Heart rate variability in patients with variant angina: effect of the presence of significant coronary stenosis

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Power spectrum analysis; Variant angina; Coronary artery disease; Angiography.

Background. **The syndrome of variant angina occurs in patients with a wide spectrum of coronary disease ranging from angiographically normal coronary arteries to severe three-vessel disease. Survival and choice of therapy for these patients are determined by the extent of underlying fixed coronary obstruction. We examined whether heart rate variability (HRV) due to reduced vagal outflow may correlate with the severity of coronary stenoses in such patients.**

Methods. **Fifteen men and 2 women with clinically unstable variant angina underwent 24-hour Holter monitoring from which low and high-frequency power, standard deviation of mean 24-hour RR interval, proportion of adjacent RR intervals that differed by more than 50 ms, and mean root square of differences between successive RR intervals were extracted by power spectral analysis. Coronary angiography was later performed to determine coronary pathology and verify variant angina. As controls we studied an age-matched control group of 8 subjects (5 men, 3 women) with no clinical and/or electrocardiographic evidence of coronary heart disease or spasm as shown by negative treadmill exercise and hyperventilation tests.**

Results. **All measured components of HRV were significantly lower in the 9 patients with severe coronary artery disease compared to the 8 patients with normal coronary arteries or < 40% stenosis. The two groups were otherwise similar in terms of age and clinical parameters.**

Conclusions. **These preliminary findings on a small but carefully selected group of patients with variant angina indicate that the analysis of HRV can select patients with severe disease for a more intensive approach. These findings require confirmation on a larger patient series.**

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Introduction

Variant angina can occur in a wide spectrum of coronary artery diseases, ranging from patients with angiographically normal arteries to those with severe three-vessel disease[1]. It is important to determine coronary anatomy in such patients as choice of therapy and outcome are strongly influenced by the extent and severity of the underlying coronary obstructions[2-5]. Many studies have demonstrated that both variant angina[6] and coronary artery disease are associated with impaired vagal output to the heart[7-15], and there is evidence that reduced heart rate variability (HRV) due to reduced vagal outflow may be related to the severity of hemodynamically significant coronary stenoses[15]. We hypothesized that in variant angina, the indices of parasympathetic activity might alter more in patients with severe coronary artery disease than in those with mild coronary stenoses. We therefore carried out a preliminary study on a small number of patients with clinically unstable variant angina to test this hypothesis, and in particular to determine whether HRV indices are related to the presence or absence of organic heart disease.

Methods

Patients. We studied 17 patients (15 men and 2 women) with variant angina and clinical instability (defined as at least one episode of chest pain in the 12 hours prior to admission). Variant angina was determined clinically by the presence of all of the following: a) burning or squeezing retrosternal chest pain at rest; b) ST segment elevation of at least 2 mm on the electrocardiogram during pain which disappeared on pain relief and was not present at baseline; c) pain relief with nitroglycerine in less than 5 min; and d) no subsequent evidence of myocar-

dial necrosis. None of the patients had a history of myocardial infarction, cardiomyopathy, valvular heart disease, diabetes mellitus or congestive heart failure.

As a control group we studied 8 age-matched subjects (5 men, 3 women) with no clinical and electrocardiographic evidence of coronary heart disease as shown by negative exercise and hyperventilation tests. All had a normal echocardiogram.

Study protocol. All patients were hospitalized in our coronary unit where they underwent two-channel (modified V_5 and V_1 leads) 24-hour Holter electrocardiographic monitoring within 12 hours of admission. HRV was analyzed from the recordings using a Holter analysis system (Marquette Series 8000, Milwaukee, WI, USA). The only medications given during monitoring were nitrates (i.v.) and heparin. After classification of the QRS morphology, the longest and the shortest RRs on the RR interval histogram examined and all QRS complexes that were artifactual or ectopic were eliminated from the recording by holding the level at 0 until the next valid RR interval. Only normal to normal RR intervals were retained.

Next we analyzed the time and frequency characteristics of HRV. Fast Fourier transform was performed to separate RR interval fluctuations into their characteristic frequencies and to determine the square roots of areas under the power spectrum. From the 24-hour HRV power spectra we calculated the power within two frequency bands:

• 0.04-0.15 Hz, low frequency (LF) power which reflects increased sympathetic or parasympathetic tone modulated by baroreflex activity[16-18];

• 0.15-0.40 Hz, high frequency (HF) power, a specific measure of vagal tone, modulated primarily by breathing[16,19-26].

We also determined the following time domain HRV measures: the standard deviation of the mean RR intervals for all 5-min segments (SDANN); the proportion of adjacent RR intervals that differed by more than 50 ms (pNN50); and the mean square root of the difference between successive RR intervals (rMSSD). These measures have been established as reliable markers of parasympathetic activity[25,27].

Cardiac catheterization. Following clinical stabilization and 48 hours after withdrawal of medical therapy, all patients underwent left ventriculography and selective coronary angiography using the Judkins technique. Coronary angiograms were digitized and analyzed using commercially available equipment (Toshiba, DFP-60A, Nasu, Japan) and each lesion was studied in at least three different projections. For eccentric lesions the projection with the most severe narrowing was evaluated. All measurements were carried out blindly by two cardiologists. Discrepancies were resolved by discussion. Subsequently provocative testing was carried out in 15 patients by injection of ergonovine or by hyperventilation (30 respirations/min for 5 min) to confirm variant angina. These tests induced severe coronary vasoconstriction and angina associated with a marked ST segment elevation in all 15. The remaining 2 patients were not stimulated because spontaneous coronary artery spasm had been observed in the initial angiography. Based on the angiographic findings the patients were divided into those with < 50% coronary artery (Group 1) and those with Ž 50% artery narrowing (Group 2).

Statistical analysis. Data were expressed as means ± SD. The χ^2 test was used to assess differences between groups and a p value of • 0.05 was considered statistically significant.

Results

Group 1 consisted of 8 patients (7 men, 1 woman, mean age 59 ± 7 years) with angiographically normal coronary arteries or with only minimal stenosis (< 40% reduction in diameter). Group 2 consisted of 9 patients (8 men, 1 woman, mean age 61 ± 6 years) with severe coronary artery disease. The angiographic findings are summarized in table I. There were no differences in age, left ventricular ejection fraction, presence of hypertension, hypercholesterolemia, smoking, or history of angina at rest between the two groups (Table II). Total ischemic time and number of episodes in the day preceding admission were comparable in the groups of patients (Table II).

Table I. Angiographic findings.

	LAD (%)	CX (%)	RCA (%)	Spasm	Stimulus
Group 1					
1	32			LAD	Spontaneous
2	21			LAD	Hyperventilation
3	38			LAD	Hyperventilation
4				LAD	Hyperventilation
5			32	RCA	Ergonovine test
6		37		CX	Hyperventilation
7	28			LAD	Spontaneous
8	33			LAD	Ergonovine test
Group 2					
1	76			LAD	Hyperventilation
2	88			LAD	Hyperventilation
3	92			LAD	Hyperventilation
4		74	88	RCA	Hyperventilation
5		76		CX	Ergonovine test
6	78			LAD	Spontaneous
7	82			LAD	Hyperventilation
8	65			LAD	Hyperventilation
9			90	RCA	Hyperventilation

CX = circumflex branch; LAD = left anterior descending branch; RCA = right coronary artery.

Table II. Clinical features.

	Group 1 (n = 8)	Group 2 (n = 9)
Mean age (years)	59 ± 7	61 ± 6
Exertional angina	2	4
Rest angina	8	9
> 3-month history of rest angina	6	5
Left ventricular ejection fraction (%)	50 ± 4	51 ± 3
Hypercholesterolemia	4	3
Hypertension	3	3
Smoking	6	6
Total ischemic time during 24-hour Holter monitoring (min)	4.3 ± 1	4.2 ± 2
No. anginal episodes in the day preceding admission	3 ± 1	3 ± 2

Heart rate variability parameters. Patients with severe stenosis (Group 2) had lower indices of parasympathetic activity, measured as time-domain parameters of HRV than Group 1 and the control group (Table III). Furthermore LF and HF power were significantly lower in Group 2 than Group 1 (Table III, Fig. 1) and the control group (Table III).

Time- and frequency-domain parameters of HRV were slightly more but not significantly lower in patients with angiographically normal coronary arteries than in the control group (Table III).

Table III. Comparison of time- and frequency-domain variables between Group 1 and Group 2 patients.

	Group 1	Group 2	Control
Mean RR	902.56 ± 67	878.86 ± 14	923.55 ± 24
	NS		NS
SDANN (ms)	103.89 ± 26	75.3 ± 20	110 ± 12
	*		*
	NS		
pNN50 (%)	11.5 ± 12	0.53 ± 1	12.5 ± 10
	*		*
	NS		
rMSSD (ms)	52 ± 33	14.5 ± 4	58 ± 23
	*		*
	NS		
[LF] Ln (ms²)	5.52 ± 1	4.21 ± 1	5.82 ± 2
	*		*
	NS		
[HF] Ln (ms²)	4.45 ± 1	2.8 ± 1	4.78 ± 1
	*		*
	NS		

HF = high frequency power (0.15-0.40 Hz); LF = low frequency power (0.04-0.15 Hz); pNN50 = percentage of differences between adjacent normal RR intervals that are > 50 ms over 24 hours; rMSSD = mean square root of the difference of successive RR intervals; SDANN = the standard deviation of the mean RR intervals for all 5-min segments. * $p < 0.01$.

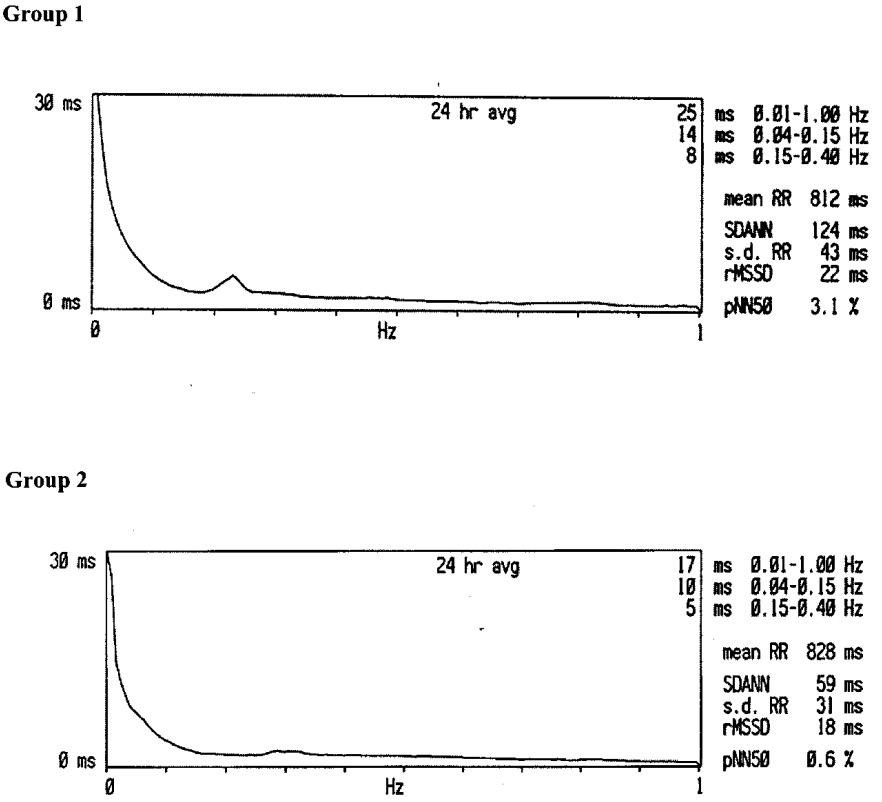

Figure 1. *Examples of spectral analysis of RR interval variability. pNN50 = percentage of differences between adjacent normal RR intervals that are > 50 ms over 24 hours; rMSSD = mean square root of the difference of successive RR intervals; SDANN = standard deviation of the mean RR intervals for all 5-min segments; s.d. RR = global standard deviation of RR intervals over 24 hours.*

Mean RR was slightly more but not significantly lower in patients with variant angina and coronary artery disease compared to patients with spasm and angiographically normal coronary arteries and in the control group (Table III).

Discussion

We have found that, in our small groups of patients with clinically unstable variant angina, the time and frequency measures of HRV were significantly lower in the group with severe coronary disease than in the group without significant stenoses.

Analysis of HRV has been proposed as a method for assessing autonomic cardiac function that provides specific information on changes in autonomic tone resulting from the interaction between the sympathetic and parasympathetic nervous activity. The HF component of HRV is synchronous with the respiratory cycle and is considered to be a reliable marker of parasympathetic activity in the supine position[16,19-26]. The HF component is known to be almost completely mediated by the parasympathetic nervous system[16-18]. Time-domain parameters are also related to vagal activity[25,27]. Based on these data, we conclude that the reduced values of these parameters observed in our patients with severe coronary artery disease are due to a reduction in the vagal component of HRV.

These findings are consistent with those of earlier studies[7-9,11-14] that reported impaired vagal outflow to the heart in patients with coronary artery disease, including those without acute myocardial infarction or chronic heart failure[10,15]. Some studies[15,28] have reported a linear relation between a reduction in vagal function and the angiographic severity of coronary disease, while others found no such a relation[10,12]; we investigated too few patients to confirm or deny such a correlation.

Both the cause and mechanism of the association between decreased vagal activity and coronary artery disease are unknown. Some authors have suggested that reduced vagal function results from damage to intrinsic cardiac nerves by infarction or ischemia[29]; others have supposed it reflects increased sympathetic activity, decreased parasympathetic activity, or both, due to impaired left ventricular function[30]. Hayano et al.[15] have shown that cardiac vagal outflow, as assessed by power spectral analysis of HRV, is decreased in coronary artery disease irrespective of the level of left ventricular function or whether or not there is a history of myocardial infarction function, and therefore supposed that the reduction was directly related to the presence of coronary artery disease.

Both the treatment and prognosis of variant angina are strongly influenced by coronary anatomy[2-4]. Patients with severe coronary disease often require revascularization by surgery or coronary angioplasty as their symptoms cannot be controlled by drugs. Those with mild obstruction more often respond to calcium antagonists. Nakamura et al.[31] reported on 349 patients with variant angina, only 101 of whom had coronary stenoses of Ž 75%, and only 21/101 had multivessel disease. In the whole group followed for a mean of 3.4 years, sudden death occurred in 2% and myocardial infarction in 5%. The authors attributed this relatively good prognosis to the low prevalence of organic coronary lesions and to the fact that 98% of patients were treated with calcium blockers. Walling et al.[3] reported on 217 patients with variant angina followed for a mean of 65 months. Survival without infarction at 1 and 5 years was 93 and 83% in patients without coronary stenoses of Ž 70%, 85 and 74% in subjects with single-vessel disease and 65 and 45% in patients with multivessel disease.

The above data clearly show that it is important to know the coronary anatomy in variant angina. Therefore it would be useful to have a reliable, non-invasive means of distinguishing patients with normal or only mildly abnormal coronary arteries from those with severe obstructions, without recourse in all cases to coronary angiography (particularly in small or non-specialist centers). This would allow optimization of treatment and reduction of costs. Unfortunately clinical features alone do not reliably differentiate such patients[32]. Moreover, during the active phases of the disease other examinations such as stress test or echo-stress are contraindicated.

Our results suggest that analysis of HRV may be a reliable means of detecting severe coronary artery disease in patients with variant angina. Furthermore the technique is relatively inexpensive, safe, and non-invasive. We suggest therefore that the method merits further study on more patients. It would also be important to determine whether similar reductions in HRV indices are present during the quiescent phases of variant angina. In 5 patients who underwent renewed Holter monitoring a month after clinical stabilization, HRV parameters apparently returned to normal[6]; however to our knowledge these are the only published data available on this issue. The number of anginal episodes in the day preceding admission was similar in the two groups. We cannot exclude that a greater number of silent episodes occurring in patients with significant coronary artery disease could have affected the results. However a number of papers have shown that, although asymptomatic episodes usually outnumber those with symptoms, in general a relationship exists between symptomatic and asymptomatic events. In all patients a de novo diagnosis was made during our examination. Therefore no patient received any antianginal drug in the period preceding admission. During electrocardiographic monitoring patients were treated with intravenous nitrates which reduced the number and the duration of ischemic episodes. Therefore, although we cannot exclude a difference in HRV between normal controls and patients with spasm and no coronary artery dis-

ease, these parameters were certainly much more impaired in patients with spasm and severe coronary stenoses.

In conclusion, our findings indicate that in patients with variant angina there is an association between reduction of the vagal components of HRV and the severity of coronary artery disease, and suggest that HRV analysis may be a simple and easy method of obtaining, in the early unstable phase of variant angina, important prognostic and diagnostic information. Clearly larger studies are needed to confirm these preliminary findings.

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