

Altered heart rate variability depend on the characteristics of coronary lesions in stable angina pectoris

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ABSTRACT

Objective: Dysfunction of cardiac autonomic nerve system is considered as one of risk factors for coronary atherosclerotic heart disease. Heart rate variability (HRV) has been used to study the correlation between damage of coronary artery and dysfunction of autonomic nervous system. We hypothesize the correlation between damage of coronary artery and dysfunction of autonomic nervous system by HRV among subjects with stable angina.

Methods: A 236 subjects who diagnosed as stable angina pectoris by elective coronary angiography, were divided into two groups by Gensini score system (GS):GS \leq 32 (GS1) and GS $>$ 32 (GS2). Subgroups were divided based on location of stenosis lesions and the number of coronary artery disease. 86 subjects suspicious with stable angina pectoris with normal coronary angiography were selected as the control group. All subjects were received 24-hour ambulatory electrocardiogram and the result of time-domain HRV was analyzed (SDNN, SDANN, SDNNind, RMSSD, PNN50).

Results: Compared with control group, SDNN, SDNNind and RMSSD lower in GS1, and SDNN, SDANN, SDNNind, RMSSD, PNN50 lower in GS2; compared with GS1, SDNN was lower in GS2. Compared with control group, SDNN in one-vessel, SDNN, SDANN in two-vessel diseased and in three-vessel diseased were lower, and compared with two-vessel diseased, SDNN, SDANN lower in three-vessel diseased. Compared with right-coronary artery diseased, SDNN and SDANN in left-coronary artery diseased group were lower, while compared with lesions in left circumflex, SDNN in lesions in left anterior descending artery lower.

Conclusion: HRV may play a crucial role in estimating the correlation between damage of coronary artery and dysfunction of autonomic nerve system. (*Anatol J Cardiol* 2015; 15: 496-501)

Keywords: heart rate variability, stable angina pectoris, autonomic nervous system

Introduction

Heart rate variability (HRV), which means alteration of intervals among continuous sinoatrial node beats including R-R interval, is a noninvasive, practical and reproducible test for detecting autonomic nervous system function (1-4). It is believed that reduction of HRV reflects inability or attenuation of autonomic nerve system and alteration of sinoatrial node's response. Moreover, reduced HRV may be related to worse cardiovascular disease (5). Recently, researchers have frequently used time-domain parameters to assess the prognosis effect of HRV among patients suffering different kinds of cardiovascular disease including myocardial infarction, chronic heart failure,

unstable angina and diabetes (6-8). Other studies have shown that dysfunction of autonomic nerve system may be effective in development of atherosclerosis (9), but this theory remains controversial, especially for among patients with stable angina (10). Furthermore, it is uncertain that whether flexible to explore correlation between them with HRV or not (11-13). Currently, most studies assessing HRV among subjects with coronary atherosclerotic heart disease have less significance because of specific selection requirements. The significance of HRV among subjects excluded with stable angina and its prediction value in coronary obstruction has been unknown yet (12). In this article, we hypothesize correlation between damage of coronary artery and dysfunction of autonomic nervous system by HRV among subjects with stable angina.



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Table 1. Key characteristics of subjects

	Control groups n=86	Disease groups n=236	t/ χ^2	P
Age, years	62.1±10.2	59.8±9.5	1.884	0.060
Male, (%)	67 (77.9)	198 (83.9)	1.553	0.213
Smoker, (%)	34 (39.5)	82 (34.7)	0.627	0.428
SBP, mm Hg	128±20	132±22	1.478	0.140
DBP, mm Hg	76±8	74±9	1.816	0.070
BMI, kg/m ²	24.6±4.1	23.7±3.5	1.948	0.052
LVEF, (%)	58.1±8.1	56.4±7.6	1.136	0.455
Total cholesterol, mg/dL	166.3±21.1	171.6±23.5	1.839	0.067
HDL, mg/dL	54.5±15.0	52.9±16.3	0.796	0.427
LDL, mg/dL	95.6±28.8	92.5±28.2	0.868	0.386
Triglycerides, mg/dL	76.8±34.2	70.7±35.5	1.377	0.169
ACE inhibitors (%)	51 (59.3)	122 (53)	1.467	0.226
ARBs (%)	9 (10.4)	24 (10)	0.006	0.938
Statins (%)	61 (70.9)	190 (80)	3.364	0.067

ACE - angiotensin converting enzyme; ARB - angiotensin II receptor blockers; BMI - body mass index; DBP - diastolic blood pressure; HDL - high density lipoprotein; LDL - low density lipoprotein; LVEF - left ventricular ejection fraction; SBP - systolic blood pressure

Table 2. Selected HRV measures (Time domain measures)

Parameter	Unit	Description
SDNN	ms	SD of all normal R wave (N-N) intervals
SDANN	ms	SD of all 5min average N-N intervals
SDNN index	ms	Mean of the SDs for 5 min segments
RMSSD	ms	Square root of mean of the sum of squares of successive N-N interval difference. Reflects vagal modulation
pNN 50%		Number of successive N-N intervals differing by >50ms divided by the total number of successive N-N intervals. Reflects vagal function

Methods

Subjects

Out of 322 subjects receiving selective CAG, 236 patients, hospitalized due to stable angina pectoris because of a history (198 male patients and 38 female patients with the mean age of 59.8±9.5 years) in Cardiology Department of the affiliated He fei Hospital of Anhui Medical University from December 2012 to March 2013 were enrolled in this study. Subjects were diagnosed and confirmed by CAG, including left anterior descending artery (LAD), left circumflex (LCX) and right coronary artery (RCA) affiliated with main coronary artery. According to Gensini score (14), all subjects (one-vessel diseased, 98; two-vessel diseased, 74; three-vessel diseased, 64) were divided into two groups: GS≤32 (GS1) and GS>32 (GS2). Based on lesion [(defined as >50% luminal diameter stenosis, meanwhile, subjects were divided into three subgroups: RCAp-m, LADp-m and LCXp-m (p-m i.e proximal-middle)]. The control

group (n=86, male 57 and female 29, the mean age 62.1±10.2 years) suspicious with stable angina pectoris involved with normal coronary artery by CAG. All subjects with other complications were excluded including valvular heart disease, severe liver and kidney dysfunction, diabetes, rheumatic diseases, hyperthyroidism, connective tissue disease, heart failure, atrial flutter actions and fibrillation and infection. Meanwhile, the cases of chronic obstructive lesions, left main lesions, old myocardial infarction, coronary artery bypass grafting or percutaneous coronary intervention, were excluded also. There was no statistical significance (p>0.05) among items including gender, age, LVEF, history of hypertension between two groups (Table 1).

Data of dynamic electrocardiogram collection

All subjects were familiarized with the research protocol and 48 hours before this study, unless necessary, had suspended any agents influencing heart rate. Finally, they were asked to stay in a quiet room and have a rest for 15 minutes. Electrodes were connected and the results were analyzed by the same doctor. Data of 24-hour ambulatory ECG for all subjects were collected from 9:00 am to the same moment in the next day. Assessment of arrhythmia was conducted by a technician who was blind to group distribution. HRV parameters value was analyzed by using the ECG-92C multi-channel electrocardiograph (Shanghai Photoelectric Electronic Medical Instruments Co. Ltd, Shanghai, China). Time-domain analysis indicators are including SDNN, SDANN, SDNNindex, RMSSD and PNN50 by the beat-to-beat or N-N intervals. Each parameter was shown in the following form (Table 2).

Table 3. HRV indicators among three groups (unit=ms)

Variable	Controls (n=86)	GS1≤32 (n=136)	GS2>32 (n=100)	P
SDNN	121.9±17.6	112.3±25.1 ^a	101.5±21.4 ^{ab}	0.002
SDANN	104.8±24.3	102.4±21.2	97.1±20.3 ^a	0.045
SDNNind	50.5±24.4	43.0±18.3 ^a	40.1±19.2 ^a	0.002
RMSSD	35.9±17.3	30.6±20.8 ^a	27.7±16.2 ^a	0.010
PNN 50 (%)	8.1±3.5	7.6±3.3	6.6±5.2 ^a	0.034

^awas significant compared with control group,
^bwas significant compared with GS1≤32;
Abbreviations as in Table 2. GS - Gensini score

Table 4. HRV indicators of groups divided by number of coronary artery diseased (unit=ms)

Variable	Controls (n=86)	One-vessel diseased (n=98)	Two-vessel diseased (n=74)	Three-vessel diseased (n=64)	P
SDNN	121.9±17.6	112.6±22.2 ^a	101.1±25.0 ^{ab}	89.1±20.7 ^{abc}	0.001
SDANN	104.8±24.3	97.8±31.4	95.6±26.2	82.1±28.0 ^{abc}	0.001
SDNNind	50.5±24.4	45.3±22.6	43.8±24.2	40.4±22.0	0.063
RMSSD	35.9±17.3	31.4±21.0	32.5±26.1	29.7±19.3	0.306
PNN 50 (%)	8.1±3.5	8.2±4.1	7.3±4.2	6.8±4.0	0.091

^awas significant compared with control group
^bwas significant compared with one-vessel diseased
^cwas significant compared with two-vessel diseased
two - double; one-single; Three - triangle; others abbreviations as in Table 2

Angiographic assessment

All subjects were catheterized percutaneously via femoral artery with standard Judkin's technique, or right brachial artery with the Sone's technique. The angiographic characteristics including lesions, stenosis percentage, and the index coronary angiogram of all coronary lesions was obtained by totally reviewing angiogram. CAD was defined as >50% luminal diameter stenosis was found in at least one major epicardial coronary artery. The Gensini score system was used to estimate coronary diseased severity. The stenosis degree of the lumen in coronary arteries was classified as 1 for 1-25% stenosis, 2 for 26-50%, 4 for 51-75%, 8 for 76-90% and 16 for 91-99%. The scores were then multiplied by a factor representing the importance of the lesions in coronary artery system. Among location scores, 5-point was made for left main lesion; 2.5 for proximal left anterior descending (LAD) or left circumflex (LCX) artery; 1.5 for mid segment LAD and LCX; 1 for distal segment of LAD and LCX, first diagonal branch, first obtuse marginal branch, right coronary artery, posterior descending artery, and intermediate artery; and 0.5 for second diagonal and second obtuse marginal branches. The classification of lumen stenosis was determined based on consensus opinion of two experienced interventional cardiologists.

Results

HRV indicators and the comparison about the time-domain indicators of HRV in three groups were shown in Table 3. The

Table 5. HRV indicators of coronary artery lesions and control group (unit=ms)

Variable	Controls (n=86)	RCAp-m (n=46)	LCXp-m (n=72)	LADp-m (n=44)	P
GS		29.4±13.2	30.6±18.2	35.6±15.8	0.155
SDNN	121.9±17.6	116.5±27.0	114.9±29.4	103.8±26.8 ^{abc}	0.007
SDANN	104.8±24.3	101.3±19.7	97.3±20.1	90.1±23.0 ^{ab}	0.004
SDNNind	50.5±24.4	40.7±24.2	44.2±22.0	40.5±25.2	0.055
RMSSD	35.9±17.3	30.2±18.5	29.5±16.7	30.0±17.7	0.080
PNN 50 (%)	8.1±3.5	7.7±5.3	7.2±4.2	6.4±3.4	0.139

^awas significant compared with control group
^bwas significant compared with
LAD - left anterior descending; LCX - left circumflex artery; p-m - proximal to middle;
RCA - right coronary artery; others abbreviations as in Table 2

difference of all indicators among the three groups were statistical significance. In coronary artery diseased groups of GS1, the values of SDNN, SDNNind and RMSSD were significantly lower than that of control group (p<0.05). In GS2, the values of SDNN, SDANN, SDNNind, RMSSD and PNN50 were significantly lower than that of control group (p<0.05). Furthermore, compares with GS1, the values of SDNN in GS2 was also significantly lower (p<0.05). HRV indicators among four groups which divided by the numbers of coronary artery diseased were shown in Table 4. Only the difference of SDNN and SDANN were statistical significance among the four groups. Compared with control group, SDNN in one-vessel, SDNN, SDANN in two-vessel diseased and in three-vessel diseased were lower significantly (p<0.01), and compared with two-vessel diseased, SDNN, SDANN were lower significantly in three-vessel diseased (p<0.01). SDNN in two-vessel diseased was lower significantly (p<0.05), but SDANN no difference. HRV indicators of coronary artery lesions and control groups were show in Table 5. Only the difference of SDNN and SDANN were statistical significance among the four groups. Compared with right-coronary artery diseased, SDNN and SDANN in left-coronary artery diseased group were lower significantly (p<0.05), while compared with lesions in left circumflex, SDNN in left anterior descending artery was lower significantly (p<0.01).

Statistical analysis

Key characteristics and clinical parameters were shown as mean±SEM and n (%), Qualitative data was compared with chi-square test (χ²), and one-way analysis of variance (ANOVA) were used to determine difference among the coronary artery diseased groups and control group, LSD method was used for multiple comparisons. SPSS19.0 software was used and the significance was set as p<0.05.

Ethics

All subjects signed their written informed consent before participating this study. The process of the study was conducted according to regulations of revised edition of the Declaration of Helsinki, 1964. The study was approved by the Ethics Committee

on the guidelines for experiment in Anhui Medical University (NO 04/2012).

Discussion

In our study, we used HRV to assess the correlation between dysfunction of cardiac autonomic nervous and stable angina pectoris. The study indicated, from HRV indicators that compared with control group, dysfunction of cardiac autonomic nervous was found widely in patients suffered stable angina pectoris. What we found in this study is consistent with the hypothesis- dysfunction of cardiac autonomic nervous can shown in patients suffered stable angina pectoris, especially for those who has lower parasympathetic nerve activity (as shown by low values of the time domain indexes). The result is also supported by other studies, for instance, Pivatelli et al. (12) found that parasympathetic nerve activity was reduced significantly in patients with stable angina pectoris.

In this study, Gensini score system was used to make quantitative scores for assessing diseased severity of every coronary artery in stable angina pectoris. It showed that compared with mild group, SDNN, SDANN, SDNNind, RMSSD and PNN50% in severe group were lower, especially for SDNN and SDANN ($p < 0.01$), which indicated that positive correlation was between development of coronary artery diseased and myocardial ischemia and dysfunction of cardiac autonomic nerve in stable angina pectoris. Previously, other studies also have reported similar results (11, 13, 15). Most indicators of HRV were crucial indexes in this study. But, interestingly, the alteration of RMSSD related to parasympathetic nerve in HRV is not identical in different studies, which means there is no clear correlation between severity of coronary artery disease and RMSSD (16, 17). Actually, in this study, compared with mild group, RMSSD in severe group was lower, probably because of different Gensini score method selected.

The number of coronary artery diseased was reflection of area of myocardial ischemia, and on the other hand, also of severity of coronary atherosclerosis. It was shown that probably correlation between HRV and the number of coronary artery diseased. Our study indicated, compared with control group, negative correlation was found between the number of coronary artery diseased and indicators of HRV in patients with stable angina pectoris. Comparison in both two different groups indicated that SDNN, SDANN in three-vessel diseased group were significantly lower than one-vessel group ($p < 0.05$), and it also suggested negative correlation leading to dysfunction of cardiac autonomic nerve and more worse diseases was shown between the number of coronary artery diseased and HRV, meanwhile, other clinical practice have similar reports. Takei et al. (17) found that among ACS patients, all indicators of HRV in multivessels diseased group were lower significantly than one-vessel diseased.

From data of HRV, the distribution of cardiac autonomic nerve probably also related to lesions of coronary artery diseased. Even nowadays, there is different opinion focusing on

difference of HRV between left- and right-coronary artery diseased. Janowska-Kulifiska et al. (18) found that some indicators including RMSSD in left-coronary artery diseased were significantly lower than that of right-coronary artery diseased and the result suggested blood supplement of sinoatrial node was not the only factor influencing HRV. Meanwhile, some other studies indicated SDNN, SDANN reflecting dysfunction of coronary autonomic nerve were lower in left-coronary artery diseased, inverse, no significant change about indicators of HRV in right-coronary artery diseased were found, which shown that there was correlation between the distribution of cardiac autonomic nerve and lesions of coronary artery disease in cardiology (19, 20). However, Kanadaşı et al. (21), has reported there was no significant correlation between HRV and lesions of coronary artery diseased (left- and right-coronary artery diseased) in one-vessel diseased. The material shown among patients of stable angina pectoris, there was significant change in right-coronary artery diseased. Moreover, compared with control and right-coronary artery diseased, difference of SDNN and SDANN of HRV in left-coronary artery diseased was significant, especially for LAD lesion ($p < 0.01$). We found the dysfunction of cardiac autonomic nerve is not only factor related to severity but lesions of myocardial ischemia among patients of stable angina pectoris.

There is now insufficient material about the exact mechanism which causes reduction of HRV in stable angina pectoris. Other studies have indicated that rather than common coronary risk factors, cardiac autonomic nerve system may also attribute to development of atherosclerosis (22). The psychosomatic factors, particularly depressive illness, may attribute to atherosclerosis development (23), which means that there may be an underlying mechanism involving activation of the sympathetic nerve system. Several studies also demonstrated the correlation between condition of autonomic nerve system and cardiovascular events (24, 25). Furthermore, other researchers have pointed out that cardiac autonomic nerve system dysfunction associated with the development of diabetes in healthy individuals, increased risk value of atherosclerosis development (26). Thus, dysfunction of cardiac autonomic nervous system is thought to be an important factor in development of atherosclerosis. This may partly explain why HRV decreased in patients with stable angina pectoris.

As above material shown, the severity of coronary artery diseased is reflected by HRV. As an effective method, HRV can detect imbalance caused by dysfunction of cardiac autonomic nerve to determine worse myocardial ischemia.

This study focusing on HRV, aimed to create a noninvasive, economical and risk-free method in clinical evaluation and diagnosis of significant coronary artery disease among patients with stable angina pectoris.

Study limitations

There was also some limitation in our study. Firstly, patients based on the pre-set criteria and received subsequent treat-

ment due to stable angina pectoris, manifested anxiety symptom, which was a lower risky factor for inducing acute myocardial infarction. Meanwhile, patients who suffered left main coronary artery and complete occlusion were excluded. All criteria were set to reduce interference from other unstable variables during our study, but enrollment of the patients will lead to statistical error in our analysis. Secondly, the sample size was relatively inadequate to continue significant sub-groups analysis, which limited analysis of correlation between stable angina pectoris and HRV. Although dysfunction of the markers was indirect, superiority of clinical data including golden standard of measuring CAD with diagnostic psychiatric intervention and HRV with domain parameters was remarkable in this study. Thirdly, the cross sectional taken in our study was not compatible to the detection of dysfunction during disease period to determine whether rehabilitation can affect the markers. Finally, result of multiple comparisons was not included in our statistical analysis. We did our best to try to reduce interference from medical agents about HRV, but necessary agents including β -receptor blocker were still administered among some worse patients. But, luckily, compared with control groups, no statistical significance was found.

Conclusion

As this study shown, HRV is related to occlusion severity, multivessels and left coronary artery diseased. Negative correlation is indicated between all indicators of HRV and cardiac events including sudden death. The analysis of HRV among patients suffering CAD, playing important clinical role in treatment and assessment of prognosis, is effective in predicting disease severity and screening high risky population.

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