Background: Heart rate variability (HRV) has been shown to be a useful measure of autonomic activity in healthy and mitral valve prolapsed (MVP) subjects. However, the effects of posture and gender on HRV in symptomatic MVP and normal adults had not been elucidated in Taiwan.

Methods: A total of 118 MVP patients (7 males, 39 ± 7 years old; and 111 females, 42 ± 13 years old) and 148 healthy control (54 males, 28 ± 4 years old; and 94 females, 26 ± 6 years old) were investigated. The diagnosis of MVP was confirmed by cross-sectional echocardiography. A locally developed Taiwanese machine was used to record the HRV parameters for MVP and control groups in three stationary positions. Thereafter, the HRV time-domain parameters, and the frequency-domain parameters derived from fast Fourier transform or autoregressive methods were analyzed.

Results: The MVP group showed a decrease in time domain parameters and obtunded postural effects on frequency domain parameters more so than the control group. Though the parasympathetic tone was dominant in female (higher RMSSD, nHF and lower nLF vs. male), the sympathetic outflow was higher in MVP female (lower SDNN, NNS50 and higher nLF vs. normal female). While the parasympathetic activity was lower in male, sympathetic outflow was dominant in MVP male (lower nHF and higher nLF vs. normal male).

Conclusions: Both MVP female and male subjects had elevated levels of sympathetic outflow. The obtunded postural effects on frequency domain measures testified to the autonomic dysregulation of MVP subjects.

Key Words: Arrhythmia • Autonomic nerve system • Heart rate variability • Mitral valve prolapse

INTRODUCTION

Mitral valve prolapse (MVP) is a common valvular heart disease characterized by the displacement of an abnormally thickened mitral valve leaflet in the left atrium during cardiac systole as a result of redundant leaflets or chordate tendinea.1,2 It is well-known that MVP is a heterogeneous disorder with varieties of pathological, clinical and echocardiographic manifestations.3,4 The overall prognosis of patients with MVP is excellent, but a small subset develops serious complications including pronounced mitral regurgitation, embolic stroke, infective endocarditis, and arrhythmia.5 It has been reported that MVP patients, especially when symptomatic, have an autonomic dysfunction which probably involves both the sympathetic and parasympathetic systems. A predominant sympathetic tone and diminished vagal activity in these patients is linked to the
pathogenesis of the disease and a consequence of emerging symptoms.\(^5\) Thus, finding a feasible modality to analyze the autonomic nervous system (ANS) of MVP victims seems to be of particular clinical importance.

Previous experimental evidence suggests that heart rate variability (HRV) is one of the useful methods in evaluating the autonomic modulation of the heart to quantify risk in a wide variety of both cardiac and non-cardiac disorders.\(^7,8\) HRV measures the variations of the time intervals between consecutive heartbeats, which vary mostly under control of the ANS.\(^9,10\) When the time intervals between consecutive heartbeats, which tell different discriminating power, respectively.\(^7,14,15\) Autoregressive (AR) analyses provided a similar but sub-synergistic and increased adrenergic activities than control.\(^19\) Therefore, previous studies examining gender differences in autonomic regulation demonstrate that women have significantly greater parasympathetic input to cardiac regulation than do age-matched men.\(^16-18\) In contrast, a study of women with the MVP syndrome demonstrated an autonomic dysfunction with decreased parasympathetic and increased adrenergic activities than control.\(^19\) Therefore, previous studies examining gender differences in healthy populations report contradictory findings from MVP victims. Furthermore, ANS is also affected by different stationary postures (e.g. lying down, sitting and standing) which modulate the balance of sympathetic and parasympathetic input of the heart. Parasympathetic nerves are more active in the lying position, and sympathetic nerves are augmented in an orthostatic position. A change of posture in male or female with or without MVP would present a variety of autonomic modulations.

Therefore, our study aimed to compare the autonomic balance of three different stationary postures between males and females, with or without MVP, based on short-term HRV analysis. In addition, we also tested the correlation between parameters measured by FFT and AR methods, respectively.

**MATERIALS AND METHODS**

**Subjects**

Patients who had disorders such as ischemic or rheumatic heart disease, diabetes mellitus, thyroid disorders, stenotic valvular heart disease, severe left ventricular dysfunction, patients taking drugs affecting cardio-respiratory responses or alcohol were excluded (Table 1). All subjects were asked to avoid smoking and drinking any caffeinated beverages during the study. The protocol was consistent with the ethical guidelines of the Research Committee of Taipei Medical University and the relevant standards of the revised Declaration of Helsinki (1983). All participants gave informed consent.

<table>
<thead>
<tr>
<th>Table 1. Patient characteristics</th>
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<tbody>
<tr>
<td>MVPMale</td>
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<tr>
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<tr>
<td>Age (yrs)*</td>
</tr>
<tr>
<td>MR (+)</td>
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<tr>
<td>LA (mm)*</td>
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<tr>
<td>LVEDD (mm)*</td>
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<tr>
<td>LVESD (mm)*</td>
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<td>LV EF (%)*</td>
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<tr>
<td>Diabetes mellitus</td>
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<td>Hypertension</td>
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<tr>
<td>Systolic BP (mmHg)*</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)*</td>
</tr>
<tr>
<td>ALT (U/L)*</td>
</tr>
<tr>
<td>Creatinine (mg/dl)*</td>
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</tbody>
</table>

* Values are mean ± SD.

ALT, alanine aminotransferase; Diastolic BP, diastolic blood pressure; LA, left atrial diameter; LVEDD, left ventricular end-diastolic diameter; LV EF, ejection fraction of left ventricle; LVESD, left ventricular end-systolic diameter; MR, mitral regurgitation; MVP, mitral valve prolapsed; SD, standard deviation; Systolic BP, systolic blood pressure.
A total of 118 MVP patients (7 males, 39 ± 7 years old and 111 females, 42 ± 13 years old) who had been diagnosed with MVP after evaluation by transthoracic echocardiography at Taipei Medical University Hospital cardiology clinic from November 2008 to January 2013. Another 148 healthy control (54 males, 28 ± 4 year-old and 94 females, 26 ± 6 year-old) who had normal 12-lead electrocardiogram (ECG) without previous history of medical disease from National Chiao-Tung University and residents in Hsinchu were recruited for the study.

**Echocardiography**

In all subjects, transthoracic two-dimensional and Doppler echocardiographic examinations were performed by experienced echocardiographers, using a Vivid 7 echocardiographic system (General Electric Ultrasound, US), using 2.5-3.5 MHz transducers. The measurements were obtained according to the standards of the American Society of Echocardiography, using the parasternal long axis and apical 4-chamber windows. The diagnosis of MVP was confirmed by cross-sectional echocardiography that showed definite prolapse (posterior/superior displacement) of anterior and/or posterior leaflet of the mitral valve beyond the plane of mitral annulus in the parasternal long-axis view and apical 4-chamber view. Prolapse of a leaflet in the apical 4-chamber view alone was excluded because of frequent false positive diagnoses due to non-planar or saddle-shaped mitral annulus. Classic prolapse was defined as superior displacement of the mitral leaflets, by more than 2 mm during systole, with a maximal leaflet thickness of at least 5 mm during diastole.2-4

**HRV recordings**

All the subjects were asked to rest for five minutes before each HRV recording (lying, sitting and standing). The recordings were all taken during the daytime (between 9:00 AM to 4:00 PM) to avoid the diurnal influence of the autonomic regulation. A locally developed Taiwanese machine (DailyCare BioMedical’s ReadMyHeart) was used to record the HRV parameters. One lead ECG (modified lead II, put the pad one on right shoulder and the other on left flank) was used for signal collection and analysis. The data were then exported as a text file to the HRV analysis software complying with guidelines recommended by the Taskforce of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology standards for measurement of HRV.7 The QRS complexes were detected and labeled automatically by the machine. The results of the automatic analysis were reviewed subsequently and the errors in R-wave detection or R-R were manually corrected for ectopic/missed beats. In the present study, manual editing or interpolation of the R-R intervals was performed using the following guidelines: if a significantly higher R-R interval (representing an ectopic beat) was noted, then that reading was deleted and the average of the two adjacent R-R intervals replaced the deleted one. If a significantly lower value (representing a missed beat) was noted, that R-R interval was deleted and replaced with the previous R-R interval. Once the R-R intervals were imported into the computed program, the software automatically analyzed the HRV in both time and frequency domains.

**Analysis of HRV**

HRV was assessed automatically by the machine from the calculation of the mean R-R interval and its standard deviation measured on short-term (5 minutes) electrocardiogram, normal-to-normal (NN) R-R interval data obtained from the edited time sequence of R-wave and QRS labeling were then transferred to a personal computer. The SDNN, RMSSD and NN50 were used for comparison of time-domain parameters.

For frequency domain HRV parameters analysis, spectral power was quantified by FFT and AR methods for the following frequency bands: total power (TP, ≤0.4Hz), very low frequency (VLF, 0.003-0.04Hz), low frequency (LF, 0.04-0.15Hz), high frequency (HF, 0.15-0.4 Hz), normalized low frequency (nLF), normalized high frequency (nHF) and LF/HF ratio. These parameters were defined in accordance with the 1996 ACC/AHA/ESC consensus.7

**Statistical analysis**

All HRV data were expressed as mean ± standard deviation (SD) and % ratio. A one-way repeated-measures analysis of variance (ANOVA) followed by Tukey’s post-hoc test was used to characterize changes in HRV variables between three stationary positions. The parameters between two groups were compared using Student’s t-test, and the normal distribution was proven by

469 Acta Cardiol Sin 2016;32:467–476
Kolmogorov-Smirnov test. A p value of < 0.05 was considered as statistically significant in all cases.

RESULTS

Postural effect on time domain parameters

As shown in Figure 1A, standing position decreased the SDNN, RMSSD and NN50 of normal adults and MVP subjects as compared with those parameters in the lying position, whereas sitting position also decreased RMSSD of normal adults and MVP subjects as compared with that in the lying position. The MVP subjects had decreased SDNN in all three positions, decreased RMSSD in sitting posture, and decreased NN50 in lying and sitting position as compared with normal adults, as shown in Figure 1B.

Postural effect on frequency domain parameters

As shown in Figure 2A, both sitting and standing position decreased the TP and nHF, and increased the nLF and LF/HF ratio as compare with lying position in normal adults. The similar postural effects were also found in MVP subjects except that the sitting position cannot decrease the TP in MVP subjects as it did in normal adults. Furthermore, FFT and AR methods show similar postural effects on all frequency-domain parameters in normal and MVP subjects. As shown in Figure 2B, the MVP subjects had lower TP in the lying position, but had higher TP in the sitting and standing position. MVP subjects also had higher nHF, lower nLF and LF/HF parameters in the sitting and standing positions. Both FFT and AR methods show similar results of all frequency domain in normal and MVP subjects.

Gender difference on time domain parameters

As shown in Figure 3A, normal and MVP female subjects had higher RMSSD and NN50 than male in a lying position. As shown in Figure 3B, MVP male had lower SDNN, RMSSD and NN50 in the lying position, lower RMSSD and NN50 in the sitting position than the normal male. Meanwhile, MVP females had lower SDNN in the sitting position and lower NN50 in both the lying and sitting positions than normal female.

![Figure 1](image)

**Figure 1.** Postural effects on time domain parameters in normal and MVP subjects. (A) Postural effects on SDNN, RMSSD and NN50 in normal adults (n = 148) and MVP subjects (n = 118). * p < 0.05, # p < 0.01, vs. lying position. (B) Comparison of SDNN, RMSSD and NN50 between normal (n = 148) and MVP subjects (n = 118). * p < 0.05, # p < 0.01, vs. normal adults. MVP, mitral valve prolapsed.
Gender difference on frequency domain parameters

As shown in Figure 4A, both FFT and AR methods revealed that normal female had higher nHF, lower nLF and LF/HF than normal male in all three positions. As shown in Figure 4B, both FFT and AR methods revealed that MVP female had higher nHF and lower nLF than MVP male in all three positions. FFT method showed MVP female had lower LF/HF in both lying and sitting positions, but AR method showed MVP female had lower LF/HF than MVP male in lying position.

MVP effects on frequency domain parameters

As shown in Figure 5A, both FFT and AR showed a similar result in male subjects. MVP male had a lower TP in all three positions and lower nHF in the lying position. FFT method revealed that MVP male also had lower nHF in the sitting position, which was not found by AR method. Both FFT and AR showed MVP male had higher nLF in the lying position, higher LF/HF in the lying position and lower LF/HF in the sitting and standing positions. As shown in Figure 5B, both FFT and AR showed identical result in female subjects. MVP female had decreased TP in all three positions than the normal female had. There were no nHF and LF/HF differences in all three positions between normal and MVP females, but MVP female had increased nLF in the lying position.

DISCUSSION

The present study revealed distinct postural effects and gender differences on autonomic function between MVP subjects and normal control. Since orthostatic posture often involves activation and/or inhibition of either component of the autonomic nervous system, it is use-
ful to categorize the abnormal autonomic response and potential cardiac risk in each gender of MVP patients. The first major finding was that a standing posture favored the sympathetic activity (decreased SDNN and NN50) and the orthostatic position (sitting and standing) attenuated parasympathetic outflow (decreased RMSSD) in both normal and MVP subjects (Figure 1A), whereas MVP subjects possess higher sympathetic tone (smaller SDNN and NN50) and lower parasympathetic activity (lower RMSSD) than normal control (Figure 1B). The second major finding indicated that orthostatic decreased parasympathetic outflow (lower TP and nHF), and increased sympathetic tone (higher nLF and LF/HF) were also found by frequency domain in normal and

Figure 3. Gender difference on time domain parameters in normal and MVP subjects. (A) Comparison of SDNN, RMSSD and NN50 between male and female in normal or MVP subjects, respectively. * p < 0.05, # p < 0.01, vs. male. (B) Comparison of SDNN, RMSSD and NN50 between normal and MVP subjects in male or female, respectively. * p < 0.05, # p < 0.01, vs. normal subjects.
MVP subjects (Figure 2A). MVP victims had higher sympathetic tone (lower TP) in the lying position, but lower sympathetic tone (higher TP and nHF, lower LF/HF) in the sitting and standing position than normal adults (Figure 2B). The third major finding was that both normal and MVP females had higher parasympathetic tone (higher RMSSD and NN50) than male in the lying position (Figure 3A). MVP male had high sympathetic and low parasympathetic tone (lower SDNN, NN50 and RMSSD) in the lying position than normal male. MVP female had higher sympathetic tone (lower SDNN and NN50) in sitting position than normal female (Figure 3B). The fourth major finding was that normal and MVP female had higher parasympathetic and lower sympathetic tone (higher nHF, lower nLF) than normal and MVP male (Figure 4). Lastly, the fifth major finding was that MVP male had a higher sympathetic and lower parasympathetic tone (lower TP, higher nLF and lower nHF) than normal male in lying position. However, MVP male had lower sympathetic tone (lower LF/HF) in the sitting and standing positions (Figure 5A). MVP female had increased sympathetic tone (lower TP, higher nLF) than normal female (Figure 5B).

In brief, MVP subjects had higher sympathetic and lower parasympathetic activity. Orthostatic posture significantly increased the sympathetic tone in normal adults, but not in MVP subjects. This novel finding indicates an obtunded sympathetic response to orthostatic position in MVP subjects, which was found particularly in MVP male. MVP male had higher sympathetic outflow, meanwhile MVP female had higher parasympathetic tone. However, MVP female possesses higher sympathetic outflow than normal female. The mechanisms underlying the gender difference in cardiac autonomic function has not been fully elucidated. It has been proposed that middle-aged women and men have a more dominant parasympathetic and sympathetic regulation of heart rate, respectively. The gender-related
difference in parasympathetic regulation diminishes after 50 years of age, whereas a significant time delay for the disappearance of sympathetic dominance occurs in men.20 Our studies of gender differences in autonomic regulation demonstrate significantly greater parasympathetic activity in women, which further depict an underlying cardioprotective mechanism in females before menopause.

MVP affects up to 2.4% of the general population and has a benign course with excellent prognosis for most patients.21,22 However, a minority of patients develops significant complications, including infective endocarditis, cerebrovascular events, progressive MR, and sudden cardiac death.5,6,12,23 MVP usually associated with the coexistence of symptoms that cannot be explained on the basis of valvular regurgitation alone. These various accompanying symptoms comprise palpitations, orthostatic rhythm disturbances, atypical chest pain, exertional dyspnea and neuropsychiatric symptoms.24 Abnormal autonomic regulation has been reported to be responsible for symptomatic subjects with a complex of presenting symptoms such as elevated circulating concentrations of catecholamines and enhanced β receptor affinity, suggesting the existence of a hyperadrenergic state, diminished vagal tone and other autonomic malfunctions.24,25 Similar to previous reports, our finding in patients with MVP indicated decreased parasympathetic activity in addition to abnormal adrenergic activity and response, which potentiate the occurrence of clinical symptoms and arrhythmogenesis.26-30

Autonomic imbalance indicated by HRV may contribute to disease progression, is an indicator of disease pathogenesis, and is a better predictor of poor prognosis than other hemodynamic measures in cardiac diseases. Autonomic dysregulation may also be a key determinant in the origin and progression of MVP, thus our finding not only accounts for the clinical symptoms and progression of valvular insufficiency but also has future

**Figure 5.** MVP effects on frequency domain parameters in male or female. (A) Comparison of TP, nHF, nLF and LF/HF between normal and MVP in male subjects. *p < 0.05, † p < 0.01, vs. normal subjects. (B) Comparison of TP, nHF, nLF and LF/HF between normal and MVP in female subjects. *p < 0.05, † p < 0.01, vs. normal subjects. Abbreviations are in Figure 2.
implications for pharmaceutical and mechanical treatment.

Though the FFT and AR methods resulted in a comparable frequency-domain analysis in our MVP and normal subjects, FFT appears to have showed a bit higher sensitivity in a short-term recording.

**Study limitations**

Our study did have several limitations. One limitation was that the respiratory rate was not controlled when measuring the interbeat intervals over the five-minute recording period. Research has shown that the reliability of HRV measures was increased when respiratory rate was regulated. Furthermore, part of the intra-subject variability was also due to the natural change of factors such as mood, alertness and mental activity, which are very difficult to control for in any study. In addition, subjects were enrolled in a district general hospital and a university, respectively, and they are not perfectly age and sex matched. HRV derived from the short-term five minute ECG recording, although it has been claimed to be highly correlated to the 24-hour ECG recording, their clinical value needs to be further studied. Besides, we cannot exclude the impacts of circadian variation since the HRV signals were collected from 9:00 A.M. to 4:00 P.M. The unadjusted age, height and weight might (BMI) also affect the HRV data.

**CONCLUSIONS**

In this investigation, we found that the normal female subjects were dominated by parasympathetic activity, whereas MVP female and male had prevailing levels of sympathetic outflow. The obtunded postural effects on frequency domain measures underscored the autonomic dysregulation of MVP subjects.

**REFERENCES**

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