ORIGINAL ARTICLE

TIME DOMAIN ANALYSIS OF HEART RATE VARIABILITY IN PATIENTS WITH CORONARY ARTERY DISEASE

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Background: Heart rate variability is a non-invasive predictive marker of ventricular arrhythmias. Heart rate variability quantifies autonomic nervous system which underlies development of ventricular arrhythmias. Reduced heart rate variability is an indicator of high risk for ventricular arrhythmogenesis. Patients with coronary artery disease may develop ventricular arrhythmias which may lead to sudden cardiac death. Current study was planned to carry out time domain analysis of heart rate variability in patients with coronary artery disease. **Methods:** Forty patients having coronary artery disease with at least one stenotic lesion of greater than 70% of the vessel lumen were included. Patients with diabetes mellitus, atrial fibrillation, structural heart diseases and bundle branch block were excluded. DMS 300 4A Holter monitors were used to obtain long-term 12-lead digital ECG recordings. CardioScan premium luxury software was used for analysis of heart rate variability. **Results:** The mean values of heart rate variability in patients were SDNN (102.15±3.66 ms), SDNNi (45.83±11.09 ms), SDANN (90.45±24.66 ms), RMSSD (24.98±7.26 ms) and pNN50 (6.88±6.12 ms). On comparison with normal reference values there was a significant decrease (p<0.05) in all parameters except RMSSD (p=0.145). SDNN was decreased in 38 (88%), SDANN in 36 (83%), SDNNi in 28 (70%), RMSSD in 27 (68%) and pNN50 in 25 (63%) patients. The difference between frequency of patients with decreased heart rate variability was statistically significant (p<0.05) except pNN50 (p=0.155). **Conclusion:** Heart rate variability decreases significantly in patients with coronary artery disease as compared to normal reference values taken from healthy individuals.

Keywords: Heart rate variability, coronary artery disease, myocardial ischemia, Holter monitoring
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INTRODUCTION

Heart rate variability (HRV) is a physiological phenomenon which can be defined as temporal fluctuation of beat to beat intervals during normal sinus rhythm.[1] It is reflected as variations in heart rate around the mean value. Heart rate variability is also known as cardiac cycle length variability or RR variability. The discovery of dissimilarity in beat to beat intervals by Stephen Hales (1733) unbolted the entrance of new research horizons especially in the field of cardiac electrophysiology.[2] Since then heart rate variability has been studied comprehensively in multiple research ventures.[3] During the last few decades, heart rate variability has been documented as a marker to detect activity of autonomic nervous system.[4] Most of the researchers agree that in near future, heart rate variability will be incorporated into the routine examination. It is forecasted that heart rate variability will become a part of vitals chart due to its authenticated results in providing insight into the autonomic nervous system.[5]

According to the guidelines provided by the task force of European society of cardiology and North American society of pacing and electrophysiology, heart rate variability can be calculated in time domain using various methods.[6] Time domain methods are the simplest way to analyse heart rate variability. They rely on time interval utility therefore named time domain methods in which consecutive heart rate or RR intervals between two successive normal QRS complexes are recorded. The NN (normal to normal) Intervals are measured in milliseconds. Statistical time domain parameters are principally arithmetical derivatives demonstrating dispersion of normal to normal beat intervals from the mean cardiac cycle length. For analyzing ECG recording by statistical time domain parameters, data should be preferably recorded for 24 hours. Only the normal to normal heart beat intervals are edited and then their numerical derivatives are developed through simple statistical formulas.[7]

Reduction in heart rate variability is related to poor prognosis for many pathological conditions whereas increased variability is a healthy attribute[8]. Knowledge of heart rate variability helps in quantifying the autonomic nervous system which controls heart rhythm. Unstable autonomic nervous system activity, also known as dysautonomia is acknowledged as a predictor of ventricular tachyarrhythmias which may lead to sudden cardiac death.[9]

Majority of sudden cardiac deaths in ischemic heart disease result due to enhanced sympathetic activity which favours genesis of life threatening arrhythmias, whereas parasympathetic activity exerts anti-fibrillatory effect.[10] A number of non-invasive

techniques have been developed for risk prediction in these patients with an intention to forecast patients at high risk of sudden cardiac death.[11] These include heart rate variability, signal averaged electrocardiography, QT dispersion and T-wave alternans etc.[12]

Myocardial ischemia is mostly caused by occlusions of coronary vessels due to coronary artery disease.[13] Ischemia induces metabolic and ionic imbalance across the myocardium. These changes can cause heterogeneity of impulse propagation in ischemic tissues and decreased ventricular refractoriness.[14] Heart rate variability is reduced in coronary artery disease patients that denote amplified sympathetic activity. Tachycardia due to increased sympathetic activity with coexistence of myocardial ischemia may lead to fatal ventricular arrhythmias.[15]The objective of the current study was to carry out time domain analysis of heart rate variability in patients with coronary artery disease and to compare the heart rate variability with normal reference values obtained from healthy individuals.

SUBJECTS AND METHODS

This was a cross-sectional comparative study carried out at Department of Cardiac Electrophysiology, Armed Forces Institute of Cardiology in collaboration with Army Medical College, Rawalpindi from April to August 2014. An official approval was obtained prior to commencement of the study from Medical Ethics Committee of Army Medical College. Written informed consent was taken from all the patients undergoing the study.

Forty patients with coronary artery disease of either sex and any age were recruited through non-probability purposive sampling. Coronary artery occlusion was diagnosed by cardiologists on the basis of coronary angiography. Patients having significant coronary artery disease with at least one stenotic lesion of greater than 70% of the vessel lumen were included. Patients with diabetes mellitus, systemic arterial hypertension, structural heart diseases and bundle branch block were excluded.

DMS 300-4A Holter monitors were used to obtain 12-lead ECG recording. Digital ECG data were transferred to the computer and analyzed by using CardioScan premium luxury software. After complete editing of the 24-hour digital ECG recording. Data devoid of erroneous beats, ectopics and artefacts were used for heart rate variability analysis. Statistical time domain parameters used were SDNN, SDNNi, SDANN, RMSSD and pNN50. Heart rate variability analysis was done in three selected leads. The leads were selected on the basis of least artefacts present in them. Distorted and erroneous recordings with abundance of aberrant beats and artefacts were not selected for heart rate variability as only normal to normal intervals were needed for the analysis.

Statistical analysis was done using SPSS-22. Qualitative variables were presented as frequency and percentages whereas quantitative variables as mean and standard deviation. Variables studied were SDNN, SDANN, SDNNi, RMSSD and pNN50. As the data followed a normal distribution it was compared with standard normal values accepted by Task Force Committee,[16,17] using 'one sample *t*-test'.

RESULTS

There were 40 patients with mean age of 55.20±8.03 years ranging from 34 to 68 years. Male to female ratio was 39:1. The mean value of SDNN, SDNNi, SDANN, RMSSD and pNN50 were 102.15±23.66, 45.83±11.09, 90.45±24.66, 24.98±7.26 and 6.88±6.12 milliseconds, respectively (Table-1).

Table-1: Time domain variables of heart rate variability in coronary artery disease patients (n=40)

Variables	Values (Mean±SD)
SDNN (ms)	102.15±23.66
SDNNi (ms)	45.83±11.09
SDANN (ms)	90.45±24.66
RMSSD (ms)	24.98±7.26
pNN50 (%)	6.88±6.12

Shapiro Wilk test revealed that data followed 'normal distribution' hence parametric one sample *t*-test was applied for comparisons of heart rate variability indices with normal reference values (Table-2).

Table-2: Comparison of time domain indices of heart rate variability in coronary artery disease patients with normal values (n=40)

Time domain variables	Values (Mean±SD)		*p*
	Patients	Normal	
SDNN (ms)	102.15±23.66	141±39	0.001*
SDNNi (ms)	45.83±11.09	54±15	0.001*
SDANN (ms)	90.45±24.66	127±35	0.001*
RMSSD (ms)	24.98±7.26	27±12	0.145
pNN50 (%)	6.88±6.12	9±7	0.034*

*significant

There was significantly reduced heart rate variability in all the time domain parameters of coronary artery disease patients ($p<0.05$). The *p*-values of only one time domain parameter (RMSSD) was above 0.05; however its mean value also showed a decline as compared to the normal reference values. SDNN was reduced in 38 (88%) of patients, SDANN in 36 (83%), SDNNi in 28 (70%), RMSSD in 27 (68%) and pNN50 in 25 (63%) patients. The difference between frequency of patients with decreased and normal heart rate variability as calculated by binominal test, was significant in all the parameters ($p<0.05$) except pNN50 ($p=0.155$) (Table-3).

Table-3: Frequency and percentages of patients with normal and decreased time domain variables of heart rate variability (n=40)

Time domain variables	Frequency		*p*-value
	Decreased	Normal	
SDNN	38 (88%)	2 (12%)	0.001*
SDANN	36 (83%)	4 (17%)	0.001*
SDNNi	28 (70%)	12 (30%)	0.018*
RMSSD	27(68%)	13 (32%)	0.040
pNN50	25 (63%)	15 (27%)	0.155*

*significant

DISCUSSION

Heart rate variability in coronary artery disease patients is attributed to ischemia related changes. Autonomic nervous system imbalance in the form of reduced vagal and enhanced sympathetic activity is supposed to be the basis of reduced heart rate variability in patients with coronary artery disease.[18] Research evidence suggests that distorted vagal nerve endings and enhanced release of norepinephrine from sympathetic nerve fibres is the underlying mechanism of altered autonomic nervous system activity.[19] Chronic ischemia causes modification in allocation of autonomic nerve fibers.[14] Enhanced inhomogeneity in autonomic innervation may augment sympathetic and reduce vagal intonation in coronary artery disease patients leading to reduced heart rate variability.[19]

Feng *et al* carried out a study to compare heart rate variability in coronary artery patients with normal controls.[20] Their study included 236 patients with coronary artery disease and 86 healthy controls. They studied time domain indices of heart rate variability like SDNN, SDANN, SDNNi, RMSSD and pNN50. Their study concluded that overall heart rate variability was decreased in patients with coronary artery disease. Our results of decreased heart rate variability due to coronary occlusion are also supported by study conducted by Karjalainen *et al*. They carried out a study in coronary artery disease patients with and without diabetes mellitus and found an overall significant decrease in SDNN in coronary artery disease patients.[18] Another study was conducted by Laing *et al* in 17 patients of coronary artery disease. Their results showed that there was a significant decrease in RMSSD in coronary artery disease patients which on cardiac rehabilitation increased. Decreased RMSSD shows diminished vagal modulation and increased sympathetic stimulation in coronary artery disease patients.[21]

A review study conducted by Oliveira et showed various follow-up studies affirming that there is decreased inter beat variability in coronary artery disease patients that makes them more prone to fatal ventricular arrhythmias.[22] However the series concerned have integrated coronary artery disease patients with and without myocardial infarctions. A case control study carried out by Huikuri *et al* in 20 coronary artery disease patients without myocardial infarction and 20 healthy controls showed a significant difference of frequency domain parameters between the groups. They analysed that superior heart rate variability shown by sleep awake rhythm was decreased in coronary artery disease patients.[23] Results of all the studies mentioned above are comparable to our study reporting that heart rate variability is reduced in patients with coronary artery disease.

CONCLUSION

Heart rate variability decreases significantly in patients with coronary artery disease. Reduced heart rate variability is reflective of heightened sympathetic activation which puts these patients on the risk of ventricular arrhythmogenesis. These patients need to be kept under medical surveillance to avoid arrhythmogenic events leading to adverse outcomes including sudden cardiac death.

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