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Factors Influencing Heart Rate Variability in Patients with Severe Aortic Valve Disease

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Summary

Background and hypothesis: Heart rate variability (HRV) is an accepted tool for the assessment of cardiovascular autonomic tone. There are no sufficient data concerning its application to patients with severe aortic valve disease (AVD) requiring cardiac surgery.

Methods: It was the aim of this study to examine HRV and its physiologic correlates in patients with severe aortic valve disease requiring cardiac surgery. The correlates of time domain indices of HRV obtained from 24-h Holter electrocardiographic recordings were analyzed in 36 consecutive patients (23 men and 13 women, mean age 62 ± 11 years) with AVD prior to cardiac surgery (aortic stenosis: 17 patients, aortic valve regurgitation: 3 patients, combined aortic valve disease: 16 patients).

Results: Low values of HRV were found in the entire study group: SDNN 96.8 ± 30.9 ms, SDNNI 39.3 ± 14.4 ms, SDANN 86 ± 28.9 ms, and RMSSD 30 ± 18.1 ms. In a univariate analysis, there was no significant correlation between the time domain measures of HRV and age, gender, medication, left ventricular ejection fraction, peak aortic pressure gradient, fraction of aortic valve regurgitation, and left ventricular mass assessed by echocardiography. Patients in advanced functional classes of heart failure [New York Heart Association (NYHA) III or IV] had significantly lower values for SDNN (83.8 ± 33.6 vs. 107.3 ± 24.7 ms; $p<0.05$) and SDANN (72.7 ± 29.4 vs. 96.6 ± 24.3 ms; $p<0.05$) than patients in NYHA class I or II. Reassessment of HRV 1 week after aortic valve replacement was performed in 17 patients and showed a significant further decrease of SDNN (102.4 ± 29.7 vs. 61.5 ± 23.5 ms; $p<0.001$), SDNNI (40.7 ± 13.6 vs. 23.4 ± 12.4 ms; $p<0.001$) and SDANN (91.8 ± 29.2 vs. 54.2 ± 22.8 ms; $p<0.001$).

Conclusion: Patients with AVD requiring cardiac surgery reveal reduced time domain indices of HRV. This observation is pronounced in patients with a progressed clinical class of heart failure, whereas hemodynamic and echocardiographic parameters seem to have no significant influence on HRV parameters in this population. In addition, there is evidence of a further reduction of HRV time domain indices 1 week after uncomplicated aortic valve replacement.

Key words: autonomic nervous system, heart rate variability, aortic valve disease

Introduction

Heart rate variability (HRV) is known to be a reliable quantitative marker of cardiovascular autonomic activity. Reduced HRV is associated with an adverse prognosis in survivors of myocardial infarction[1,2] and patients suffering from congestive heart failure.[3–5] To date, this method has not been applied to patients with severe aortic valve disease. In those patients, even after successful valve replacement, sudden cardiac death has been observed in 7–38%.[6] Impaired sympathovagal balance might contribute to the genesis of arrhythmic events in this clinical setting. It was therefore the aim of our study to examine HRV and its physiologic correlates in patients with severe aortic valve disease requiring cardiac surgery.

Methods

In a prospective study, we assessed time domain HRV parameters in consecutive patients with severe aortic valve disease before and 1 week after aortic valve replacement. Patients

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with atrial fibrillation, diabetes mellitus, permanent pacemaker implantation, and on chronic therapy with beta blockers were excluded from the study. Clinical data including age, gender, medication, and functional class of heart failure were collected. Left ventricular (LV) mass was determined by echocardiography using the method of Devereux *et al.*[7] and was indexed for body surface area. Hemodynamic parameters such as peak-to-peak aortic pressure gradient or the extent of aortic regurgitation and LV ejection fraction were obtained from angiographic evaluations. In addition, coronary angiography was performed to assess concomitant coronary artery disease.

Ambulatory 24 h electrocardiogram (ECG) recordings (Tracker, Reynolds Medical, Hertford, U.K.) of bipolar leads CM1 and CM5 were analyzed (Pathfinder 700, Reynolds Medical, Hertford, U.K.). After standard Holter analysis, the data files were reviewed and edited by the same investigator for careful elimination of ectopic beats and artifacts. The following time domain indices of HRV were obtained: standard deviation (SD) of normal RR intervals (SDNN), SD of 5 min mean RR intervals (SDANN), mean of the SDs of all normal RR intervals for all 5 min segments (SDNNI), and the root mean square of successive differences of RR intervals (RMSSD).

Statistical Analysis

Data are presented as mean ± SD. Pearson product–moment correlation was performed to assess a possible correlation between time domain HRV parameters and age, peak aortic pressure gradient, LV ejection fraction, LV mass, and LV mass index. Continuous variables were compared using the unpaired *t*-test. In cases of abnormally distributed parameters, the Mann-Whitney U-test was applied. A p-value < 0.05 was considered significant.

Results

Forty-nine consecutive patients with high-grade aortic valve disease were screened. Thirteen patients had to be excluded because of chronic atrial fibrillation (9 patients) or chronic pacemaker therapy (4 patients). Thus, our study population consisted of 36 consecutive patients. The characteristics of the patients are shown in Table I. All patients were symptomatic: 24 patients had recurrent episodes of dyspnea, 17 patients had recurrent episodes of chest pain, 10 patients had a history of acute heart failure, and 9 patients experienced syncope or presyncope. No patient had a history of a previous myocardial infarction. During the study, 31% of the patients were on digitalis, 11% on angiotensin-converting enzyme (ACE) inhibitors, 19% on calcium antagonists, 58% on diuretics, and 47% on nitrates. Left ventricular hypertrophy was found in 82% of the patients.

For HRV analysis, a mean recording time of 22.2 ± 3.2 h was suitable. Time domain analysis of HRV revealed relatively low values for the entire study group (Table II). Pearson product–moment correlation showed no evidence of linear correlation between time domain HRV parameters and age, LV ejection fraction, peak aortic pressure gradient, LV mass or LV mass index (Table III). Also, there was no influence of gender, medication, the fraction of aortic regurgitation, or the presence of concomitant coronary artery disease on the results

TABLE I Characteristics of the study population

Number of patients	36
Age (years)	62 ± 11
Male	23 (64%)
Aortic valve stenosis	17 (48%)
Aortic valve regurgitation	3 (8%)
Combined aortic valve disease	16 (44%)
Concomitant CAD	16 (44%)
NYHA class III–IV	16 (44%)
LVEF(%)	59.3 ± 15.3
Peak aortic pressure gradient (mmHg)	61.5 ± 19
Aortic regurgitation fraction > II	6 (15%)
Left ventricular mass (g)	324 ± 108
Left ventricular mass index (g/m^2)	179 ± 61

Abbreviations: CAD = coronary artery disease, NYHA = New York Heart Association, LVEF = left ventricular ejection fraction.

TABLE II Time domain parameters of heart rate variability of the entire study group

No. of patients	36
SDNN (ms)	96.8 ± 30.9
SDNNI (ms)	39.3 ± 14.4
SDANN (ms)	86 ± 28.9
RMSSD (ms)	30 ± 18.1

Abbreviations: SDNN = standard deviation from the mean of the normal RR intervals; SDNNI = mean of the standard deviations of all normal RR intervals for all 5-min segments; SDANN = standard deviation of the mean of RR intervals in all 5 min segments; RMSSD = root mean square of successive RR differences.

TABLE III Correlation between time domain parameters of heart rate variability and patient characteristics

	SDNN	SDNNI	SDANN	RMSSD
Age	r = 0.27	r = 0.3	r = 0.23	r = 0.04
LVEF	r = 0.15	r = −0.04	r = 0.19	r = 0.04
Peak aortic pressure gradient	r = −0.18	r = −0.33	r = −0.09	r = −0.3
Left ventricular mass	r = 0.0002	r = 0.21	r = −0.04	r = 0.11
Left ventricular mass index	r = −0.04	r = 0.2	r = −0.09	r = 0.13

Abbreviations: r = correlation coefficient. Other abbreviations as in Tables I and II.

of HRV analysis. Time domain indices of HRV were not different in patients with pure aortic stenosis, pure aortic regurgitation, or combined aortic valve disease. Patients with advanced heart failure classified as New York Heart Association (NYHA) class III or IV revealed significantly lower values for SDNN and SDANN than patients in NYHA class I or II (Table IV).

Reassessment of HRV could be performed in 17 (47%) patients 1 week after successful aortic valve replacement. Nineteen patients needed to be excluded: 4 patients developed atrial fibrillation after surgery, an insertion of a permanent pacemaker was necessary in 2 patients, 5 patients refused a second 24 h Holter ECG, and 8 patients were referred to other hospitals early after surgery. One week after cardiac surgery, a significant further decrease of the HRV parameters SDNN, SDNNI, and SDANN was observed (Table V).

TABLE IV Time domain parameters of heart rate variability and functional class of heart failure

	NYHA I–II	NYHA III–IV	p Value
No. of patients	20	16	
SDNN (ms)	107.3 ± 24.7	83.8 ± 33.6	<0.05
SDNNI (ms)	42.3 ± 12.4	35.5 ± 16.1	NS
SDANN (ms)	96.6 ± 24.3	72.7 ± 29.4	<0.05
RMSSD (ms)	28.5 ± 18	32.2 ± 17.2	NS

Abbreviations as in Tables I and II.

TABLE V Time domain parameter of heart rate variability before and after aortic valve replacement

	Before	After	p Value
No. of patients	17	17	
SDNN (ms)	102.4 ± 29.7	61.5 ± 23.5	<0.001
SDNNI (ms)	40.7 ± 13.6	23.4 ± 12.4	<0.001
SDANN (ms)	91.8 ± 29.2	54.2 ± 22.8	<0.001
RMSSD (ms)	29.7 ± 19.1	27.3 ± 22.8	NS

Abbreviations as in Table II.

Discussion

Heart rate variability analysis has been proven to be a reliable noninvasive method for the assessment of sympathetic and vagal inputs to the heart. Our study is the first attempt to investigate HRV in patients with severe aortic valve disease. In these patients, cardiac dysfunction is characterized by a pressure overload status in the setting of high-grade aortic stenosis or by a volume overload in patients with pure aortic regurgitation. In many cases, both mechanisms will compromise cardiac function, leading to LV hypertrophy and subsequently to congestive heart failure. We found diminished values for HRV time domain parameters in the whole study group, which might reflect a predominant sympathetic stimulation of the diseased heart. However, a correlation between peak aortic pressure gradient or the fraction of aortic valve regurgitation and time domain measures of HRV could not be found. Depressed values for HRV have been observed in patients with LV hypertrophy compared with normal subjects.[8] In our study, we found no correlation between the extent of LV mass and HRV indices.

There was no detectable correlation between LV ejection fraction and HRV parameters in contrast to patients with severe mitral regurgitation, in whom a significant correlation between SDANN and LV ejection fraction was found.[9] Other studies dealing with patients suffering from congestive heart failure report controversial results for the relationship between HRV and depressed LV function. Casolo *et al.*[3] found lower values for HRV time domain parameters in patients with LV ejection fraction <30%, whereas Kienzle *et al.*[4] found no correlation between HRV parameters and LV performance in patients with congestive heart failure.

Angiotensin-converting enzyme inhibitors are known to influence autonomic tone in patients with congestive heart failure.[10] In our study population, chronic therapy with ACE inhibitors had no influence on HRV indices.

The principal finding of this study is that time domain indices of HRV correlate with the severity of symptoms of congestive heart failure in the investigated patient population. We found significant lower values for SDNN and SDANN in patients in NYHA functional classes III and IV than in patients in NYHA classes I and II. Recently published data[5] showed evidence of a significant correlation between spectral measures of HRV and progression of NYHA functional class in patients with congestive heart failure, whereas in another study[4] none of the HRV indices were related to NYHA functional class.

In the early phase after successful aortic valve replacement, there is no evidence that normal autonomic control of the heart can be restored. On the other hand, we found a further decrease of the HRV parameters after cardiac surgery. This is probably related to the surgical procedure itself, as reported in another study dealing with patients after coronary artery bypass grafting.[11] This fact could be a possible explanation for the relatively high incidence of sudden cardiac death observed after aortic valve replacement.[6] Further studies are needed to clarify whether an amelioration of the HRV parameters can be observed during long-term follow-up.

Conclusion

Patients with severe aortic valve disease reveal reduced time domain indices of HRV. This observation is pronounced in patients in an advanced functional class of heart failure, whereas hemodynamic and echocardiographic parameters seem to have no significant influence on HRV indices in this population. The relationship between time domain indices of HRV and symptomatic functional status in our study population may be of possible practical value in the management of patients with asymptomatic aortic valve disease for assess-

ment of appropriate timing for surgery. Follow-up studies after aortic valve replacement are needed to evaluate the prognostic value of depressed HRV time domain parameters, as assessed 1 week after cardiac surgery, to identify patients at risk of cardiac death.

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