Role of Heart Rate Variability Testing in Predicting Coronary Stenosis in Non-Acute Clinical Setting

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ABSTRACT

BACKGROUND

Reduced heart rate variability (HRV) is associated with an increased risk of cardiovascular morbidity and mortality. The aim of the study was to determine whether reduced HRV is predictive of angiographic coronary artery disease (CAD).

METHODS

This study was done among 71 clinically stable subjects who underwent elective coronary angiography for diagnosis or pre-operative evaluation. High frequency (HF; 0.15 – 0.40 Hz), low frequency (LF; 0.04 – 0.15 Hz), LF / HF ratio, total power ≤ 0.4 Hz were used as the conventional indices of HRV. Analysis of variance (ANOVA) and chi square test was used to assess the statistical analysis. Statistical significance analysis was carried out with International Business Machines Statistical Package for the Social Sciences (IBM SPSS) version 22.

RESULTS

Out of 71 subjects, only 58 were available for final analysis. 20 subjects had normal coronary arteries, 19 had single vessel disease and remaining 19 had multi vessel disease. The HF power of HRV showed decreasing trend as the severity of angiographic stenosis increased. The median values of LF power for single vessel disease and multi vessel disease were 148 ms^2 and 160 ms^2 respectively. The group without coronary artery disease has a median of 215 ms^2 for LF power. The median HF power was lower in single vessel disease group (133 ms^2) compared to group with normal coronaries (139 ms^2) and it was very low in multi vessel disease (81 ms^2) group compared to group with normal coronaries.

CONCLUSIONS

A weak association of HF and LF power of HRV with degree of angiographic stenosis was observed.

KEYWORDS

Heart Rate Variability, Coronary Angiogram, Angiographic Stenosis

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BACKGROUND

The gold standard for detecting the presence and severity of coronary artery disease (CAD) is invasive coronary angiography.[1] There have been reports of possible overuse and low yield of elective invasive coronary angiography in the literature for investigation of suspected CAD.[2,3]

The documentation of clinical justification for opting an invasive strategy is also poor. The Framingham Risk Scores have been linearly associated with the extent of angiographic disease, but a number of common variables were poor indicators of CAD, including cholesterol, smoking, blood pressure and high sensitivity C-reactive protein.[4-7]

There is a clear need for additional methods to predict coronary artery disease before coronary angiography so that unnecessary angiograms can be avoided.[8,9] Unnecessary angiograms can be avoided in non-acute cases, if reliable predictors of angiographic coronary disease are available. Heart rate variability (HRV) depends on sympathetic and parasympathetic balance.[10] Altered Heart rate variability (HRV) has been associated with adverse outcomes in heart disease. Reduced HRV is associated with an increased risk of cardiovascular morbidity and mortality and has been traditionally associated with increased risk of sudden cardiac death in various populations.[11,12] But the usefulness of heart rate variability (HRV) in predicting coronary stenosis in non-acute cardiac setting has not been evaluated in detail. Low HRV has been shown to be independently predictive of increased mortality in post-myocardial infarction patients and heart failure patients, in contrast with the data of the general population.[11]

Hence, this study was carried out to determine whether reduced HRV is predictive of angiographic CAD. The aim of the study was to determine whether reduced HRV is predictive of angiographic CAD, and to determine the association between HRV parameters like HF power, LF power and LF / HF ratio with coronary angiographic stenosis.

METHODS

A hospital based cross-sectional observational study was done on patients attending tertiary care hospital, Hyderabad for elective diagnostic coronary angiography. Participants were enrolled following written informed consent by convenient sampling. The study was cleared by internal ethical committee. 70 patients who attended the hospital for elective diagnostic coronary angiography from July 2018 to December 2019 were included.

Inclusion Criteria

Patients included in the study were patients of stable ischemic heart disease undergoing diagnostic coronary angiography, valvular heart disease in sinus rhythm undergoing coronary angiogram and those undergoing coronary angiography for other reasons like preoperative evaluation. Patients taking beta blockers were also included in the study.

Exclusion Criteria

Patients with acute coronary syndrome, cardiac rhythm disturbances and conduction disturbances were excluded from the study. Patients with previously known normal coronary anatomy, diagnosed by coronary angiography before patient recruitment were excluded from the study.
All patients underwent electrocardiogram (ECG) and heart rate variability assessment before coronary angiography.

Electrocardiograms (ECG)

Base line twelve-lead ECG of the patient was recorded using standard techniques with the participants in supine position using a portable ECG device. Base line ECG was analysed for the presence of ischemic features and rhythm abnormalities, and was classified as normal or abnormal.

Heart Rate Variability Measurement

HRV was measured in all participants when a good quality ECG signal was obtainable and when QRS width and PR interval were stable for correct acquisition of the RR interval. Three leads were used to obtain the ECG signal with participants lying supine, asked to breathe normally and left undisturbed during the capture time for 5 or 10 minutes. To simulate actual clinical use, no attempt was made to control patient or environmental factors (ex: coffee and alcohol consumption) or to rest the participant before HRV capture.

ADInstruments software and hard ware (PowerLab) were used to quantify normal-to-normal RR intervals and deconstruct HRV into component frequencies, graphing variance as a function of frequency (power spectral density analysis). HF (0.15 - 0.4 Hz) is driven mainly via parasympathetic innervation of the heart. LF (0.04 - 0.15 Hz) is driven mainly by sympathetic innervation of the heart. Frequency domain indices were recorded and analysed such as-

- Total power a frequency range ≤ 0.4 Hz.
- HF (high frequency, frequencies in a range of 0.15 - 0.4 Hz).
- LF (low frequency frequencies in a range of 0.04 - 0.15 Hz).
- LF / HF index.

Coronary Angiography

Coronary angiography was performed using standard procedures and guidelines and classified as angiographically a) normal, b) single vessel disease and c) two vessel and three vessel disease. The presence of obstructive CAD is defined as more than 50 % stenosis in one or more native epicardial arteries or a main tributary.

Statistical Analysis

Presence of obstructive CAD was the primary outcome variable. Indices of HRV parameters like HF power, LF power and LF / HF ratio were the main explanatory variables. Descriptive analysis was carried out and values were represented as mean ± SD, median with inter-quartile range

and standard deviation for quantitative variables, frequency and proportion for categorical variables. ANOVA was used to assess statistical significance for quantitative variables while chi square test was used to assess statistical significance for categorical variables. Data was entered in Microsoft excel and analysis was carried out with IBM SPSS version 22. P value < 0.05 was considered statistically significant.

RESULTS

	Parameters	Number (%)
Age group (in years)	30 - 40	50 (71.44 %)
	41 - 60	10 (14.28 %)
	> 60	10 (14.28 %)
Gender	Male	40 (57 %)
	Female	30 (43 %)
Previous history of stable ischemic heart disease	Yes	36 (51 %)
	No	34 (49 %)
Disease	Normal Coronary angiogram	24 (34.4 %)
	Single vessel disease	23 (32.7 %)
	Double and Triple vessel disease	23 (32.7 %)

Table 1. Summary of Baseline Characteristics (N = 70)

A total of 70 subjects were included in the final analysis. Majority (57 %) of the subjects were males. Majority (51 %) had previous history of stable ischemic heart disease. Of the total 70 subjects, 23 had normal coronary arteries, 23 had single vessel disease and 23 had double or triple vessel disease.

		Study Group			
	Parameter	Normal Coronary Angiogram (N= 24)	Single Vessel Disease (N=23)	Double and Triple Vessel Disease (N=23)	P Value
Gender	Male	7 (29.17 %)	16 (69.57 %)	17 (73.91 %)	0.003 *
	Female	17 (70.83 %)	7 (30.43 %)	6 (26.09 %)	
Diabetes	Yes	15 (62.50 %)	14 (60.87 %)	15 (65.22 %)	0.954 *
	No	9 (37.50 %)	9 (39.13 %)	8 (34.78 %)	
Hypertension	Yes	20 (83.33 %)	13 (56.52 %)	16 (69.57 %)	0.134 *
	No	4 (16.67 %)	10 (43.48 %)	7 (30.43 %)	
	BMI	26.18 ± 4.81	27.13 ± 3.08	26.89 ± 4.53	0.072 $
Beta Blocker use	Yes	14 (58.33 %)	18 (78.47 %)	20 (86.96 %)	0.070 *
	No	10 (41.67 %)	5 (39.13 %)	3 (13.04 %)	

Table 2. Comparison of Demographic Parameters between Study Groups (N = 70)

*chi square test, $ ANOVA test

Parameter	Normal Coronaries	1 Vessel Disease	2 or 3 Vessel Disease	P Value
Abnormal ECG	13 (54.16 %)	18 (78.26 %)	17 (73.91 %)	0.164*
5 min heart rate (average)	76.38 ± 12.35	73.11 ± 10.18	74.85 ± 13.88	0.658 $
Total power (median + / - IQR)	898.49 ± 766.36	789.97 ± 1393.4	664.59 ± 249.23	< 0.001 $
High frequency power in ms^2 (median ± IQR)	139.38 ± 169.98	133.59 ± 156.87	81.6 ± 14.96	< 0.001 $
Low frequency power in ms^2 (median ± IQR)	215.86 ± 200.08	148.45 ± 198.72	160.96 ± 121.75	< 0.001 $

Table 3. Association of HRV Findings with CAG Results

*chi square test, $ ANOVA test

Majority (71.43 %) of subjects with normal coronary angiogram were females. In single vessel disease group, majority (70.59 %) were males and in subjects with double and triple vessel disease also, majority (75 %) were males. This difference was statistically significant (p = 0.003). Diabetes was present in all the three groups in more than 60 % of cases. Hypertension was present in 83.33 % of subjects with normal coronaries, 56.52 % in subjects with single vessel disease and 69.57 % of subjects with 2 & 3 vessel disease. The mean body mass index (BMI) was 26.18 ± 4.81 in subjects with normal coronary angiogram. It was 27.13 ± 3.08 in subjects with single vessel disease while it was 26.89 ± 4.53 in subjects with 2 & 3 vessel disease. Beta blocker use was highest (86.96 %) in 2 & 3 vessel disease group. It was 78.47 % in single vessel disease group while it was 58.33 % in normal coronary angiogram group.

In Normal coronaries group, 54.16 % had abnormal ECG while 78.26 % had abnormal ECG in single vessel disease group. It was 73.91 % in multiple vessel disease group. The average (mean) 5 minute heart rate was 76.38 ± 12.35 per minute in the normal coronary group. It was 73.11 ± 10.18 per minute in the single vessel disease and 74.85 ± 13.88 per minute in the 2 & 3 vessel disease group. It did not differ significantly among the three groups. The median total power in normal coronaries group was 898.49 + / - 766.36 ms^2. It was lower in single vessel disease group at 789.97 + / - 1393.4 ms^2 and much lower in multiple vessel disease group at 664.59 + / - 249.23 ms^2. This difference across the groups was statistically significant (p < 0.001).

The median high frequency power in normal coronaries group was 139.38 + / - 169.98 ms^2. It was lower in single vessel disease group at 133.59 + / - 156.87 ms^2 and much lower in multiple vessel disease group at 81.6 + / - 114.96 ms^2. This difference across the groups was statistically significant (p < 0.001). The median low frequency power in normal coronaries group was 215.86 + / - 200.08 ms^2. It was lower in single vessel disease group at 148.45 + / - 198.72 ms^2 but was higher in multiple vessel disease group at 160.96 + / - 121.75 ms^2. This difference across the groups was statistically significant (p < 0.001).

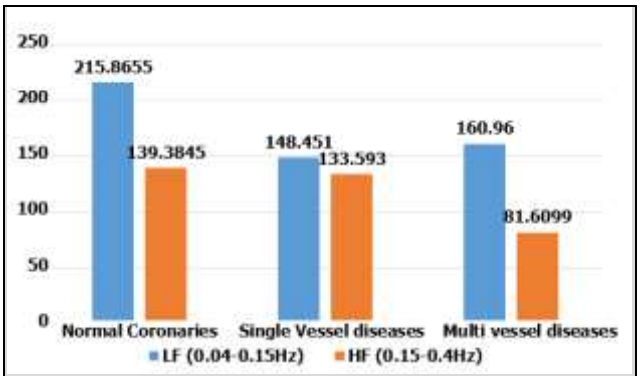

Figure 1. Median Values of LF & HF Power and Severity of CAD

DISCUSSION

One of the major causes of morbidity and mortality worldwide is CAD. There have been reports of possible overuse and low yield of elective invasive coronary

angiography in the literature for investigation of suspected CAD.[2,3] Unnecessary angiograms can be avoided in non-acute cases, if reliable predictors of angiographic coronary disease are available. Atherosclerosis being the underlying cause of cardiovascular diseases is augmented by various non-modifiable risk actors like age, sex and modifiable risk factors like hypertension, dyslipidaemia, obesity, diabetes mellitus and smoking. Altered heart rate variability (HRV) has been associated with adverse outcomes in heart disease. Reduced HRV is associated with an increased risk of cardiovascular morbidity and mortality and has been traditionally associated with increased risk of sudden cardiac death in various populations.[11,12] Hence, in the present study, the utility of heart rate variability testing in clinical practice and its relation to obstructive coronary heart disease was tested. A weak association of HF (high frequency) and LF (low frequency) power of HRV with degree of angiographic stenosis was observed in this study. Kotecha D et al.[9] in their study on 470 subjects similar to our study showed that low heart rate variability is a strong predictor of angiographic coronary heart disease. They found that in patients without CAD the LF power was 267 ms^2 and in patients with angiographic CAD it was 180 ms^2. When compared with LF less than 250 ms^2 and more than 250 ms^2, they showed that odd ratio for obstructive coronary artery disease using multivariate regression was 2.42 with 95 % confidence interval. Their study sought to determine the ability of a 5-min bedside HRV test to predict the presence of CAD. Their data demonstrated a high correlation of HRV with angiographically defined disease in patients attending elective diagnostic coronary angiography.

Hayano J et al.[13] in their study demonstrated that the magnitude of heart rate variability, particularly that of the respiratory component i.e. HF power of HRV, decreases with advancing angiographic severity of coronary artery disease. Their study demonstrated the relation between the spectral components of heart rate variability and the clinical and angiographic features of CAD.

In the present study, LF spectral power was inversely related to the extent of CAD and a cut-off value of 250 ms^2 was identified as a strong independent predictor of obstructive disease in this clinical cohort. HRV was applicable across patient subgroups, added to conventional risk factor assessment and was superior to standard 12-lead ECG recordings. In the present study, the median values of LF power for single vessel disease and multi vessel disease were 148 ms^2 and 160 ms^2 respectively as shown in figure 1. The group without coronary artery disease has a median of 215 ms^2 for LF power. Our findings were similar to that of kotecha D et al.[9] In the present study, the LF and HF power of HRV showed decreasing trend as the severity of angiographic stenosis is increasing.

Out of 71 subjects in this study, only 58 were available for final analysis. Majority of the study subjects were males. Out of 58 subjects, 34.4 % had normal coronaries while 32.7 % had single vessel disease. 32.7 % of the subjects had either multi vessel disease. The prevalence of abnormal ECG was higher in subjects with single vessel disease (78.9 %) and multi vessel disease (73.6 %) compared to subjects with normal coronaries (55.5 %). Li HR et al.[14] in their study also observed that reduced HRV was predictive of CAD in patients with stable angina, independent of traditional risk factors and Framingham risk scores. The predictive value of HRV was relevant only in subjects with high Framingham risk score or diabetes in their study. Huikuri HV et al.[15] in their study also observed that low HR variability analysed from ambulatory ECG predicts rapid progression of coronary artery disease. HR variability provided information on progression of focal coronary atherosclerosis beyond that obtained by traditional risk markers of atherosclerosis.

The average 5-minute heart rate was higher (76 per minute) in subjects with normal coronaries compared to subjects with single vessel (73 / minute) and multi vessel disease (74 / minute) in this study. The median HF power was lower in single vessel disease group compared to group with normal coronaries and it was very lower in multi vessel disease group compared to group with normal coronaries. But the median LF power did not show any trend across the various categories of angiographic findings. The median LF power was higher in subjects with normal coronaries compared to subject's single vessel, multi vessel disease. Heart rate variability (HRV) depends on sympathetic and parasympathetic balance.[10] Both the sympathetic and the parasympathetic limbs can be characterized by tonic levels of activity, which are modulated by, and respond reflexively to, physiological changes.

Heart rate provides an index of the net effects of autonomic tone on the sinus node, and carries prognostic significance. Heart rate variability, though related to heart rate, assesses modulation of autonomic control of heart rate and carrie s additional prognostic information, which in some cases is more powerful than heart rate alone.[16] Diabetes was found in all the three groups in more than 60 % of cases. Hypertension occurred in 80 % cases in the 1st group with normal coronaries, 57 % in 2nd group with single vessel disease and 68 % with 2 & 3 vessel diseases. The group with normal coronary angiogram has female predominance i.e., 71.43 %; whereas obstructive coronary artery disease occurred more commonly in males i.e., 70.59 % in those with single vessel disease and 75 % those with 2 & 3 vessel disease. Base line heart rate did not differ significantly among the three groups. Median values showed a trend towards lower power of HRV in the HF range, LF range and total power range in the groups with obstructive coronary artery disease although with wide inter quartile range.

According to statistical analysis in the present study, the association between LF power and coronary angiographic stenosis was not as strong as that was found by kotecha D et al.,[9] but weak association was found in the statistical analysis. This could be because, in the present study no attempt was made to alter the clinical settings i.e., all patients were taken to the study irrespective of their age, diabetic status, beta blocker use, coffee or tea use or the prandial state which are known to affect the autonomic nervous system and therefore the heart rate variability. These factors might be contributory to the weak association found in the present study.

CONCLUSIONS

A weak association of HF and LF power of HRV with degree of coronary angiographic stenosis was observed in this study. Our study is the first of its kind in our geographical area investigating the use of HRV in predicting coronary angiographic stenosis. This study was done to assess usefulness of heart rate variability (HRV), which depends on sympathetic and parasympathetic balance, in predicting coronary stenosis in non-acute cardiac cases. HRV analysis was done in - stable angina cases, cases needing coronary angiogram in preoperative evaluation, valvular heart cases before surgery and other cases which were not acute. One of the major limitations of the study was the small sample size and the patients were recruited from a single centre. Therefore, the study population was relatively small which could be one of the reasons for weak association. More insights into the relation of HRV with obstructive coronary artery disease might be revealed in future with further research in this field with large scale multi centric studies.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
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