Assessment of Autonomic Function in Slow Coronary Flow using Heart Rate Variability and Heart Rate Turbulence

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Abstract

Background: Slow Coronary Flow Syndrome (SCFS) is an angiographic observation characterized by angiographically normal or near-normal coronary arteries with the delayed progression of contrast dye injected into the coronary tree. Previous studies suggested that these patients had autonomic dysfunction. Life threatening arrhythmias and sudden cardiac death have also been reported in these patients.

Aim: Our aim was to assess autonomic function in slow coronary patients using heart rate variability and heart rate turbulence.

Method: We selected 40 slow coronary patients and 30 healthy individuals with normal coronary. 24 hours ambulatory holter ECG recordings were obtained from all patients. Turbulence onset (TO), Turbulence slope (TS), Time domain HRV (SDNN, Mean RR, RMSSD, Pnn50 and triangular index (TI)) were analysed and compared between two groups.

Results: There were no difference in Mean RR (ms), RMSSD (ms) and Total Snn50 between groups. But SDNN (ms) and Triangular index (TI) were different between groups.( 128.52 ± 9.32 vs 174.25 ± 73 p<0.001 and 31.74 ± 4.67 vs 42.48 ± 5.86 p<0.001 respectively), TO and TS were different between groups (1.06 ± 2.4 vs -0.16 ± 0.34 p: 0.009 and 9.47 ± 6.03 vs 14.41 ± 8.66 p: 0.021). There was a negative correlation between SDNN and mean TFC (r: -0.794 p<0.001) and positive correlation between TO and mean TFC (r:0.950 p<0.003).

Conclusion: We showed that some of HRV parameters and HRT was impaired in favor of slow coronary patients. Impaired autonomic activity may lead to the tendency to arrhythmias and may cause sudden cardiac death in slow coronary patients.

Keywords: Slow coronary; Sudden death; Hear rate variability; Heart rate turbulence

Introduction

Slow Coronary Flow Syndrome (SCFS) is an angiographic observation characterized by angiographically normal or near-normal coronary arteries, with the delayed progression of contrast dye injected into the coronary tree [1,2]. The exact mechanism is not clear. Small vessel dysfunction may be involved in this phenomenon. Increased flow resistance, increased microvascular tone, platelet dysfunction [3], early demonstration of diffuse atherosclerosis [4], inflammation [5,6] and an imbalance of vasoactive substances [7], have been suggested as underlying mechanisms. Also, the autonomic nervous system is thought to cause [8]. More importantly, life-threatening arrhythmias and sudden cardiac death have also been reported in these patients [5]. Increased sympathetic or decreased parasympathetic nervous system activity predisposes patients with Coronary Heart Disease (CHD) to ventricular tachycardia, ventricular fibrillation, sudden cardiac death [9,10] and increased mortality [11]. Intact autonomic cardiac control appears to be an important protective factor in the pathophysiology of malignant arrhythmias and sudden cardiac death [12]. Heart Rate Turbulence (HRT) and Heart rate variability (HRV) are a comprehensive evaluation of cardiac autonomic reflexes [13].

However, best of our knowledge to evaluate HRT and combined with HRT and HRV have not been reported in the literature previously. Our goal was to assess autonomic function in slow coronary patients using Heart Rate Turbulence (HRT) and Heart Rate Variability (HRV).

Method

We selected 40 patients with slow coronary flow and 30 healthy patients without slow coronary flow. We divided patients into two groups as slow coronary (group 1) and normal coronary (group 2). A detailed history and evaluation of patients was performed, 24 hours ambulatory holter ECG recordings were obtained from all patients. Turbulence onset (TO), Turbulence Slope (TS), Abnormal slope and Abnormal onset; Time domain HRV (SDNN, Mean RR, RMSSD, Pnn50 and triangular index (TI)) were analysed. The exclusion criteria were as follows: smoking habits, diabetes mellitus, hypertension, use of antihypertensive drugs, congestive heart failure, significant valvular heart disease, pacemaker implantation, atrial flutter or fibrillation, frequent ventricular pre-excitation and atrioventricular conduction

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Received July 24, 2013; Accepted October 29, 2013; Published October 31, 2013

Citation: Sarıkaya S, Altunkas F, Karaman K, Sahin S, Akyol L, et al. (2013) Assessment of Autonomic Function in Slow Coronary Flow using Heart Rate Variability and Heart Rate Turbulence. Angiol 2: 117. doi: 10.4172/2329-9495.1000117

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Coronary angiography

Selective coronary angiography was performed with the Judkins technique in multiple projections without the use of nitroglycerin. Coronary arteries were demonstrated at least four Views of the left coronary system using 6 French left coronary catheters and two views of the right coronary artery using 6 French right coronary catheters by 15 fps rate in the same cardiac catheterisation laboratory. Coronary blood flow was measured quantitatively using the mean thrombolysis in myocardial infarction frame count (TFC). Initial frame count is defined as the frame in which concentrated dye occupies the full width of proximal coronary artery lumen, touching both borders of the lumen and forward motion down the artery. The final frame is designated when the leading edge of the contrast column initially arrives at the distal end. Distal end was defined as distal bifurcation for the Left Anterior Descending (LAD) artery, the distal bifurcation of the segment with the longest total distance for the Circumflex Artery (CX), and the first branch of the posterolateral artery for the Right Coronary Artery (RCA). LAD coronary artery is usually longer than the other major coronary arteries; the TFC for this vessel is often higher. To obtain corrected TFC for LAD coronary artery, TFC was divided by 1.7 [14]. The mean TFC for each patient and control subject was calculated by adding (TFC) for LAD, CX and RCA, and then dividing the obtained value into three. Due to different durations required for normal visualisation of coronary arteries, the corrected cutoff values were 36.28 ± 2.6 frames for LAD, 22.88 ± 4.1 frames for CX and 20.48 ± 3 frames for RCA, as has been reported earlier in the literature [14]. All participants with a TFC greater than the two standard deviations of the previously published range for the particular vessel were considered to have SCF. Any values obtained above these thresholds in one of three coronary arteries (not all three) were considered to be SCF in our study. Coronary angiograms and TFC were analysed by two experienced interventional cardiologists blinded to the clinical status and laboratory measurements of the subjects

Heart rate turbulence

Turbulence Onset (TO) was defined as the difference between the mean of the first two sinus RR intervals after a Ventricular premature beat (VPB) and the last two sinus RR intervals before the VPB. The value of TO is expressed as a percentage. Positive values of TO (>0%) indicate sinus rhythm deceleration after VPB and negative values (<0%) indicate acceleration. The optimal is TO<0%. Turbulence Slope (TS) is a measurement of the following heart rate deceleration. TS is the maximum positive slope of a regression line assessed over any sequence of five subsequent sinus rhythm RR intervals, within the first 20 sinus rhythm intervals after VPB. The value of TS is expressed in milliseconds per RR interval. The normal value is over 2.5 ms/RR.

Heart rate variability

Twenty-four hours Holter recordings taken from the subjects were downloaded onto a computer and analyzed with a Holter program (Reynolds Medical Pathfinder Software, Version V8.255, Bedford, England). All patients were in sinus rhythm throughout the recording period. All records were also examined visually and removed artifacts. All of the recordings had at least 22 hours of data. All of The HRV parameters were calculated by a computer and used in this study was chosen in time domains, according to the guidelines of the European Society of Cardiology and North American Society of Pacemaker and Electrophysiology. HRV parameters were included as standard deviations of all NN intervals (SDNN), standard deviation of the averages of NN intervals in all 5-minute segments of the entire recording (SDANN), the square root of the mean of the sum of the squares of differences between adjacent NN intervals (RMSSD); the number of pairs of adjacent NN intervals differing by more than 50 ms divided by the total number of all NN intervals (pNN50).

Results

Age of patients was not different between groups (58.64 ± 9.24 and 57.48 ± 8.86 p>0.05, respectively). Body Mass Index (BMI), glucose, Low Density Lipoprotein (LDL), High Density Lipoprotein (HDL), Triglyceride (TG) was not different between two groups (Table 1). TFC of LAD, CX, RCA and mean TFC were different between groups as expected (Table 1). There were no difference in Mean RR (ms), RMSSD (ms) and Total Snn50 between groups (Table 2). But SDNN (ms) and TI were different between groups. (128.52 ± 9.32 vs 147.25 ± 73 p<0.001 and 31.74 ± 6.67 vs 42.48 ± 5.86 p<0.001, respectively). Parameters of HRT were shown in Table 2. TO and TS were different between groups (1.06 ± 2.4 vs -0.16 ± 0.34 p<0.009 and 9.47 ± 6.03 vs 14.41 ± 8.66 p<0.021) (Table 2). There was a negative correlation between SDNN and mean TFC (p: -0.834 p<0.001) (Figure 1), and there was a positive correlation between TO and mean TFC (p: 0.350 p: 0.003) (Figure 2).

Statistical Analyses

The statistical analyses were performed using software (SPSS 18.0).

Table 2: Parameters of HRT and HRV in both groups.

| Slow coronary | normal coronary | p     |
|---------------|-----------------|-------|
| Mean RR (ms)  | 788 ± 48        | 736 ± 76 | p>0.05 |
| SDNN          | 128.52 ± 9.32   | 174.25 ± 73 | p<0.001 |
| RMSSD (ms)    | 34 ± 11         | 42 ± 14 | p<0.05 |
| Total Snn50   | 9866 ± 4900     | 87881 ± 5300 | p>0.05 |
| Triangular index (TI) | 31.74 ± 4.67 | 42.48 ± 5.86 | p<0.001 |
| Total slope   | 9.47 ± 6.03     | 14.41 ± 8.66 | 0.021 |
| Total onset   | 1.06 ± 2.4      | -0.16 ± 0.34 | 0.009 |

BMI: Body Mass Index; LDL: Low Density Lipoprotein; TG: Triglyceride; HDL: High Density Lipoprotein; TFC: Thrombolysis In Myocardial Infarction Frame Count; LAD: Left Anterior Descendent Artery; CX: Circumflex Artery; RCA: Right Coronary Artery
Parametric values were given as mean ± standard deviation, and non-parametric values were given as a percentage. To compare parametric continuous variables, Student's t-test or analysis of variance was used; to compare nonparametric continuous variables, the Mann–Whitney U-test or the Kruskall–Wallis test was used. Categorical data were compared by Chi-square distribution. Pearson correlation analyses were done to determine the correlation between mean TFC and SDNN and TO. Two-tailed P-values of less than 0.05 were considered to indicate statistical significance.

**Discussion**

In the present study, we demonstrated SDNN and TI was decreased in slow coronary patients compared to patients with normal coronary. Also, TO and TS of HRT were impaired in favor of slow coronary patients. These results suggested that autonomic function in slow coronary patients was impaired. There was a negative correlation between SDNN and mean TFC and positive correlation between TO and mean TFC. These results showed that autonomic function in slow coronary patients was associated with rate of coronary flow. Autonomic function was impairing with decreasing of coronary flow.

The coronary slow flow phenomenon is an angiographic finding characterized by delayed opacification of the epicardial coronary arteries in the absence of significant stenosis, spasm, dissection or thrombus. Several mechanisms have been proposed for the SCF phenomenon, including small-vessel disease, microvascular vasomotor dysfunction, diffuse atherosclerosis and endothelial dysfunction [4,15,16]. Cesar et al. [17] showed myocardial ischemia in patients slow coronary artery with myocardial perfusion sinthigraphy. Beltrame et al. [2] have reported the presence of an increased resting coronary vasomotor tone in coronary resistance vessels in patients with slow coronary flow. Information about the cause and clinical manifestations of coronary slow flow is insufficient, but the autonomic nervous system is thought to contribute [8]. Previous studies showed that p wave duration and p wave dispersion and QT dispersion (QTd), corrected QT (QTc) was increased in patients with slow coronary flow due to microvascular ischemia, and/or altered autonomic control of the cardiovascular system [16,18]. Kosus et al. [19] showed that HRV was decreased in patients with slow coronary artery. But this relationship was not associated with TFC score. In the present study, our findings were consistent with the previous study and HRV was impaired in slow coronary patients. Also, we demonstrated that HRV was negatively correlated with rate of coronary flow. Autonomic function was impairing with decreasing of coronary flow.

The coronary vascular bed is wholly innervated by both the sympathetic and parasympathetic divisions of the autonomic nervous system [20,21]. Intact autonomic cardiac control appears to be an important protective factor in the pathophysiology of malignant arrhythmias and sudden cardiac death [12]. Increased sympathetic or decreased parasympathetic nervous system activity predisposes patients with Coronary Heart Disease (CHD) to ventricular tachycardia, ventricular fibrillation, sudden cardiac death [9,10] and increased mortality [11]. Decreased vagal activity and increased sympathetic activity, both of which are risk factors predicting death was found in both healthy adults and adults with exit cardiovascular disease [22–27]. Heart Rate Turbulence (HRT) and Heart Rate Variability (HRV) are a comprehensive evaluation of cardiac autonomic reflexes [13]. Heart rate variability (HRV) analysis has been used as a predictor of sudden cardiac death, and as a useful tool for assessing autonomic cardiac functions [28,29]. Decrease in HRV is an indicator of increase in sympathetic tone, decrease in vagal tone, and is associated with increased fatal ventricular arrhythmias [30]. Some measures of heart period variability had a strong and significant independent association with all-cause mortality [31]. Kosus et al. [19] showed that HRV was decreased in patients with slow coronary artery, but this correlation was not associated with TFC score. In the present study, our findings were consistent with previous studies and HRV was impaired in slow coronary patients. Also, we demonstrated that HRV was negatively correlated with rate of coronary flow. Autonomic function was impairing with decreasing of coronary flow.

Heart Rate Turbulence (HRT), which reflects a response of heart rate to a premature ventricular beat is a new, noninvasive
electrocardiographic predictor of cardiac death [13,32,33]. HRT is a new high-risk predictor that has substantial predictive value for cardiac events in patients with AMI [34,35]. Ghuran et al. [13] showed that HR turbulence predict fatal cardiac arrest and nonfatal cardiac arrest in a low-risk post-acute myocardial infarction population. HRT previously has not been studied in slow coronary flow. In the present study, we used HRT to evaluate autonomic function in slow coronary patients. We showed that TO and TS of HRT were deteriorated in slow coronary patients. These findings suggested that autonomic function was impaired in patient with slow coronary. Also, there was a positive correlation between mean TFC and TO. This finding suggested that rate of coronary slow is associated with autonomic function.

In our study, we used HRT and HRV to evaluate autonomic function of slow coronary patients. HRT and combined HRT and HRV have not been previously studied in this kind of patients. We showed that autonomic function using HRT and HRV was impaired in slow coronary patients and autonomic functions were correlated with rate of coronary flow. Impaired autonomic activity may lead to the tendency to arrhythmias and may cause sudden cardiac death in slow coronary patients.

Conclusion
Slow coronary patients have impaired autonomic function. These patients may be under risk of life-threatening arrhythmias and sudden cardiac death

Limitation
The main limitation of our study seems to be the small sample size. Because the small sample size results in low statistical power for equivalency testing, negative results may be simply due to chance. We could not assess that whether these patients suffered with SCD in the future, so Long-term follow-up and comprehensive prospective studies are needed to determine the predictive value of HRT and HRV in this population.

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