# Sympathetic Overactivity in Patients with Rheumatic Mitral Stenosis

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**Background:** Mitral stenosis may increase sympathetic nervous activity by increasing left atrial pressure and reducing cardiac output. And elevated sympathetic nerve activity may be a risk factor for the development of clinical manifestations of mitral stenosis. In this study, we assessed the autonomic nervous system activity in patients with mitral stenosis by heart rate variability analysis and defined factors affecting autonomic functions.

**Methods and Results:** Fifty-four patients with rheumatic mitral stenosis were compared with an age- and gender-matched control group composed of 42 healthy individuals. SDNN, RMSSD, PNN50, and HF were lower; mean heart rate (HR), LF and LF/HF ratio were higher in the patients with mitral stenosis compared to the control group. SDNN was correlated positively with left ventricle ejection fraction (LVEF), negatively with mitral valve area, left atrial (LA) diameter, and duration of symptoms. RMSSD was correlated positively with mean transmitral gradient, negatively correlated with age; PNN50 was correlated negatively with mitral valve area and positively correlated with transmitral gradient. LF was positively and HF was negatively correlated with LA diameter; LF was correlated positively, and HF was negatively correlated with duration of symptoms. LF/HF ratio was positively correlated with LA diameter and duration of symptoms, negatively with LVEF and mean valve area.

**Conclusion:** As a result, sympathetic nervous system activity is increased in patients with mitral stenosis and sympathetic overactivity worsens their symptoms. Most significant factors that affect autonomic functions in these patients are left atrial dilatation and mitral valve area.

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mitral stenosis; sympathetic system; heart rate variability

Mitral stenosis may increase sympathetic nervous activity by increasing left atrial pressure that alters pulmonary hemodynamics and reduces cardiac output similar to congestive heart failure.[1,2] Increased sympathetic activity may lead to atrial thrombus formation by precipitating platelet aggregation,[3] may promote pulmonary congestion by stimulating renin release from the kidney,[4] increase pulmonary arterial resistance,[5] and shorten the diastolic filling period by increasing heart rate.[2] Therefore, elevated sympathetic nerve activity may be a risk factor for the development of clinical manifestations of mitral stenosis.

Heart rate variability (HRV) analysis has been extensively used to evaluate autonomic modulation of sinus node and to identify patients at risk for an increased cardiac mortality.[6] HRV analysis is shown to reflect a sympatho-vagal balance and used previously to define the role of autonomic nervous system activity in certain cardiac disorders.[7,8] In this study, we assessed autonomic nervous system activity in patients with mitral stenosis by HRV analysis and defined factors affecting autonomic functions.

## MATERIAL AND METHODS

### Patients

Fifty-four consecutive patients with mitral stenosis and sinus rhythm being evaluated for percutaneous mitral commissurotomy between January 2002 and November 2003 were enrolled in the

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study. All clinical, echocardiographic, and HRV analysis data were collected prospectively. Patients with more than mild mitral regurgitation, significant aortic valve disease, mitral valve prolapse, coronary heart disease, diabetes mellitus, hypertension, thyroid disorders were excluded from the study. A control group was composed of healthy individuals evaluated in our polyclinics subsequently. Dyspnea was the major complaint in the patients and classified according to American Thoracic Society Scale of Dyspnea.[9]

### Transthoracic Echocardiography

The transthoracic studies were done by a standard technique using Vingmed System Five machine with a 2.5-MHz probe. M-mode measurements were taken according to the recommendations of the American Society of Echocardiography.[10] The mitral valve area was measured by continuous-wave Doppler using the pressure half-time method. The mean transmitral diastolic pressure gradient was estimated from the maximal transmitral flow velocity using a modified Bernoulli equation. Left atrial diameter was taken in the parasternal long-axis view in M-mode at endsystole. The measurements were made in three beats. Mitral regurgitation was graded by color Doppler echocardiography as recommended by Helmcke et al.[11]

### Heart Rate Variability Analysis

All patients underwent 3-channel 24-hour Holter ambulatory ECG monitoring (Biomedical System Century 2000/3000 Holter System, Version 1.32). Recordings were analyzed by "Biomedical Systems Century 2000/3000 HRV Package System," following manual adjustment of R-R intervals. Patients were instructed to behave in a normal manner with usual daily physical activity. Analog data were digitized at 200 Hz and edited by a cardiologist. The validation procedure consisted of beat labeling and tagging of noisy regions. The continuous series of R-R intervals (tachogram) was obtained and all 5-min segments with at most five isolated ectopic beats were retained for spectral analysis. Recordings with <18 hours of data or <85% of qualified sinus beats were excluded. The time and frequency domain analysis of HRV was performed according to the recommendation of the task force.[6] The mean heart rate, standard deviation of all N-N intervals (SDNN), root mean square of successive differences (RMSSD), number of N-N intervals that differed by more than 50 milliseconds from adjacent interval divided by the total number of all N-N intervals (PNN50) were measured in the time domain analysis of HRV. A reduced SDNN has been considered to reflect a diminished vagal and an increased sympathetic modulation of the sinus node.[6] The power spectrum of HRV was measured using fast-Fourier transform analysis in four frequency bands: <0.0033 Hz (ultra low frequency, ULF), 0.0033 to 0.04 (very low frequency, VLF), 0.04 to 0.15 (low frequency, LF), and 0.15 to 0.40 (high frequency, HF). HF was used as a marker of a parasympathetic nervous system and LF was used a marker of sympathetic activity.[6] The power of these components was stated as a normalized unit (nu). The normalization procedure is crucial for the interpretation of data.[12] We also measured the ratio of low-to-high frequency power (LF/HF) reflecting the sympathovagal balance. High values (>2) were considered to reflect a shift of sympathovagal balance toward a sympathetic predominance.[12] For frequency domain parameters three circadian periods were considered, the complete 24 hours, and the diurnal and nocturnal periods defined on the basis of patient diaries. Diurnal periods covered lengths of at least 6 hours to a maximum of 10 hours; nocturnal periods covered a minimum of 4 hours to a maximum of 6 hours. Normalized LF and HF components were defined dividing the corresponding raw power by total power minus the power in the VLF band [LFnu = LF/(TP − VLF)]. All drugs that may affect HRV analysis were withheld for at least five half-times.

### Statistical Analysis

Continuous variables are presented as mean ± SD and discrete variables are expressed as frequencies and percentages. For continuous variables, differences between patients with and without CAVB were tested using Student's *t*-test, and for categorical variables chi-square (or Fischer's exact test) was used. Pearson's correlation analysis was performed to define the correlation between echocardiographic, clinic parameters, and heart rate variability.

## RESULTS

Fifty-four patients (16 male and 38 female) with rheumatic mitral stenosis were enrolled in the

**Table 1.** Echocardiographic Findings of the Patients with Mitral Stenosis

| | Mean | Range |
|---|---|---|
| Mitral valve area ($cm^2$) | 1.03 ± 0.1 | 0.8 |
| Transmitral mean gradient (mmHg) | 13.7 ± 3.3 | 8 |
| Systolic pulmonary arterial pressure (mmHg) | 50.6 ± 9.1 | 35 |
| Left atrial diameter (cm) | 4.4 ± 0.26 | 3.8 |
| Left ventricle ejection fraction (%) | 61.8 ± 3.3 | 55 |
| Mitral regurgitation | Minimal 24/54 (44.4%) 106/54 (11.1%) | |

study and compared with a control group composed of 42 healthy individuals (14 male and 28 female). Echocardiographic findings of the patients with mitral stenosis are given in Table 1. All the patients were symptomatic for a mean duration of 18.8 ± 7.7 months. There were no significant differences between the two groups as to age and gender. But SDNN, RMSSD, PNN50, and HF (day, night, and 24 hours) were lower, mean heart rate (HR), LF (day, night, and 24 hours) and LF/HF (day, night, and 24 hours) ratios were higher in patients with mitral stenosis compared to the control group (Table 2).

Mean HR was positively correlated with age (r = 0.3) and duration of symptoms (r = 0.4). SDNN was found to be correlated positively with LVEF (r = 0.6), negatively with mitral valve area (r = −0.5), left atrial diameter (r = −0.3), and duration of symptoms (r = −0.7). RMSSD was correlated positively with mean transmitral gradient (r = 0.4), negatively correlated with age; PNN50 was correlated negatively with mitral valve area (r = −0.5) and positively correlated with mean transmitral gradient (r = 0.4). LF was positively correlated (r = 0.6) and HF was negatively (r = −0.6) correlated with LA diameter; LF was correlated positively (r = 0.6) and HF was negatively correlated (r = −0.7) with duration of symptoms. LF / HF ratio reflecting sympathovagal balance was positively correlated with LA diameter (r = 0.7) and duration of symptoms (r = 0.7), negatively correlated with LVEF (r = −0.5) and mean valve area (r = −0.6). Symptoms of the patients were positively correlated with mean HR (r = 0.6), LF (r = 0.6), LF/HF (r = 0.5) and negatively correlated with SDNN (r = −0.5) (Table 3).

## DISCUSSION

Sympathetic activity may be increased in association with a reduction in cardiac index in patients with mitral stenosis since a significant

**Table 2.** Comparison of Clinical Characteristics and Heart Rate Variability Parameters of Patients with Mitral Stenosis and Control Group

| Variables | Control (n = 42) | Mitral Stenosis (n = 54) | P |
|---|---|---|---|
| Age (years) | 28.4 ± 8.9 | 30.9 ± 11.0 | 0.3 |
| M/F | 14/28 | 16/38 | 0.4 |
| Mean HR (beats/min) | 68.0 ± 9.0 | 76.1 ± 10.9 | 0.001 |
| SDNN (ms) | 138.2 ± 12.2 | 105.0 ± 59.4 | 0.001 |
| RMSSD (ms) | 50.6 ± 18.9 | 40.4 ± 25.9 | 0.01 |
| PNN50 (%) | 24.9 ± 10.8 | 15.3 ± 10.7 | 0.01 |
| Day | | | |
| LFnu | 62.6 ± 9.6 | 80.1 ± 3.5 | 0.001 |
| HFnu | 35.5 ± 7.8 | 18.9 ± 6.2 | 0.001 |
| LF/HF | 2.7 ± 0.6 | 4.5 ± 0.8 | 0.001 |
| Night | | | |
| LFnu | 52.8 ± 8.1 | 68.9 ± 4.4 | 0.001 |
| HFnu | 45.8 ± 6.7 | 30.4 ± 5.2 | 0.01 |
| LF/HF | 1.2 ± 0.4 | 2.8 ± 0.4 | 0.001 |
| 24 Hours | | | |
| LFnu | 56.8 ± 8.8 | 77.4 ± 6.1 | 0.001 |
| HFnu | 38.8 ± 7.8 | 22.6 ± 6.2 | 0.01 |
| LF/HF | 1.7 ± 0.8 | 3.8 ± 1.8 | 0.001 |

M = male; F = female; HR = heart rate.

decrease in stroke index has been related to sympathetic activation in patients with congestive heart failure.[13,14] However, increased left atrial or pulmonary arterial pressure may alter sympathetic activity through cardiopulmonary mechanisms.[2] A reduction in afferent activity from the baroreceptor is considered a possible cause of sympathetic activation.[15,16] Ashino et al.[2] demonstrated that arterial and cardiopulmonary baroreflex are impaired in patients with mitral stenosis and this impaired baroreflex sensitivity is normalized after mitral balloon valvuloplasty. They concluded that central sympathetic outflow to the skeletal muscle was increased mainly due to a reduction in cardiac output that decreases afferent activity from the baroreceptors. Similarly, we found that SDNN and LF/HF ratio are moderately correlated with left ventricle ejection fraction. Yuasa et al. also found that muscle sympathetic activity and plasma norepinephrine concentrations are significantly decreased and cardiopulmonary baroreflex sensitivity is improved after percutaneous mitral balloon valvuloplasty[17] in accordance with Ashino et al. However, there was no significant correlation between cardiopulmonary baroreflex sensitivity and hemodynamic parameters such as arterial pressure, heart rate, cardiac output, mean capillary wedge pressure, right atrial pressure, and left ventricular end-diastolic pressure. They claimed that a functional rather than anatomic abnormality is more likely to be important in the pathogenesis of cardiopulmonary baroreflex abnormalities and improvement in cardiopulmonary baroreflex sensitivity may contribute to the attenuation of sympathetic activity after mitral valvuloplasty.

Plasma norepinephrine concentrations at rest are found to be similar in patients with mitral stenosis and the control subjects.[2,18] However, plasma norepinephrine concentrations are considered a relatively insensitive index of sympathetic activity since only small amounts of norepinephrine released from peripheral nerve endings reach systemic circulation.[19,20] In addition, norepinephrine clearance is found to be increased in patients with cardiac dysfunction and low cardiac output.[21] But Ashino et al.[2] demonstrated that plasma norepinephrine concentrations decreased significantly after balloon valvuloplasty suggesting a generalized reduction in sympathetic activity after valvuloplasty. Moreover, mitral valvuloplasty significantly decreases the

**Table 3.** Correlation Between Heart Rate Variability Parameters and Echocardiographic Variables

| | MVA | Mean Gradient | SPAP | LA Diameter | LVEF | Age | Duration of Symptoms | Symptom Class |
|---|---|---|---|---|---|---|---|---|
| HR | r = −0.05, P = 0.6 | r = 0.15, P = 0.3 | r = 0.2, P = 0.1 | r = 0.1, P = 0.1 | r = 0.2, P = 0.3 | r = 0.3, P = 0.005 | r = 0.4, P = 0.02 | r = 0.6, P = 0.001 |
| SDNN | r = −0.5, P = 0.005 | r = 0.15, P = 0.3 | r = 0.13, P = 0.4 | r = −0.3, P = 0.01 | r = 0.6, P = 0.006 | r = −0.05, P = 0.7 | r = −0.6, P = 0.001 | r = −0.5, P = 0.001 |
| RMSSD | r = −0.1, P = 0.4 | r = 0.4, P = 0.001 | r = 0.14, P = 0.3 | r = 0.09, P = 0.5 | r = 0.2, P = 0.2 | r = −0.3, P = 0.03 | r = −0.3, P = 0.08 | r = −0.3, P = 0.2 |
| PNN50 | r = −0.5, P = 0.005 | r = 0.4, P = 0.007 | r = 0.1, P = 0.5 | r = 0.02, P = 0.9 | r = 0.2, P = 0.3 | r = −0.2, P = 0.1 | r = −0.3, P = 0.08 | r = −0.2, P = 0.08 |
| LF | r = 0.01, P = 0.9 | r = 0.1, P = 0.5 | r = 0.08, P = 0.6 | r = 0.6, P = 0.001 | r = −0.3, P = 0.08 | r = 0.2, P = 0.8 | r = 0.6, P = 0.001 | r = 0.6, P = 0.001 |
| HF | r = −0.01, P = 0.9 | r = −0.1, P = 0.5 | r = −0.08, P = 0.6 | r = −0.6, P = 0.001 | r = 0.2, P = 0.08 | r = 0.1, P = 0.9 | r = −0.7, P = 0.001 | r = 0.2, P = 0.3 |
| LF / HF | r = −0.6, P = 0.001 | r = 0.08, P = 0.9 | r = −0.06, P = 0.6 | r = 0.7, P = 0.001 | r = −0.5, P = 0.04 | r = 0.3, P = 0.2 | r = 0.7, P = 0.001 | r = 0.5, P = 0.001 |

MVA = Mean valve area; SPAP = Systolic pulmonary arterial pressure; LA = left atrium; HR = heart rate.

increase in norepinephrine concentrations during exercise.[18]

We found that HRV parameters reflecting sympathetic activity are increased and HRV parameters reflecting parasympathetic activity are decreased with an increase in left atrial diameter. Stretching the right atrium produces an acceleration of the heart and a definite increase in sympathetic nerve activity.[22] But left atrial stretch causes biphasic responses: an initial sympathetic nerve inhibition and slower heart beat followed by sympathetic excitation and heart acceleration. Vagal activity, which was greatly augmented by sinus distension, was decreased by atrial stretch, while previously inhibited sympathetic activity due to sinus distension was augmented by stretch of the atrium. The effect of stretch on vagal activity seems to depend to a degree on the prestimulus level.[22,23] Therefore, chronic atrial stretch may explain the sympathetic overactivity in patients with mitral stenosis. However, effects of hormonal factors are contradictory. In patients with mitral stenosis, atrial natiruretic peptide (ANP) is augmented.[24] But ANP exerts a sympathoinhibitory action in heart failure and normal men.[25,26] ANP may play an important role in cardiovascular regulation by influencing sympathetic nerve activity and heart rate in addition to the direct vasodilating and renal effects.[27] Brunner et al.[28] demonstrated a sympathoinhibitory effect of brain natriuretic peptide (BNP) at BNP concentrations within the physiologic range, whereas high-dose BNP, when arterial and filling pressures fell and reflex sympathetic stimulation is expected, systemic and cardiac sympathetic nervous activity equates to baseline values. Whether this effect is specific to BNP or related to reduced filling pressure remains to be determined. Similarly, intravenous arginine vasopressin at lower doses is shown to inhibit renal sympathetic activity by causing excitation of the nucleus tractus solitarii neurons.[29]

As a result, sympathetic nervous system activity is increased in patients with mitral stenosis and sympathetic overactivity worsen their symptoms. Most significant factors that affect autonomic functions in these patients are duration of symptoms, left atrial dilatation, and mitral valve area.

Lack of plasma norepineprine, ANP, and BNP measurements is the most significant limitation of the study.

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