

Heart rate variability and heart rate turbulence in mild-to-moderate aortic stenosis

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KEYWORDS

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Aims To study heart rate (HR) variability and HR turbulence parameters in mild-to-moderate aortic stenosis (AS) and to disclose whether any relationship exists between these parameters and echocardiographic findings.

Methods and results Forty-three asymptomatic patients with mild-to-moderate AS (AS group) were studied. Echocardiographic parameters and HR variability and HR turbulence indices obtained over 24 h Holter ECG recordings were compared with those of an age and sex matched control population free of cardiovascular disease. Correlation between echocardiographic findings and HR variability and HR turbulence indices was also studied in the AS group. All HR variability parameters except mean RR interval, RMSSD, and pNN50 and one HR turbulence parameter, turbulence onset, were significantly disturbed in the AS group. Echocardiographic findings of diastolic dysfunction had significant correlations with HR variability and HR turbulence parameters in AS patients.

Conclusion Sympatovagal imbalance as shown by disturbed HR variability and HR turbulence parameters was demonstrated for the first time in patients with mild-to-moderate AS. This imbalance, which was shown to be correlated with echocardiographic findings of diastolic dysfunction, may lead to arrhythmic complications in this seemingly low-risk patient population.

Introduction

Mild and moderate aortic stenosis (AS) is generally believed to be benign conditions, but in a recent study,¹ the clinical outcomes of patients with mild-to-moderate AS was shown to be worse than commonly assumed and both cardiac and non-cardiac mortality were found to be higher when compared with controls.

Heart rate (HR) variability² and HR turbulence^{3–5} are indices that reflect the autonomic balance in various disease states. Both have been shown to have prognostic value in patients with systolic left ventricular dysfunction, but their value in diastolic dysfunction has not been well defined yet. In symptomatic patients with severe AS, HR variability parameters have been demonstrated to be disturbed,^{6,7} however HR variability and HR turbulence parameters have not been studied in the setting of mild and moderate AS.

In this study, our aim was to examine HR variability and HR turbulence in patients with mild and moderate AS and

to find out whether any relationship exists between these parameters and echocardiographic findings.

Methods

After a search of our echocardiography lab database spanning the years 2004–2007, asymptomatic patients younger than 70 years who had mild-to-moderate degree 'pure AS' as defined previously⁸ were asked to participate in the study. Echocardiographic parameters and 24 h Holter ECG recordings were obtained from those who consented and these indices were compared with those of an age and sex matched control population who had no cardiovascular disease. All the patients were in class I according to New York Heart Association classification.

Exclusion criteria were as follows: (i) hypertension; (ii) diabetes mellitus; (iii) atrial fibrillation; (iv) coronary artery disease defined as >50% narrowing in at least one coronary artery in a previous angiogram; (v) history of myocardial infarction, acute coronary syndrome, or typical angina pectoris; (vi) hyper or hypothyroidism; (vii) systolic dysfunction (ejection fraction <55%); (viii) concomitant valvular diseases such as mitral stenosis (mitral valve area <2.5 cm²) and moderate-to-severe aortic or mitral regurgitation; (ix) anti-arrhythmic drug use including beta blockers and calcium channel blockers; (x) New York Heart Association classification class 2 or higher symptom level; (xi) age >70 years.

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The control group comprised an age and sex matched population free of cardiovascular disease, including systemic hypertension, who had at least five ventricular premature beats on their 24 h Holter recordings because HR turbulence could not be measured in the absence of extrasystoles.

The echocardiographic and Holter examinations were performed within 2–5 days in each participant.

Echocardiography

All patients underwent a complete transthoracic echocardiographic examination including two dimensional, colour flow, and pulsed Doppler as well as tissue Doppler imaging with a GE-Vingmed Vivid 7 system (GE-Vingmed Ultrasound AS, Horten, Norway) using a 2.5–3.5 MHz transducer. Standard transthoracic views were used to obtain left ventricular ejection fraction (EF), left ventricular end-diastolic diameter (LVEDD), interventricular septal diameter (IVSD), and left ventricular posterior wall diameter (PWD) in diastole. Left ventricular mass (LV mass, in grams) was calculated according to the following formula: $1.04 \times [(LVEDD + IVSD + PWD)^3 - LVEDD^3] - 13.6$ (diameter in centimetres).⁹ All dimensions were indexed to

body surface area (BSA) which was calculated as follows: $BSA (m^2) = 0.0001 \times 71 - 84 \times Weight(kg)^{0.425} \times Height(cm)^{0.725}$. LV mass index was also calculated by dividing LV mass by BSA.

With continuous Doppler, mean and peak gradients between the left ventricle and aorta were assessed and aortic valve area (AVA) was calculated. These were taken as parameters of AS severity.

Transmitral pulsed wave Doppler tracings were recorded in the apical 4-chamber view: early (E) and atrial (A) peak velocities, E/A ratio, isovolumic relaxation time (IVRT) (ms), isovolumic contraction time (IVCT) (ms), and ejection time (ET) were calculated. Myocardial performance index (MPI) was measured as follows: $(IVRT + IVCT)/ET$.

With tissue Doppler imaging, in apical 4-chamber view, a 5 mm pulsed Doppler sample volume was placed at the level of the septal mitral annulus. Peak systolic (Sm), peak early (Em), and late (Am) diastolic mitral annular velocities and Em/Am ratio were calculated.

The intraobserver variability of echocardiographic measurements was <6% and all examinations were performed by an experienced echocardiographer who had no knowledge of the patient's clinical information.

Table 1 Clinical characteristics of patients and the control group

	Aortic stenosis (n = 43)	Control group (n = 50)	P-value
Age (year)	51.8 ± 8.3	54.4 ± 9.0	NS
Male sex	27 (62.8%)	31 (62.0%)	NS
Systolic blood pressure (mmHg)	115 ± 18	113 ± 17	NS
Diastolic blood pressure (mmHg)	74 ± 12	73 ± 11	NS
Left ventricular parameters			
Ejection fraction (%)	66.4 ± 3.0	67.2 ± 2.3	NS
LVEDD (mm)	46.8 ± 3.2	46.4 ± 4.0	NS
(mm/m ²)	26.0 ± 1.6	25.6 ± 1.8	NS
LVESD (mm)	29.5 ± 2.7	30.1 ± 2.9	NS
(mm/m ²)	16.4 ± 1.3	16.6 ± 1.4	NS
IVSD (mm)	12.7 ± 1.5	9.6 ± 1.1	<0.001
(mm/m ²)	7.1 ± 1.0	5.3 ± 0.8	<0.001
PWD (mm)	12.4 ± 1.4	9.3 ± 1.2	<0.001
(mm/m ²)	6.9 ± 1.0	5.2 ± 0.8	<0.001
LV mass (gr)	222.0 ± 41.2	150.7 ± 31.6	<0.001
LV mass index (gr/m ²)	125.0 ± 29.6	82.7 ± 14.7	<0.001
Number of ventricular ectopic beat in 24 h	450 ± 315	201 ± 145	<0.001
During day-time (07:00–23:00)	343 ± 240	158 ± 108	<0.001
During night (23:00–07:00)	107 ± 78	43 ± 39	<0.001
Time domain HR variability			
Mean R–R interval (ms)	767.7 ± 79.3	783.7 ± 84.4	NS
Heart rate (per min)	78.2 ± 8.0	76.5 ± 8.5	NS
Heart rate (13:00–14:00) (per min)	88.5 ± 9.8	86.3 ± 10.2	NS
SDNN (ms)	125.7 ± 24.8	141.6 ± 17.7	<0.001
SDANN (ms)	110.0 ± 23.8	126.1 ± 15.4	<0.001
SDNN index (ms)	47.2 ± 12.4	59.8 ± 11.6	<0.001
pNN50 (%)	12.7 ± 6.8	13.2 ± 7.6	NS
RMSSD (ms)	33.9 ± 9.9	34.4 ± 10.2	NS
Triangular index	31.8 ± 8.9	40.9 ± 11.7	0.006
Frequency domain HR variability			
LFnu	27.5 ± 7.9	20.7 ± 4.7	<0.001
HFnu	8.8 ± 2.2	13.1 ± 3.1	<0.001
LF/HF ratio	3.7 ± 1.3	2.0 ± 0.7	<0.001
Heart rate turbulence			
Turbulence onset	−0.09 ± 1.06	−0.61 ± 0.74	0.008
Turbulence slope (ms/RR)	5.21 ± 3.37	6.49 ± 3.32	0.067

EDD, end-diastolic diameter; ESD, end-systolic diameter; HF, high frequency power; HFnu, normalized high frequency power; IVSD, interventricular septal diameter; LF, low frequency power; LFnu, normalized low frequency power; LV, left ventricle; pNN50, proportion of adjacent R–R intervals differing by >50 ms in the 24 h recording; PWD, posterior wall diameter; RMSSD, square root of the mean squared differences of successive normal-to-normal intervals; SDANN, standard deviation of the average normal-to-normal intervals calculated over 5 min periods of the entire recording; SDNN, standard deviation of all normal-to-normal intervals.

Heart rate variability and heart rate turbulence

All the participants underwent a 24 h Holter recording to assess HR variability and HR turbulence parameters. Twenty-four hour Holter evaluations were performed by an experienced physician who was totally blind to the study population. Holter ECG was performed on a 3-channel digitized recorder (Del Mar Reynolds Medical Ltd, Hertford, UK). Before analysing the data they were manually preprocessed. Recordings lasting for at least 18 h and of sufficient quality for evaluation were included in the analysis. In case these criteria were not achieved, the recordings were repeated.

The time domain HR variability indices were analysed by using statistical and geometrical methods. By using statistical methods, the RMSSD [the square root of the mean squared differences of successive normal-to-normal (NN) intervals], the SDNN (the standard deviation of all NN intervals), the SDNN index (the mean of the deviation of the 5 min NN intervals over the entire recording), the SDANN (standard deviation of the average NN intervals calculated over 5 min periods of the entire recording), and the pNN50 (proportion of adjacent R-R intervals differing by >50 ms in the 24 h recording) were measured. By using geometrical methods, the HR variability triangular index (TI) (total number of all NN intervals divided by the height of the histogram of all NN intervals measured on a discrete scale with bins of 7.8125 ms (1/128 s) was measured. Also mean R-R interval was calculated. All of them were measured according to the Task Force of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology.²

The frequency domain analysis of HR variability included the total power, high frequency (HF) component (0.15–0.40 Hz), low frequency (LF) component (0.04–0.15 Hz), and very low frequency (VLF) component (0–0.04 Hz). The normalized HF power (HFnu = $100 \times \text{HF power}/\text{total power}$), normalized LF power (LFnu = $100 \times \text{LF power}/\text{total power}$), and low/high frequency power ratio (LF/HF ratio = $\text{LF power}/\text{HF power}$) were measured to give the relative changes in the frequency domain. Spectral analysis was performed with short-segments with averaging of parameters.

Heart rate turbulence parameters were calculated using an algorithm adapted from the Web page popularizing the non-commercial use of HRT (<http://www.h-r-t.org>). The turbulence onset which is a measure of the expected normal early sinus acceleration after a ventricular premature beat and the turbulence slope which is a measure of late sinus deceleration after a ventricular premature beat constitute the two components of HR turbulence. After manual review of the 24 h Holter tracings, turbulence onset and turbulence slope were determined according to the previously published method.^{3,10} A turbulence onset value below 0% indicates early sinus acceleration and is considered normal and a turbulence slope value above 2.5 ms/R-R interval indicates the normal expected late deceleration.

Statistical analysis

Continuous variables were given as mean $\pm$ SD; categorical variables were defined as percentages. Data were tested for normal distribution using the Kolmogorov–Smirnov test. Continuous variables of

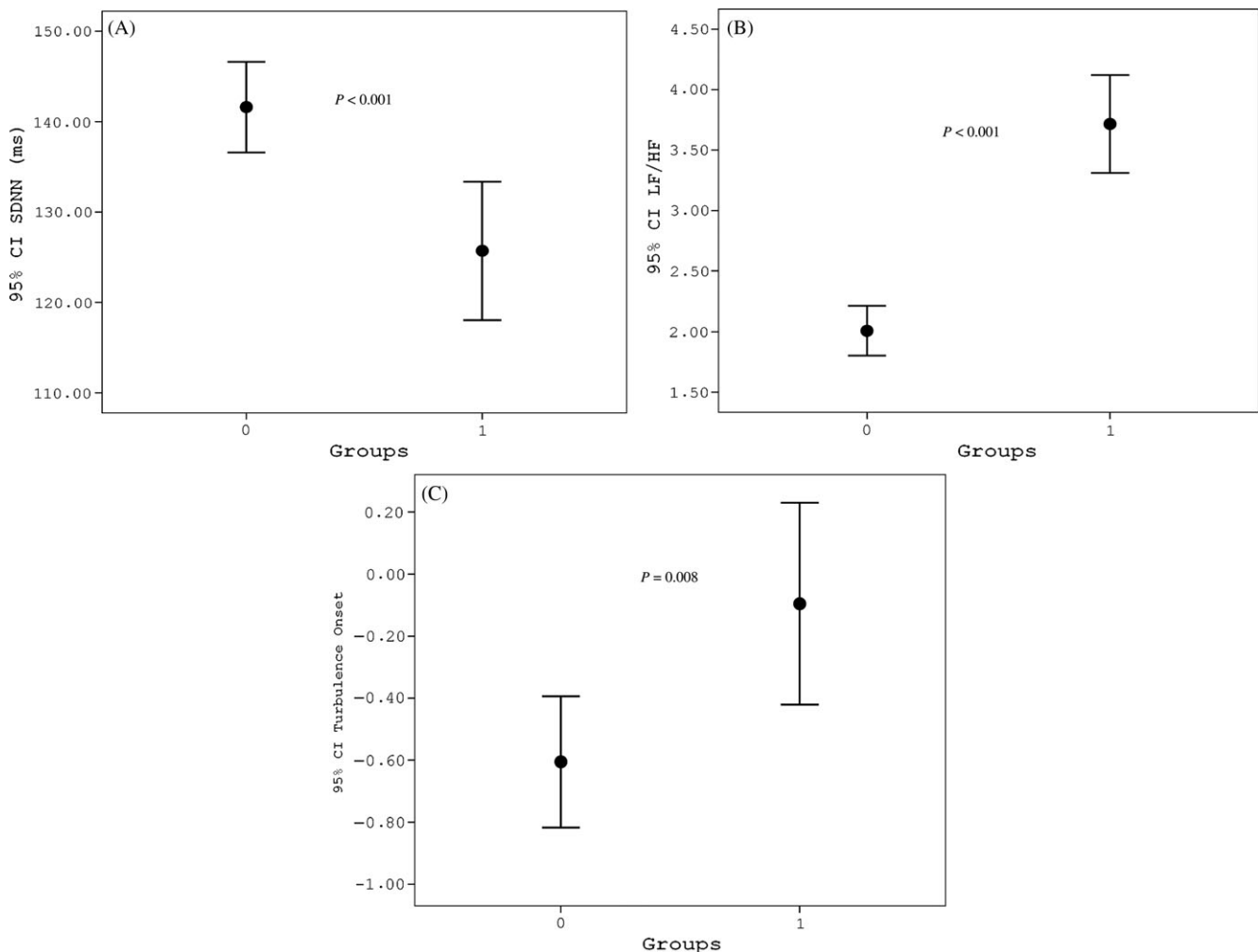


Figure 1 Heart rate variability and heart rate turbulence parameters in both groups. Group 0: Aortic stenosis; Group 1: Control group. CI, confidence interval; HF, high frequency power; LF, low frequency power; SDNN, standard deviation of all normal-to-normal intervals.

Table 2 Extensive echocardiographic parameters of patients with aortic stenosis

Transvalvular aortic gradient (mmHg)	
Maximum	42.9 ± 8.7
Mean	25.0 ± 6.2
Aortic valve area (cm ²)	1.57 ± 0.27
(cm ² /m ²)	0.88 ± 0.18
Doppler echocardiography	
Mitral E velocity (cm/s)	65.1 ± 11.6
Mitral A velocity (cm/s)	59.8 ± 10.6
E/A ratio	1.12 ± 0.29
Tissue Doppler	
Em (cm/s)	8.4 ± 1.5
Am (cm/s)	8.0 ± 1.1
Em/Am ratio	1.06 ± 0.20
LVIVRT (ms)	88.3 ± 22.7
LVIVCT (ms)	86.0 ± 16.6
LVET (ms)	326.3 ± 48.7
MPI	0.55 ± 0.16
E/Em ratio	7.9 ± 1.5

A, arial (late) peak mitral velocity obtained from pulsed Doppler; Am, late diastolic mitral annular velocity obtained from tissue Doppler; E, early peak mitral velocity obtained from pulsed Doppler; Em, early diastolic mitral annular velocity obtained from tissue Doppler; ET, ejection time; IVCT, isovolumic contraction time; IVRT, isovolumic relaxation time; LV, left ventricle; MPI, myocardial performance index.

normally and non-normally distributed data were compared with an independent *t*-test and Mann-Whitney *U*-test, and the χ^2 test was used for the categorical variables. Pearson correlation coefficient was used for correlation analysis. The HR variability and HR turbulence variables which showed a difference between the two groups were then subjected to analysis of covariance to verify the influence of diastolic dysfunction on the results obtained in the parametric tests (independent *t*-test). All tests of significance were two-tailed. Statistical significance was defined as $P < 0.05$. The SPSS statistical software (SPSS for windows 15, Inc., Chicago, IL, USA) was used for all statistical calculations.

Results

Forty-three patients with AS (19 mild, 24 moderate) and 50 control subjects were enrolled in the study. The clinical characteristics, HR variability and HR turbulence parameters of the whole population are shown in *Table 1*. Of the 43 patients with AS, 24 had bicuspid aorta, 10 had rheumatic AS, and the rest 9 had degenerative AS. Mean age of the patients with bicuspid aorta and rheumatic AS was similar (48.3 ± 8.0 vs. 47.9 ± 10.1 , $P > 0.05$) but patients with degenerative AS were significantly older (65.4 ± 5.3 , $P < 0.01$). Only five of the patients with rheumatic AS had fibrotic mitral valves but none of them had significant mitral valve regurgitation or stenosis. All the other echocardiographic findings were similar among AS patients with different aetiologies.

All the time domain HR variability parameters except mean RR interval, RMSSD, and pNN50 were significantly lower in the AS group. LFnu and LF/HF ratio were higher and HFnu was lower indicating an altered sympatovagal balance in AS group. All the patients with AS had enough number of ventricular ectopic beats for analysis of HR turbulence. HR turbulence parameters were also found to be depressed in AS. Among them, turbulence onset was

Table 3 Correlation between echocardiographic findings and indices derived from 24 h ECG findings in patients with aortic stenosis

	LVMI		IVRT		MPI		Em/Am ratio		E/Em ratio		Mean gradient		Maximum gradient		AVA	
	r	P-value	r	P-value	r	P-value	r	P-value	r	P-value	r	P-value	r	P-value	r	P-value
SDNN (ms)	-0.37	0.031	-0.46	0.002	-0.49	0.001	0.49	0.001	-0.50	0.001	-0.14	0.37	-0.10	0.53	0.18	0.25
SDANN (ms)	-0.33	0.033	-0.38	0.011	-0.34	0.028	0.29	0.06	-0.43	0.004	-0.21	0.18	-0.16	0.31	0.24	0.10
Triangular index	-0.34	0.039	-0.36	0.017	-0.44	0.003	0.405	0.007	-0.43	0.005	-0.17	0.28	-0.19	0.23	0.23	0.11
SDNN index (ms)	-0.44	0.001	-0.36	0.018	-0.40	0.008	0.34	0.028	-0.29	0.06	-0.20	0.21	-0.16	0.32	0.20	0.19
LFnu	0.34	0.041	0.36	0.017	0.53	0.001	-0.30	0.049	0.34	0.028	-0.08	0.58	-0.09	0.56	0.11	0.47
HFnu	-0.45	0.001	-0.19	0.233	-0.243	0.116	0.25	0.10	0.04	0.78	0.19	0.22	0.23	0.15	-0.09	0.57
LF/HF ratio	0.40	0.011	0.33	0.029	0.45	0.002	-0.27	0.08	0.21	0.17	0.02	0.91	-0.01	0.96	-0.13	0.41
Turbulence onset (%)	0.44	0.003	0.63	0.001	0.5	0.001	-0.45	0.001	0.27	0.08	-0.02	0.88	0.01	0.94	0.05	0.73
Turbulence slope (ms/RR)	-0.21	0.11	-0.12	0.438	0.01	0.934	-0.17	0.26	-0.14	0.39	-0.21	0.11	-0.2	0.10	0.25	0.10

Am, late diastolic mitral annular velocity obtained from tissue Doppler; AVA, aortic valve area; E, early peak mitral velocity obtained from pulsed Doppler; Em, early diastolic mitral annular velocity obtained from tissue Doppler; HF, high frequency power; HFnu, normalized high frequency power; IVRT, isovolumic relaxation time; LF, low frequency power; LVMI, left ventricular mass index; LFnu, normalized low frequency power; MPI, myocardial performance index; SDNN, standard deviation of the average normal-to-normal intervals calculated over 5 min periods of the entire recording; SDNN, standard deviation of all normal-to-normal intervals.

the one which reached statistical significance between two groups. Some representatives of these parameters are shown in *Figure 1*.

None of the individuals in the control group had a sign of diastolic dysfunction and left ventricular hypertrophy. All these individuals had E/A ratio > 1 and none had LV hypertrophy, even hypertension. Echocardiographic findings of patients with AS are summarized in *Table 2*. Among patients with AS, LVMI, IVRT, MPI, E_m/A_m ratio, and E/ E_m ratio had significant correlations with some of the HR variability and HR turbulence parameters (*Table 3*). LVMI, MPI, and E_m/A_m ratio had the strongest correlations when compared with other parameters. No correlation was observed between AVA, transvalvular gradients, and HR variability and HR turbulence parameters (*Table 3*). The correlations between SDNN, turbulence onset, and some echocardiographic parameters are highlighted in *Figures 2* and *3*.

Multivariate analysis was performed to show whether the two groups differ in individual HR variability and turbulence indices when adjusted for differences in LVMI. The results are shown in *Table 4*. Frequency domain HR variability parameters were still significantly deranged in AS, but

turbulence onset, SDNN, and SDANN were not different between the two groups after adjustment for LVMI.

Discussion

To the best of our knowledge, this study is the first to explore HR variability and HR turbulence parameters in asymptomatic patients with mild-to-moderate AS. Altered sympathovagal balance, as shown by disturbed HR variability and HR turbulence, was observed in these patients and this alteration was found to be correlated with echocardiographic findings of diastolic dysfunction like MPI, E_m/A_m ratio, and LVMI but not those of AS severity like AVA and transaortic pressure gradient.

Mild-and-moderate AS, once assumed to be a relatively benign condition, has been shown to have 1.8 times higher mortality when compared with controls in a recent study.¹ Our results may support this finding because decreased HR variability and HR turbulence indices are associated with increased mortality in several disease states especially in patients with systolic dysfunction.²⁻⁵

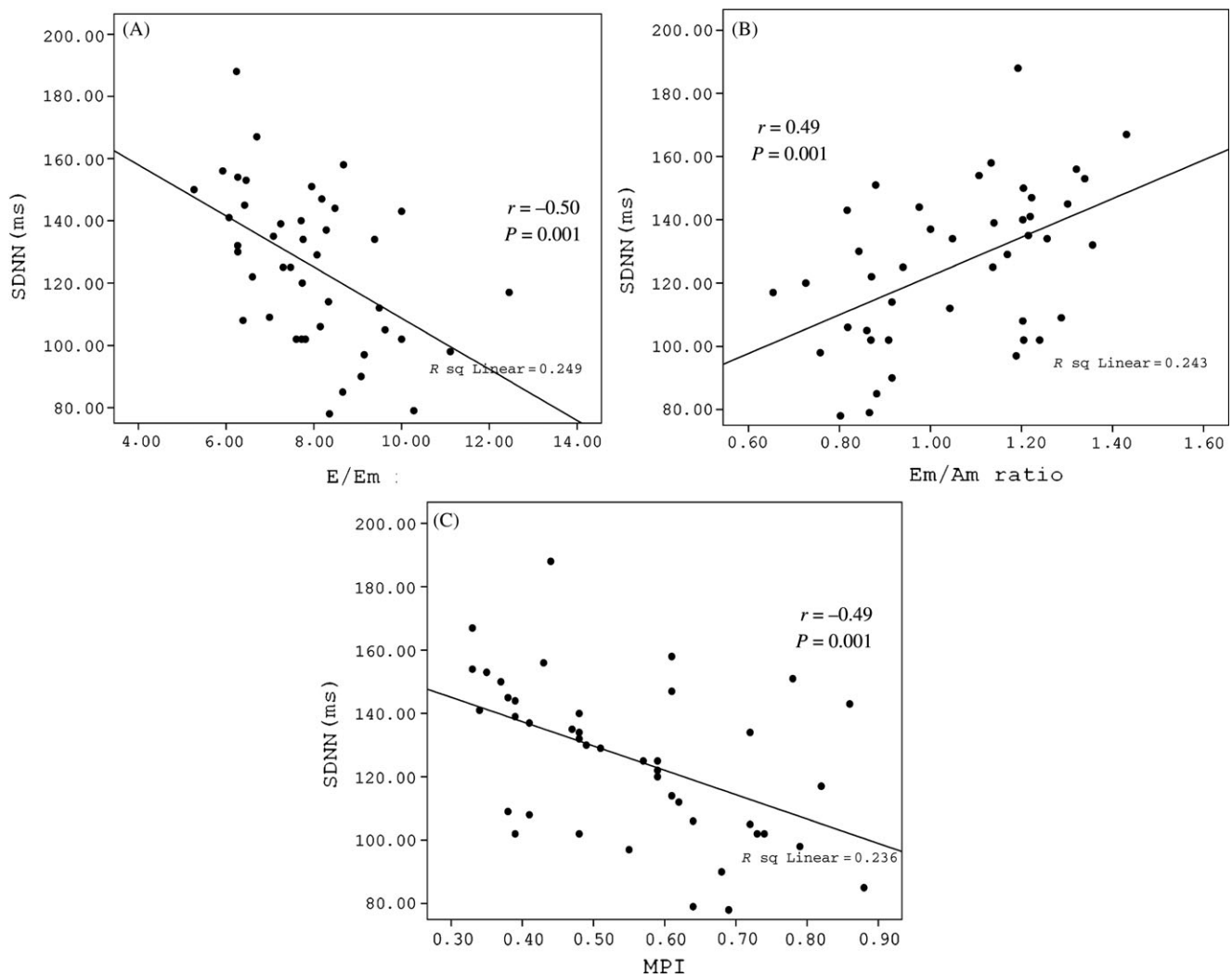


Figure 2 The correlations between SDNN and some echocardiographic parameters in aortic stenosis. Am, late diastolic mitral annular velocity obtained from tissue Doppler; E, early peak mitral velocity obtained from pulsed Doppler; Em, early diastolic mitral annular velocity obtained from tissue Doppler; MPI, myocardial performance index; SDNN, standard deviation of all normal-to-normal intervals.

Depression of HR variability parameters have been shown to be improved 1 year after valvular replacement in patients with severe AS.⁶ In another study,⁷ decreased HR variability parameters was found to be further decreasing 1 week after aortic valve replacement. Both of these studies include patients with severe and symptomatic AS requiring surgery. To our knowledge, no previous study has focused on HR variability and HR turbulence in the setting of asymptomatic mild-to-moderate AS.

Among the time domain HR variability parameters, SDNN, SDANN, and SDNN index were found to be decreased in mild-to-moderate AS. The effect of short-term respiratory variations in HR which is assumed to be vagally mediated is very low, and these parameters are thought to be mostly effected by the sympathetic system activity.¹¹ LF/HF ratio, LFnu, and the frequency of ventricular ectopic beats were found to be higher in patients with AS when compared with controls. HFnu and turbulence onset, two other parameters mostly related to parasympathetic activity, were also found to be disturbed in AS patients. These findings constitute evidence for autonomic dysfunction characterized

by sympathovagal imbalance which may lead to arrhythmic complications like ventricular tachycardia, ventricular fibrillation, and sudden death in mild-to-moderate AS. RMSSD and pNN50 which are supposed to be quite robust parameters of vagally mediated HR variability were similar in AS and control groups in our study. Alter *et al.*¹² found even increased RMSSD and similar pNN50 values in AS. This is a surprising finding in our study which needs further evaluation.

Heart rate turbulence which is a relatively new index of autonomic dysfunction has never been studied in diastolic dysfunction and AS. It is a reliable indicator of baroreceptor sensitivity.^{10,13} Turbulence onset denotes the acceleration of sinus rate immediately after a ventricular premature beat and is known to be due to vagal withdrawal.¹⁴ This phenomenon was found to be significantly depressed in our patients with mild-moderate AS. Additionally, increased sympathetic tonus at basal conditions may also blunt the vagal withdrawal. Turbulence slope, which is mediated by both sympathetic and parasympathetic activity was also disturbed in our patient group, albeit to a statistically

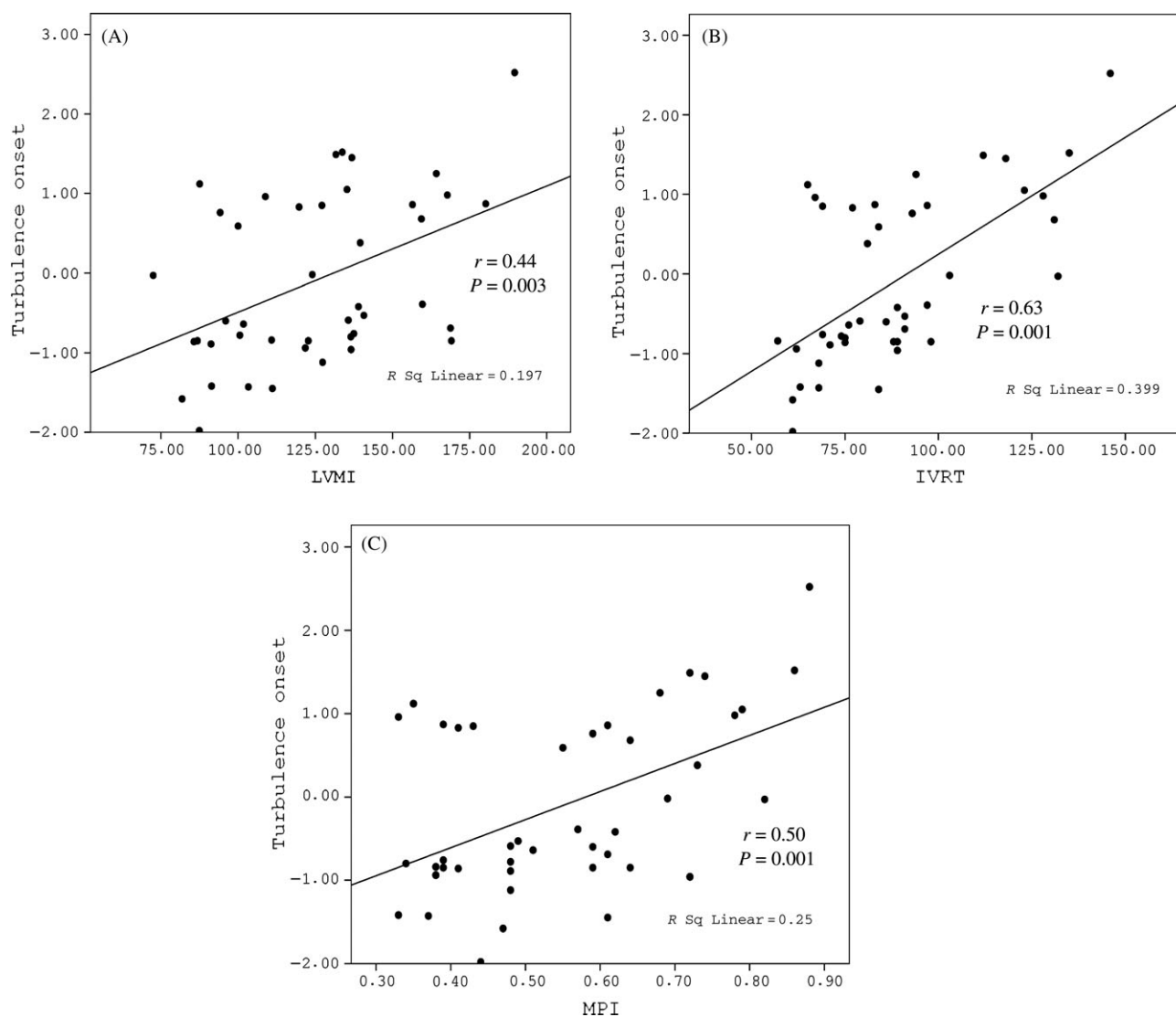


Figure 3 The correlations between turbulence onset and some echocardiographic parameters in aortic stenosis. IVRT: Isovolumic relaxation time, LVMI: Left ventricular mass index, MPI: Myocardial performance index.

Table 4 The heart rate variability and turbulence indices after adjustment for left ventricular mass index

	Aortic stenosis (n = 43)	Control group (n = 50)	P-value
Time domain HR variability			
SDNN (ms)	132.9 ± 3.7	135.4 ± 3.4	0.657
SDANN (ms)	115.9 ± 3.5	121.0 ± 3.2	0.346
SDNN index (ms)	48.7 ± 2.2	58.5 ± 2.0	0.005
Triangular index	33.8 ± 1.9	39.2 ± 1.7	0.07
Frequency domain HR variability			
LFnu	21.1 ± 1.1	27.1 ± 1.2	0.001
HFnu	10.0 ± 0.5	12.1 ± 0.4	0.003
LF/HF ratio	3.5 ± 0.2	2.2 ± 0.2	<0.001
Heart rate turbulence			
Turbulence onset	−0.38 ± 0.16	−0.36 ± 0.14	0.915
Turbulence slope (ms/RR)	4.93 ± 0.62	6.73 ± 0.56	0.062

Adjustment for left ventricular mass index was performed by analysis of covariance.

HF, high frequency power; HFnu, normalized high frequency power; LF, low frequency power; LFnu, normalized low frequency power; SDANN, standard deviation of the average normal-to-normal intervals calculated over 5 min periods of the entire recording; SDNN, standard deviation of all normal-to-normal intervals.

non-significant degree. As a result, we can prove the sympathovagal imbalance in AS also with these HR turbulence parameters.

Another important finding of our study is the correlation between echocardiographic indices of diastolic dysfunction and HR variability and HR turbulence parameters. The relationship between left ventricular hypertrophy and decreased HR variability parameters was previously shown by Mandawat *et al.*¹⁵ In a recent study,¹² these parameters were only related to age and LV mass regardless of the aetiology of left ventricular hypertrophy. In our study, the correlation between some indices of diastolic dysfunction and HR variability and HR turbulence parameters was demonstrated for the first time and the strongest correlation was found between LVMI, MPI, Em/Am ratio, and HR variability and HR turbulence parameters. More importantly, no correlation was observed between echocardiographic indices of AS severity (transaortic pressure gradient and AVA) and HR variability and HR turbulence parameters. This means that the development and the degree of diastolic dysfunction *per se*, regardless of the severity of AS, is correlated with autonomic dysfunction in patients with mild-to-moderate AS. Even these correlations do not imply necessarily a 'cause and effect' relationship; close follow-up of patients who develop echocardiographically evident diastolic dysfunction for especially arrhythmic complications due to autonomic dysfunction may be necessary.

On multivariate analysis, after adjustment for LVMI, turbulence onset, SDNN, and SDANN were similar in both groups, but some parameters of autonomic dysfunction were still different between the two groups. Accordingly, we can conclude that SDNN, SDANN, and turbulence onset were mainly affected from evolving diastolic dysfunction, but frequency domain HR variability parameters and

turbulence slope were altered independently of LV hypertrophy.

Currently no specific therapy is recommended for patients with mild and moderate AS,⁸ however measurement of HR variability and turbulence parameters in AS seems to be promising to determine patients at risk of arrhythmia. Those patients who have deranged HR variability and turbulence parameters may be treated with beta blockers to correct the sympathovagal imbalance and therapeutic effect of these agents may be monitored by subsequent HR variability and HR turbulence measurements.¹⁶

There are several limitations of our study. First of all, the population size is small because our aim was to study the HR variability and turbulence parameters in patients with 'pure' AS, a patient subset not so easy to find. Secondly, the number of ventricular premature beats was more than expected in the control group. The reason was that individuals who had <5 extrasystoles were not enrolled in the study. A final limitation is that Doppler and tissue Doppler indices of diastolic dysfunction were not available in control subjects so that multivariate analysis was performed using LVMI only.

In conclusion, sympathovagal imbalance indicated by disturbed HR variability and HR turbulence was demonstrated for the first time in patients with mild-to-moderate AS in our study. Being a predictor of arrhythmic complications, this finding opens a discussion on the presumably benign prognosis of these patients. The correlation of disturbed HR variability and turbulence with echocardiographic indices of diastolic dysfunction but not with those of AS severity is a finding that deserves future research, but still poses a clinical demand for close follow-up of patients with mild-moderate degree AS and echocardiographic findings of diastolic dysfunction.

Conflict of interest: none declared.

References

- Rosenhek R, Klaar U, Schemper M, Scholten C, Heger M, Gabriel H *et al.* Mild and moderate aortic stenosis. Natural history and risk stratification by echocardiography. *Eur Heart J* 2004;25:199–205.
- Camm AJ, Malik M, Bigger JT, Breithardt G, Cerutti S, Cohen RJ *et al.* Task Force of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology. Heart rate variability: Standards of measurement, physiological interpretation, and clinical use. *Eur Heart J* 1996;17:354–81.
- Schmidt G, Malik M, Barthel P, Schneider R, Ulm K, Rolnitzky L *et al.* Heart-rate turbulence after ventricular premature beats as a predictor of mortality after acute myocardial infarction. *Lancet* 1999;353:1390–6.
- Barthel P, Schneider R, Bauer A, Ulm K, Schmitt C, Schomig A *et al.* Risk stratification after acute myocardial infarction by heart rate turbulence. *Circulation* 2003;108:1221–6.
- Koyama J, Watanabe J, Yamada A, Koseki Y, Konno Y, Toda S *et al.* Evaluation of heart-rate turbulence as a new prognostic marker in patients with chronic heart failure. *Circ J* 2002;66:902–7.
- Vukasovic JL, Florenzano F, Adiazola P, Escobar E. Heart rate variability in severe aortic stenosis. *J Heart Valve Dis* 1999;8:143–8.
- Jung J, Heisel A, Tscholl D, Butz B, Fries R, Schafer HJ *et al.* Factors influencing heart rate variability in patients with severe aortic valve disease. *Clin Cardiol* 1997;20:341–4.
- Bonow RO, Carabello BA, Kanu C, de Leon AC Jr, Faxon DP, Freed MD *et al.* ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease): developed in collaboration with the Society

- of Cardiovascular Anesthesiologists: endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. *Circulation* 2006;**114**:e84-231.
9. Devereux RB, Reichek N. Echocardiographic determination of left ventricular mass in man. Anatomic validation of the method. *Circulation* 1977;**55**:613-8.
 10. Guzik P, Schmidt G. A phenomenon of heart-rate turbulence, its evaluation, and prognostic value. *Card Electrophysiol Rev* 2002;**6**:256-61.
 11. Kleiger RE, Stein PK, Bosner MS, Rottman JN. Time domain measurements of heart rate variability. *Cardiol Clin* 1992;**10**:487-98.
 12. Alter P, Grimm W, Vollrath A, Czerny F, Maisch B. Heart rate variability in patients with cardiac hypertrophy—relation to left ventricular mass and etiology. *Am Heart J* 2006;**151**:829-36.
 13. Lin LY, Lai LP, Lin JL, Du CC, Shau WY, Chan HL *et al*. Tight mechanism correlation between heart rate turbulence and baroreflex sensitivity: sequential autonomic blockade analysis. *J Cardiovasc Electrophysiol* 2002;**13**:427-31.
 14. Wichterle D, Melenovsky V, Simek J, Malik J, Malik M. Hemodynamics and autonomic control of heart rate turbulence. *J Cardiovasc Electrophysiol* 2006;**17**:286-91.
 15. Mandawat MK, Wallbridge DR, Pringle SD, Riyami AA, Latif S, Macfarlane PW *et al*. Heart rate variability in left ventricular hypertrophy. *Br Heart J* 1995;**73**:139-44.
 16. Brouwer J, Viersma JW, van Veldhuisen DJ, Man in 't Veld AJ, Sijbring P, Haaksma J *et al*. Usefulness of heart rate variability in predicting drug efficacy (metoprolol vs diltiazem) in patients with stable angina pectoris. *Am J Cardiol* 1995;**76**:759-63.