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Wavelet Transform Analysis of Heart Rate Variability during Dipyridamole-Induced Myocardial Ischemia: Relation to Angiographic Severity and Echocardiographic Dyssynergy

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Summary

Background: Analysis of heart rate variability (HRV) is a valuable noninvasive method for quantifying autonomic cardiac control in humans and has been utilized during dipyiridamole echocardiographic test to differentiate positive from negative test results.

Hypothesis: We aimed to evaluate, by means of HRV analysis, the influence of the angiographic severity of coronary artery disease on cardiac autonomic control during dipyridamole-induced myocardial ischemia.

Methods: We analyzed RR interval variability changes during dipyridamole-induced myocardial ischemia in 31 selected patients (mean age 54 ± 9 years) with available coronary angiography and positive dipyridamole echocardiographic test. Spectral components of HRV were assessed by means of wavelet transform analysis for the last 5 min before the beginning of the test (baseline) and for 5 min after the onset of ischemia-related events (peak dipyridamole effect).

Results: Patients were divided into three groups according to the number of coronary diseased vessels (Group A, single-vessel disease; Group B, double-vessel disease; Group C, triple-vessel disease). No difference was detectable at baseline among the three groups. After dipyridamole, low-frequency power, a measure of sympathetic modulation of heart rate, increased and echocardiographic wall motion score index worsened in all groups ($p < 0.001$). The increase in low-frequency power was more evident in Group C patients than in the other two groups ($p < 0.005$). Furthermore, after dipyridamole, a direct correlation was found between low-frequency power and wall motion score index ($r = 0.59$; $p < 0.001$).

Conclusions: These data suggest that HRV analysis performed during dipyridamole echocardiographic test provides useful information to assess the severity of coronary artery disease.

Key words: cardiac autonomic control, coronary artery disease, dipyridamole echocardiographic test

Introduction

Analysis of heart rate variability (HRV) has emerged as a valuable noninvasive method of quantifying autonomic cardiac control in humans.[1] Alterations in HRV have been found in different cardiac diseases such as congestive heart failure,[2] coronary artery disease,[3] myocardial infarction,[4] and cardiomyopathy.[5] Furthermore, reduced HRV has been demonstrated to be a powerful risk predictor of cardiac death independent of other established risk factors in patients after acute myocardial infarction[6] and in patients with coronary artery disease.[7] In patients with variant angina, a parasympathetic withdrawal has been observed before the occurrence of transient ischemia and has been proposed as a component of the mechanisms leading to spontaneous coronary vasospasm.[8] Similarly, a decreased parasympathetic activity has been observed before the occurrence of silent myocardial ischemia during ambulatory monitoring.[9] Recently, Petrucci *et al.*[10] utilized HRV analysis during dipyridamole infusion to evaluate whether time variant spectral analysis of RR interval variability makes it possible to differentiate ischemic from nonischemic responses. The aim of this study was to evaluate HRV changes during dipyridamole infusion in patients with coronary artery disease in relation to angiographic severity.

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Methods

Study Population

For the purpose of the present investigation, we selected 31 patients (24 men and 9 women; mean age 54 ± 9 years) with chest pain syndrome who met the following criteria: positive dipyridamole echocardiographic test and significant (≥ 70%) stenosis of at least one major coronary vessel at coronary angiography performed during hospitalization. Patients with negative dipyridamole test and those with positive test but without significant coronary lesions were excluded. The investigation conforms to the principles outlined in the Declaration of Helsinki, and the Institutional Committee on Human Research approved the study protocol. All patients gave written informed consent. Patients with poor echocardiographic window, diabetes, and severe hepatic, renal, or lung disease were excluded. Further exclusion criteria were angina at rest, myocardial infarction within the last 12 months, cardiac revascularization or major surgical procedures, history of severe hypertension, severe heart failure, significant valvular disease, myocarditis, thyroid disease or hypertrophic cardiomyopathy, atrial fibrillation or flutter, frequent arrhythmias, and history of ventricular tachycardia. Of the 31 selected patients, 10 had single-vessel disease (Group A), 10 had double-vessel disease (Group B), and 11 had triple-vessel disease (Group C). One Group A patient, two Group B patients, and two Group C patients had had a previous myocardial infarction.

Dipyridamole Echocardiographic Test

All tests was executed after an appropriate therapy-free interval for all cardioactive drugs. Two-dimensional echocardiographic monitoring was performed in combination with dipyridamole infusion as follows: 0.56 mg/kg body weight during 4 min, no dose for 4 min, then, if the test result remained negative, 0.28 mg/kg during 2 min. Therefore, the maximal cumulative dose achieved was 0.84 mg/kg for 10 min.[11] During each min of the procedure, blood pressure was recorded by means of arm cuff sphygmomanometer. Two-dimensional echocardiogram and standard 12-lead electrocardiogram (ECG) were continuously monitored and intermittently recorded before and during dipyridamole infusion and up to 20 min after dipyridamole administration. A commercially available ultrasound system (Hewlett-Packard - Mod. 77020 CV, Andover, Mass., USA), equipped with a 2.5 or 3.5 MHz phased-array sector scanner transducer, was used. Wall motion score index was derived for rest and peak dipyridamole echocardiograms (0 to 1 min after the end of the infusion in all patients). The left ventricle was divided into 13 segments[12] and segmental wall motion was graded according to current American Society of Echocardiography recommendations.[13] Wall motion score index was derived by summation of individual segment scores divided by the number of interpreted segments. The dipyridamole echocardiographic test was terminated at the end of the protocol or with the occurrence of one of the following events: (1) change of two or more kinetic levels for at least one left ventricular segment; (2) ST-segment displacement of 2 mm in one lead; and (3) unequivocal anginal chest pain. Pain or discomfort that can arise aspecifically during dipyridamole infusion was not considered in itself a reason for terminating the test. Dipyridamole was no longer infused when any sign of evolving ischemia appeared (peak dipyridamole effect); ECG, echocardiogram, and patient symptoms were accurately monitored, and after at least 5 min monitoring, aminophylline (40–70 mg intravenously during 1 min) was injected.

RR Interval Analysis

To evaluate HRV changes during dipyridamole infusion, continuous monitoring of ECG leads CM2 and CM5 was obtained utilizing a two-channel Holter recording (Medilog 4500 ECG Recorder, Oxford Medical Ltd, Abingdon, Oxon, U.K.). The recorder was applied 2 h before the beginning of dipyridamole infusion and the recording continued during the dipyridamole test and lasted 2 h after its termination. The ECG analogic channels were read via a modified Teac-Tascam 234 Syncaset tape deck (Teac Corporation, Tokyo, Japan) and digitized at 330 samples/s. Spectral analysis of RR interval variability is a well-established method of studying the autonomic modulation of sinus rate. A limitation of traditional batch analysis algorithms is that they require a stationary input signal; that is, the RR series has to maintain the same statistical characteristics (at least mean value and variance) throughout the entire analyzed data segment. Thus, they cannot provide a reliable estimation of spectral variables during nonstationary phenomena, such as transient myocardial ischemia. Wavelet transform has been proposed as a method particularly useful to measure the spectral content of short transients which, by the Fourier transform method, would be ignored. Therefore, we utilized this method to study the behavior of the sympathovagal balance in correspondence with dipyridamole-induced ischemia exploring HRV over very short time intervals. Wavelet multiresolution decomposition has been compared with the projection of a scene seen by a camera from distances increasing by a factor of 2. A coarser signal at step j can be found from the more detailed signal at step j–1 by a pyramidal algorithm corresponding to successive projection on an orthonormal basis.[14] Signal decomposition into low-pass (approximation) and band-pass (detail) outputs is obtained by convolution of the signal with a system of scaled and translated wavelets. In the wavelet transform, the elementary functions, called wavelets, are defined by two parameters. The first one is a time shift, while the second is no longer a frequency shift, as in the Fourier transform, but a time dilation or compression parameter of a unique basic wavelet, indirectly acting on its frequency content. Wavelet systems can be generated by several methods: cubic splines, complex exponentials, and parameters space shaping. Given a generating function h(x), the set of elementary wavelets is formally defined by $h_{a,b}(x) = |a|^{-1/2} h[(x-b)/a)]$, where a represents the dilation parameter and b the shift parameter; $|a|^{-1/2}$ is a normalization coefficient that allows

each wavelet to keep the same energy.[15, 16] With this type of basic functions, the low-frequency components of the analyzed signal will be estimated by wavelets having a long-time extent, while the high-frequency transients may be precisely located in time by shorter wavelets. In the present investigation, we had as objective the study of the transitory behavior of the RR time series in correspondence with acute ischemic episodes induced by dipyridamole administration. The original RR sequence was transformed into a regularly sampled time series by 100 ms interpolation, during which each abnormal beat, and the ones preceding and following it, were ignored and contributed only to the computation of time. The time series of all normal RR intervals (NN) was low-pass filtered, and the sampling frequency was reduced to 1.14 Hz. The RR time sequences were produced for the last 5 min before the beginning of the dipyridamole echocardiographic test (baseline) and for 5 min after the onset of ischemia-related echocardiographic, ECG, and clinical events (peak dipyridamole effect). To be eligible for the present study, data losses per tape due to persistent rhythm anomalies and artifacts could not exceed 5% of each 5-min segment of recording.

The following frequency domain measures of HRV were calculated: low-frequency power (LF) from 0.07 to 0.14 Hz, and high-frequency power (HF) >0.14 Hz; moreover, from the absolute values of these two components, we calculated the low- to high-frequency power ratio (LF/HF). The two ECG segments were also analyzed in the time domain, computing the average normal to normal RR (NN) interval and the standard deviation of all NN intervals (SDNN). Moreover, considering that differences between successive NN intervals provide an index of vagal activity that is related to short-term variations in heart rate, we calculated the root mean square successive difference (r-MSSD) and the percentage of cycles differing from the preceding one by >50 ms for each 5-min segment (pNN50).[1]

Statistics

Data were expressed as mean ± standard deviation. Because the distributions of the frequency domain measures of HRV were positively skewed, these data were transformed to their natural logarithms (ln) before statistical analysis was performed. The logarithmic transformations succeeded in producing approximately symmetric distributions and thus allowed use of parametric statistics that require near normal distribution. To take account of difference in age, analysis of covariance, with age as covariate, was used to compare blood pressure values, rate–pressure product, wall motion score index, and HRV measures among the three groups at baseline. Difference in the effect of dipyridamole infusion in relation to the number of diseased vessels was evaluated by means of repeated measures analysis of variance, with dipyridamole infusion as within-subjects factor, group as between-subjects factor, and age as covariate.[17] The strength of linear association between measures of HRV and echocardiographic data was evaluated with Pearson's correlation coefficient.

Results

Dipyridamole Echocardiographic Test

In 22 patients, ischemia developed after low-dose infusion and in 9 after high-dose infusion. Side effects due to dipyridamole were always minor and well tolerated. No difference was detectable at baseline among the three groups in blood pressure values, rate–pressure product, and HRV measures (Table I). During the test, heart rate significantly increased from basal level to peak effects in the three groups (from 74 ± 6 to 88 ± 6 in Group A; from 76 ± 3 to 86 ± 6 in Group B; and from 76 ± 3 to 88 ± 7 in Group C). On the other hand, systolic and diastolic blood pressure values decreased slightly; therefore, rate–pressure product increased slightly in all groups. Wall motion score index was comparable at baseline among the three groups and increased after dipyridamole; the worsening was more severe in Group C.

Heart Rate Variability

Results of time and frequency domain analysis of HRV are reported in Table I. As shown, after dipyridamole, r-MSSD, pNN50, and HF power, HRV measures, commonly considered to represent vagal modulation of heart rate, reduced. Differently, LF power increased and the increase was more evident in patients with triple-vessel disease. Accordingly, the LF/HF ratio increased after dipyridamole in all groups, and the increase was more evident in patients with triple-vessel disease. Noteworthy, after dipyridamole, a direct correlation was detectable between wall motion score index and LF power (Fig. 1).

Discussion

The results of our study demonstrate that HRV analysis performed during dipyridamole echocardiographic test provides useful information for the assessment of the severity of coronary artery disease. In fact, during dipyridamole-induced myocardial ischemia, we found a greater increase in LF power and in LF/HF ratio in patients with multivessel coronary artery disease than in those with less coronary involvement. Moreover, a direct relation was detectable between LF power and left ventricular wall motion dyssynergy at peak dipyridamole effect.

Extent of Coronary Artery Disease and Heart Rate Variability

The relationship between autonomic dysfunction and extent of coronary artery disease has been previously investigated by Hayano *et al.*[18] under controlled condition utilizing an autoregressive model. These authors observed that the severity of autonomic dysfunction was related to the severity of coronary artery disease, as assessed by the number of coronary arteries with significant stenoses, but not to the history of pre-

TABLE I Hemodynamic, echocardiographic, and heart rate variability data during dipyridamole echocardiographic test

Variable	Group A		Group B		Group C		p Value		
							Main effects		Interaction
	Baseline	Dipyridamole	Baseline	Dipyridamole	Baseline	Dipyridamole	Dipyridamole	Group	
SBP (mmHg)	143 ± 6	138 ± 5	138 ± 5	135 ± 6	142 ± 7	139 ± 6	<0.001	NS	NS
DBP (mmHg)	88 ± 5	82 ± 4	83 ± 5	78 ± 4	87 ± 4	81 ± 4	<0.001	NS	NS
RPP (mmHg × beats/min)	10224 ± 1184	12249 ± 967	10540 ± 433	11636 ± 1067	10809 ± 745	12280 ± 1161	<0.001	NS	NS
WMSI	1.16 ± 0.06	1.54 ± 0.09	1.18 ± 0.14	1.59 ± 0.20	1.21 ± 0.14	1.94 ± 0.32	<0.001	<0.005	<0.01
Time domain measures									
Average NN (ms)	817 ± 68	682 ± 44	786 ± 45	700 ± 49	790 ± 34	683 ± 64	<0.001	NS	NS
SDNN (ms)	62 ± 27	58 ± 24	57 ± 25	44 ± 17	59 ± 25	55 ± 26	NS	NS	NS
r-MSSD (ms)	43 ± 21	24 ± 20	42 ± 19	26 ± 22	41 ± 19	25 ± 13	<0.001	NS	NS
pNN50 (%)	6 ± 4	2 ± 2	3 ± 1	1 ± 1	4 ± 4	2 ± 1	<0.001	NS	NS
Frequency domain measures									
LF power (ms^2)	968 ± 442	1477 ± 314	1076 ± 458	1318 ± 454	1161 ± 279	2039 ± 394			
Ln LF power	6.8 ± 0.4	7.3 ± 0.3	6.9 ± 0.4	7.1 ± 0.4	7.0 ± 0.2	7.6 ± 0.2	<0.001	<0.05	<0.005
HF power (ms^2)	352 ± 139	238 ± 89	302 ± 107	205 ± 76	335 ± 174	198 ± 94			
Ln HF power	5.8 ± 0.4	5.4 ± 0.4	5.6 ± 0.5	5.2 ± 0.4	5.7 ± 0.6	5.2 ± 0.5	<0.001	NS	NS
LF/HF	3.2 ± 2.1	6.8 ± 2.1	4.7 ± 4.2	7.6 ± 4.4	4.7 ± 2.9	13.9 ± 9.1	<0.001	<0.05	<0.005

Data are expressed as mean ± standard deviation.

Group A, single-vessel disease; Group B, double-vessel disease; Group C, triple-vessel disease.

Dipyridamole = peak dipyridamole effect.

Abbreviations: DBP = diastolic blood pressure, HF = high frequency, LF = low frequency; LF/HF, low- to high-frequency ratio, Ln = natural logarithm, NN = normal RR interval, pNN50 = percentage of differences between adjacent NN intervals >50 ms, r-MSSD = root mean square successive difference, RPP = rate pressure product, SBP = systolic blood pressure, SDNN = standard deviation of all NN intervals, WMSI = wall motion score index, NS = not significant.

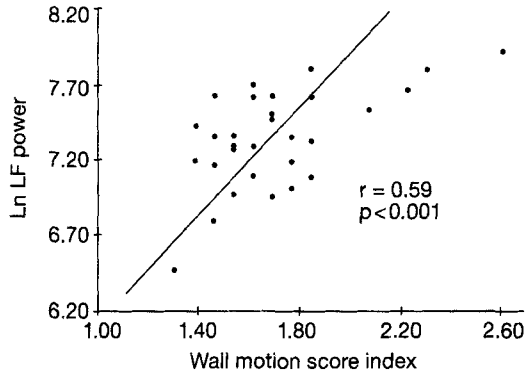

FIG. 1 Scatterplot of correlation between low frequency (LF) and wall motion score index at peak dipyridamole effect. Ln = natural logarithm.

vious myocardial infarction or to the presence of left ventricular dysfunction. These authors hypothesized that decreased cardiac vagal activity may be involved in the cause of coronary artery disease, rather than being merely the result of coronary artery disease.

Nonstationary Phenomena and Heart Rate Variability

Spectral analysis of RR interval variability is a well-established method of studying the autonomic modulation of sinus rate in stationary conditions but does not provide a reliable estimation of spectral variables during nonstationary phenomena, such as transient myocardial ischemia. Modified Wigner distributions, moving periodograms, short-term Fourier transforms, wavelet transform, and time variant spectral approach have provided accurate measures of spectral power during nonstationary situations. However, at this time, the possibility of comparing results obtained with these methods remains still to be defined.

Dipyridamole Testing and Neurovegetative Changes

Petrucci *et al.*[10] first evaluated HRV changes during dipyridamole infusion in patients with positive and negative test results, using a time variant spectral approach. These authors found that the increase in LF power expressed as LF ratio, the ratio between actual and basal absolute LF power (LF/LF_{basal} power ratio), allowed the differentiation of positive from negative test results. Considering that both dipyridamole and ischemia stimulate a sympathetic response, Petrucci *et al.* concluded that the different spectral profile observed reflects different expressions of sympathetic prevalence. In particular, these authors observed that the increase in LF power occurs in patients with positive results earlier than clear echocardiographic dyssynergy, suggesting that changes in HRV could reflect an early, perhaps biochemical stage of the ischemic cascade. A clear limitation of this study is that the absence of significant coronary artery disease was not assessed angiographically in the control group. Thereafter, Marciano *et al.*[19] evaluated HRV changes during dipyridamole echocardiographic test in patients with and without angiographically documented coronary artery disease, utilizing the wavelet transform analysis. The main finding of that study was that HRV measures in patients with angiographic evidence of coronary artery narrowing and negative dipyridamole echocardiographic test results were comparable with those of patients with coronary artery disease and positive test results. Therefore, HRV analysis during dipyridamole echocardiographic test seems to be able to detect the autonomic disturbance improving the diagnostic accuracy of dipyridamole echocardiographic test in patients with suspected coronary artery disease.

In our study, HRV measures were comparable at baseline among the three groups but became different after dipyridamole. In fact, LF power and LF/HF ratio increased more during dipyridamole echocardiographic test in Group C than in Groups A and B. The possible explanation for this finding may be a greater activation of sympathetic drive in patients with multivessel disease due to (1) an increased amount of chemical substances released during myocardial ischemia, stimulating cardiac receptors with sympathetic afferents; (2) chronic ischemia leading to a damage of the intrinsic cardiac nerves or cardiac receptors with vagal afferents; and (3) more severe alteration of cardiac geometry following dipyridamole. However, in interpreting the results of this study, it must be underlined that HRV analysis is a noninvasive tool to measure the fluctuations of cardiac autonomic outflow and not the mean level of cardiac autonomic activity. Moreover, the LF and HF components of HRV cannot be considered to be specific markers of sympathetic and vagal activities in all the conditions.[20,21] Therefore, the results of studies using power spectral analysis to evaluate cardiac autonomic control must be interpreted cautiously.

Heart Rate Variability and Left Ventricular Geometry

In our study, patients with triple-vessel disease showed a greater worsening of wall motion score index after dipyridamole. It has been demonstrated that an alteration in cardiac geometry secondary to the presence of a dysfunctional segment may increase the discharge of sympathetic afferent fibers by mechanical distortion of their sensory endings.[22] Such a sympathetic excitation interferes with tonic activity of vagal fibers directed to sinus node. In our study, patients with triple-vessel disease showed a greater worsening of wall motion score index after dipyridamole. Therefore, it is conceivable that in these patients the more severe alteration in cardiac geometry during myocardial ischemia is followed by a greater sympathetic activation. Thus, also if the changes in HRV may reflect the biochemical stage of the ischemic cascade, the segmental dyssynergy seems to play a pivotal role.

Conclusions

This study indicates that, in patients with coronary artery disease, the activation of sympathetic drive during dipyri-

damole-induced myocardial ischemia correlates with the angiographic severity of the disease. Therefore, the assessment of cardiac autonomic control by heart rate variability analysis seems to provide useful information, not only for the diagnosis of coronary artery disease but also for the assessment of its severity.

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