomic nervous system takes place and there is no additional change after that time.

Effects of reperfusion on heart rate variability are diverse and complicated. Multiple factors with opposing effects on heart rate variability come into play simultaneously after reperfusion is achieved by angioplasty. Some of these factors are altered catecholamine release due to anxiety, damage to vagal nerve endings and mitochondria due to reperfusion injury, extent of ischemia and reperfusion and the effects of ballooning. Balance between these opposing factors determines the final status of heart rate variability. Time at which heart rate variability is recorded after angioplasty is an important factor determining the ultimate balance between these opposing factors. Within 24 hours after angioplasty the factors reducing heart rate variability predominate. After about 3 to 5 days these factors fade away and the ones increasing heart rate variability take over reflecting restoration of normal autonomic balance with vagal predominance.[28] The process of improving heart rate variability continues up till about three months after angioplasty with no significant change beyond that time.

Conclusion

Reperfusion after percutaneous transluminal coronary angioplasty decreases time domain parameters of heart rate variability when recorded within 24 hours after the procedure. Whereas heart rate during the same period after angioplasty increases. Autonomic balance shifts towards sympathetic predominance as indicated by reduced heart rate variability and rise in heart rate. This makes the susceptible patients vulnerable to development of ventricular arrhythmias especially during 24 hours after angioplasty. Therefore, patients at risk of ventricular arrhythmogenesis may be kept under medical surveillance for at least 24 hours after percutaneous transluminal coronary angioplasty.

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