Complex Sympathetic Regulation in Adolescent Mitral Valve Prolapse

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Summary
Mitral valve prolapse (MVP) belongs to cardiac disorders characterized by impaired closure of mitral leaflets. We studied adolescent group of patients with MVP suffering from symptomatology that cannot be explained by mitral regurgitation alone. Several studies suggested that symptoms can be explained by autonomic, in particular sympathetic-linked dysfunction. Thus, we assessed non-invasive sympathetic indices of blood pressure and heart rate variability and electrodermal activity (EDA). Fifty-three adolescents with MVP (age: 15.1±0.4 years) and 43 healthy age- and gender-matched adolescents (age: 14.9±0.4 years) were examined. Blood pressure, heart rate and EDA were continuously recorded during 6-min rest. Evaluated parameters were: low frequency band of systolic blood pressure variability, systolic, diastolic and mean blood pressure, mean RR interval, cardiac sympathetic indices: symbolic dynamics (0V%), left ventricular ejection time (LVET), pre-ejection period (PEP), and EDA. Our findings revealed significantly higher systolic, diastolic, and mean blood pressure values, shortened mean RR interval, increased 0V%, and shortened LVET in MVP patients vs. controls (p=0.028, p<0.001, p=0.002, p<0.001, p=0.050, p<0.001; respectively). Our study revealed enhanced cardiovascular sympathetic regulation in adolescent MVP patients. We suggest that evaluation of non-invasive sympathetic parameters could represent potential biomarkers for early diagnosis of cardiovascular complications associated with MVP already at adolescent age.

Key words
Mitral valve prolapse • Autonomic nervous system • Sympathetic activity • Blood pressure • Adolescent age

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Introduction
Mitral valve prolapse (MVP) represents a disorder of closure of one or both mitral leaflets, what makes them billowing into the left atrium during cardiac cycle (systole) with or without regurgitation. The key issue for this diagnosis represents floppy mitral valve (FMV). This pathological/surgical term “floppy” is defined by intrinsic morphological changes resulting in the bulging of the mitral valve leaflets out of the mitral valve area, with elongated chordae tendineae, frequently associated with a dilated mitral annulus (Boudoulas et al. 2020). The common classification represents primary (idiopathic) or secondary (MVP is developed on the background of various diseases, such as figcarditis, cardiomyopathies, Marfan’s syndrome, etc.) MVP (Shah 2010). Based on the background of symptomatology, patients with FMV/MVP can be divided into two basic groups. First group involves patients whose symptoms are directly related to progressive mitral regurgitation and its complications. In the second group are patients whose symptoms cannot be associated only with the degree of regurgitation, but may be result of neuroendocrine or autonomic dysfunction referred as the FMV/MVP syndrome (Boudoulas et al. 2016). At present, little
attention is given to autonomic dysregulation associated with this diagnosis.

FMV/MVP syndrome includes symptoms like palpitations, orthostatic rhythm disorder, exertional dyspnea, anomalous chest pain, syncope, and neuropsychiatric symptoms (e.g. anxiety) (Shah et al. 2020). It has been proven that these symptoms cannot be explained by mitral valve abnormalities and regurgitation alone. Besides, in certain patients were symptoms present many years prior the significant mitral valve regurgitation (Boudoulas and Boudoulas 2013, Theofilogiannakos et al. 2015). Recent studies reported that reasons causing symptoms could be explained by functional abnormalities of the autonomic nervous system (ANS) or neuroendocrine dysfunction in patients with FMV/MVP syndrome (Miller et al. 2018, Boudoulas et al. 2020). Previous studies reported sympathetic overactivity and decreased vagal tone, which is probably associated with the origin and pathogenesis of MVP (Chang et al. 2016, Bilovol et al. 2019).

Heart rate variability (HRV) represents a promising tool for assessment of ANS regulatory dynamics (Shaffer and Ginsberg 2017). With respect to parasympathetic activity, Chang et al. (2016) reported decreased vagal activity in MVP patients. Moreover, our previous study in this field revealed impaired cardiovagal control indexed by short-term HRV in adolescents with MVP (Bona Olexova et al. 2020). In contrast, the evaluation of sympathetic activity from short-term HRV linear analysis is controversial (Goldstein et al. 2011). In this context, the nonlinear HRV analysis – symbolic dynamics is assumed to be better than conventional spectral indices regarding its sensitivity to sympathetically mediated heart rate fluctuations (Porta et al. 2007, Visnovcova et al. 2014). Due to the latest studies, symbolic dynamics 0V% index represents a non-invasive marker of cardiac sympathetic regulation independent on myocardial preload and afterload influencing frequently used pre-ejection period (PEP) (Mestanik et al. 2015, Silva et al. 2017). Further, sympathetic cardiac control could be indexed by well-established parameter PEP, which provides information about beta-adrenergic influences on the myocardium (Bernston et al. 2016, Garrido et al. 2020). Moreover, left ventricular ejection time (LVET) represents index of sympathetic chronotropic effects through the actions of the sinoatrial node (Hill et al. 2010). Additionally, PEP/LVET ratio is considered as the single most useful measurement of left ventricular dysfunction when either or both the PEP and LVET are in normal range (Tavakolian 2016, Corici et al. 2018).

For complex assessment of sympathetic control, vascular sympathetic modulation may be expressed by spectral analysis in the low-frequency range of the systolic blood pressure variability (LF-SBPV) reflecting thus alpha-adrenergic vascular tone (Mestanik et al. 2015, Grillletti et al. 2018). Additionally, it has been proven that short-term blood pressure variability (BPV) is comparable with long-term BPV monitoring (Jira et al. 2010). With respect to other sympathetically mediated effectors, electrodermal activity (EDA) is a non-invasive index of sympathetic cholinergic activity. Specifically, the skin’s ability to conduct electricity is related to activity of eccrine sweat glands, which reflects changes of sympathetic activity (Dawson et al. 2000, Figner and Murphy 2010). Thus, dynamic variations of the sympathetic activity estimated by EDA represents an important prognostic and diagnostic marker in autonomic dysfunction-linked diseases (Posada-Quintero et al. 2016).

Sympathetic activity has not been evaluated in such a comprehensive view in the MVP yet. Therefore, we aimed to study complex sympathetic regulation using BPV, HRV, and EDA analysis in adolescent patients with primary MVP. To the best of our knowledge, it is the first study to assess sympathetic regulation of different effectors’ responses in adolescent MVP.

**Methods**

The study was approved by the Ethics Committee of Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava in accordance with the 1964 Helsinki declaration and its later amendments. All subjects and their parents were carefully instructed about the study protocol and they gave informed written consent to participation in the study prior to the examination.

**Subjects**

We examined 53 adolescents with MVP (40 girls, 13 boys, age: 15.1±0.4 years, body mass index: 18.5±0.3 kg/m²) and age/gender-matched 43 healthy adolescents as control group (31 girls, 12 boys, age: 14.9±0.4 years, body mass index: 20.3±0.4 kg/m²). The subjects with MVP were recruited from specialized Pediatric Cardiology, external workplace of Jessenius Faculty of Medicine in Martin. The diagnosis of MVP was determined by specialist in pediatric...
cardiology. MVP was suspected according to the presence of typical midsystolic click during auscultation which occurred alone or coupled with telesystolic murmur. All patients were characterized by symptoms of palpitations, syncope, chest pain or fatigue. Additionally, non-specific changes were presented on ECG recordings, e.g. flat or inverted T waves in II, III and aVF leads. The diagnosis of MVP was definitely confirmed by cross-sectional echocardiography, showing prolapse of one or both mitral leaflets in the long-axis view and four-chamber view. Moreover, mitral regurgitation was revealed in all patients with MVP by Doppler echocardiography. The exclusion criteria for both (MVP and control) groups were following: smoking, overweight and obesity, history of recent acute illness or respiratory, endocrinological, neurological, metabolic, or infectious diseases or mental disorders. Only participants without pharmacological treatment were enrolled in the study.

Study protocol

The examinations were performed in the psychophysiological laboratory (Biomedical Centre Martin, Jessenius Faculty of Medicine in Martin) under standard conditions (quiet room, temperature: 22-23 °C, humidity: 45-55 %), with the minimalization of stimuli, in the morning hours between 8:00 and 12:00 a.m., after normal breakfast. The participants were instructed to avoid physical exercise at least 24 h prior the examination.

Firstly, anthropometric parameters were assessed by body composition analyser InBody 120 (Biospace Co. Ltd, Seoul, Korea). Afterwards, participants were asked to sit comfortably in a special armchair and rest for 10 min to avoid a potential effect of stress. Consequently, sensors for continuous recordings of the heart rate (HR), blood pressure, and EDA biosignals were applied with instruction to remain in sitting position for a 6 min at rest.

HRV nonlinear analysis – symbolic dynamics

Time series of RR intervals derived from HR were performed using Polar V800 (Polar Electro, Kempele, Finland) with sampling frequency 1000 Hz. Before analysis, the data were carefully checked for the occurrence of artefacts and 5 min sequences without artefacts were analyzed.

The basis of symbolic dynamics is the coarse-graining of data into symbols with certain given numbers (0, 1, 2, 3, 4, 5) to classify the changes in the dynamics of time series. Subsequently, the symbols are divided into patterns with length $L=3$. The patterns are grouped into 4 entities according to the types of numbers variations from one symbol to another (Porta et al. 2007). Three equal patterns (0V%, symbols without variations) represent a potentially sensitive index of complexity in beta-adrenergic sympathetic cardiac control (Porta et al. 2007, Visnovcova et al. 2014, Mestanik et al. 2015). In addition, the length of mean RR interval (ms) was calculated.

Blood pressure variability

Beat-to-beat blood pressure (BP) with sampling rate 200 Hz (Finometer MIDI Model II, Finapres Medical System, Amsterdam, the Netherlands) was monitored. Waveforms of reconstructed brachial artery pressure were used with the correction of the finger cuff pressure to the heart level via built-in height correction system. The recordings were processed using Beat-Scope Easy software (Finapres Medical System, Netherlands). Before analysis, beat-to-beat series of systolic BP were carefully checked for artefacts and subsequently artefact-free segments were resampled using cubic spline interpolation with the frequency 2 Hz. The lnLF-SBPV parameter contains cadence oscillations of systolic BP in the frequency range from 0.075 to 0.15 Hz, i.e. Mayer waves (Stauss 2007). The lnLF-SBPV index could reflect a potential marker of sympathetic vascular regulation (Zhang et al. 2002). In addition, the systolic, diastolic, and mean blood pressures (SBP, DBP, MBP, respectively) were assessed.

Systolic time intervals

The left ventricular ejection time (LVET) (ms) as the duration of the left ventricle to eject blood corresponding to the opening and closing of the aortic valve was assessed by BeatScope easy software (Finapres medical systems, Netherlands). Pre-ejection period (PEP) (ms) as the time interval between initial ventricular depolarization and opening of the aortic valve was determined by VaSera device (Fukuda Denshi Co., Ltd. Tokyo, Japan). Moreover, the PEP/LVET ratio is considered as the most effective measurement of the left ventricular dysfunction when either or both the PEP and LVET are in the normal range (norm is from 0.30 to 0.38) (Tavakolian 2016, Corici et al. 2018).

Electrodermal activity

Electrodermal activity with sampling frequency 256 Hz (FlexComp Biofeedback Infinity, Though Technology, Canada) was continuously recorded. Before analysis, the data were carefully checked for the occurrence of artefacts. Index SCL (skin conductance level) was calculated as a mean amplitude of tonic EDA. SCL describes quantitative changes in cholinergic
sympathetic control. Normal values range from 0 to 30 µS depending on the size of used electrodes (Venables et al. 1980, Dawson et al. 2007).

Statistical analysis
Statistical analysis was performed by SYSTAT (SSI, Richmond, USA). The Shapiro-Wilk normality statistical test was used for evaluation data distributions (Gaussian/non-Gaussian). The Mann-Whitney test was used for between-group comparison of BPV, HRV, and EDA indices because data were not normally distributed. A value of p≤0.05 was considered as statistically significant. BPV, HRV, and EDA parameters were expressed as median (interquartile range).

Results
The characteristics of both groups (MVP and controls) are summarized in Table 1. The mean RR interval was significantly shortened indicating tachycardia in the MVP group compared to controls (p<0.001). MVP patients showed significantly higher SBP, DBP, and MBP compared to controls (p=0.028, p<0.001, p=0.002; respectively). Moreover, cardiac sympathetic indices – LVET was significantly shortened and 0V% was significantly higher in MVP group compared to controls (p<0.001, p=0.050; respectively). No significant differences in remaining parameters were found between groups. Results are summarized in Table 2.

Table 1. Anthropometric characteristics of groups.

|                        | Mitral valve prolapse | Controls | p value |
|------------------------|-----------------------|----------|---------|
| Age (years)            | 15.00 (12.75, 17.00)  | 15.00 (13.00, 17.00) | 0.916   |
| Weight (kg)            | 50.00 (45.75, 57.85)  | 55.20 (55.10, 63.60) | 0.019   |
| Height (cm)            | 167.00 (159.38, 173.75) | 166.00 (162.00, 172.00) | 0.910   |
| BMI (kg/m²)            | 18.22 (17.14, 19.74)  | 20.02 (18.18, 21.92)  | 0.001   |
| BSA (m²)               | 1.53 (1.44, 1.66)     | 1.60 (1.50, 1.76)     | 0.070   |

Values are expressed as median (interquartile range). BMI – body mass index, BSA – body surface area. Probabilities p≤0.05 were considered to be significant.

Table 2. Parameters of blood pressure variability, heart rate variability, systolic time intervals, and electrodermal activity.

|                        | Mitral valve prolapse | Controls | p value |
|------------------------|-----------------------|----------|---------|
| BPV parameters         |                       |          |         |
| SBP (mm Hg)            | 115.50 (104.58, 125.85) | 108.33 (101.03, 117.45) | 0.028   |
| DBP (mm Hg)            | 72.43 (66.69, 79.40)   | 64.89 (61.19, 70.01)   | <0.001  |
| MBP (mm Hg)            | 91.29 (83.32, 97.39)   | 82.57 (78.68, 89.01)   | 0.002   |
| lnLF_SBPV (mm Hg²)     | 7.20 (7.02, 7.30)      | 7.05 (6.88, 7.30)      | 0.060   |
| HRV parameters         |                       |          |         |
| Mean RR interval (ms)  | 657.00 (586.00, 708.00) | 747.00 (703.00, 817.00) | <0.001  |
| 0V%                    | 40.65 (29.45, 54.36)   | 33.72 (21.36, 44.50)   | 0.050   |
| Systolic time intervals|                       |          |         |
| LVET (ms)              | 268.62 (257.38, 281.60) | 289.49 (278.64, 296.71) | <0.001  |
| PEP (ms)               | 86.00 (70.00, 100.00)  | 82.00 (75.25, 98.75)   | 0.687   |
| PEP/LVET (ms)          | 0.31 (0.26, 0.37)      | 0.29 (0.26, 0.36)      | 0.379   |
| EDA parameter          |                       |          |         |
| SCL (µS)               | 1.67 (0.87, 3.24)      | 1.14 (0.59, 3.05)      | 0.110   |

Values are expressed as median (interquartile range). BPV – blood pressure variability, HRV – heart rate variability, EDA – electrodermal activity, SBP – systolic blood pressure, DBP – diastolic blood pressure, MBP – mean blood pressure, LVET – left ventricular ejection time, lnLF_SBPV – spectral power of systolic blood pressure variability in low-frequency band, 0V% – index of the nonlinear method of HRV analysis-symbolic dynamics, PEP – pre-ejection period, SCL – skin conductance level. Probabilities p≤0.05 were considered to be significant.
Discussion

We investigated for the first time complex sympathetic activity using HRV, BPV, and EDA parameters characterizing diversity of peripheral effectors in mitral valve prolapse. The results can be summarized as follow: (1) higher complex sympathetic cardiac control (↑0V%, shortened LVET) associated with tachycardia (shortened mean RR interval) in MVP group, (2) higher systolic, diastolic, and mean blood pressure associated with a tendency towards increasing to sympathetic vasomotor activity (↑1nLF_SBP) in MVP group compared to controls. These findings revealed cardiovascular-linked sympathetic overactivity in adolescents suffering from MVP. Several mechanisms are suggested.

The higher cardiac-linked sympathetic activity in MVP is in agreement with recent study revealing prevalence of sympathetic activity by twice exceeded mode amplitude in MVP compared to controls (Bilovol et al. 2019). Moreover, our finding of isolated shortened LVET without change of PEP points to increased chronotropy associated with higher cardiovascular risk in MVP due to the fact that LVET represents an independent predictor of cardiovascular morbidity (Biering-Sørensen et al. 2018). Additionally, we can assume that left ventricle functioning is not altered in adolescent MVP yet, because ratio PEP/LVET has proven to be accurate measurement of left ventricle dysfunction (Corici et al. 2018). With respect to sympathetic vasomotor activity, our findings of increased alpha-adrenergic vascular modulation are in contrast with some other studies revealing no differences in BP, or even lower SBP and DBP during 24-BP monitoring in MVP vs. controls (da Silva et al. 2007, Delling et al. 2014). Thus, we suggest higher resting cardiovascular autonomic control that can be associated with increased cardiovascular complications in MVP already at adolescent age.

From neurophysiological aspect, the autonomic regulation of the effector organs is performed through numerous structures at all levels of the central nervous system (CNS) forming interconnected complex called central autonomic network (CAN) (Benarroch 1993). Structurally, the cardiovascular areas of the brainstem (i.e. medulla oblongata) are primarily involved in the central regulation of the sympathetic outflow. Spinal sympathetic preganglionic neurons obtain strong excitatory drive from medulla oblongata (especially neurones located in the rostral ventrolateral medulla (RVLM), which is also a vasomotor center). This excitatory flow from the RVLM may be attributable to excitatory inputs from other supramedullary regions of the CNS (e.g. pons, hypothalamus, and amygdala) (Dampney 1994, Fisher et al. 2009). We assume that MVP may have dysregulation at the subcortical level, which results in an increase of sympathetic input, especially into cardiovascular system. This hypothesis of sympathetic overactivity can be sustained by hyperadrenergic state, represented by findings of increased plasma and urine epinephrine/norepinephrine in MVP patients (da Silva et al. 2007). Additionally, Beketova et al. (2018) referred severe vasomotor disturbances in adolescents with MVP, which may indicate hyperresponsiveness of blood vessels due to excessive autonomic responsiveness.

Moreover, previous studies reported that movement of the mitral valves is not entirely passive. There is a rising possibility, that these leaflets are neurally controlled tissue. Experimental studies of mitral valves show rich innervation with postganglionic autonomic nerves patterns (Williams and Jew 2004, Itoh et al. 2009). Additionally, presence of sympathetic and parasympathetic nerves was reported along the subendocardial site on the atrial aspect of the human mitral valve (Oki et al. 1995). Mentioned part of the mitral valve represents the most susceptible area to mechanical stimuli due to MVP. Thus, mechanical stimuli from this area may be transmitted to the CNS via afferent sensory nerves which are also present in mitral valve. Han et al. (2000) suggested that an inappropriate circuit between the central and peripheral nerves in the mitral valves may be responsible for the autonomic dysfunction in MVP and subsequently could later lead to the cardiovascular complications associated with this diagnosis.

Further, the psychopathological states such as anxiety associated with emotional dysregulation could be related to sympathetic abnormal regulation in MVP. For example, anxiety and mood disorders have high prevalence among young individuals with MVP (Lung et al. 2008). According to neurovisceral integration model (Thayer and Lane 2000), the CAN represents also complex system coordinating the attentional and emotional/affective functioning, with respect to the modulation of the autonomic responses. More specifically, emotional regulation is conditioned by effective functioning of prefrontal-subcortical inhibitory
circuits (Thayer and Lane 2000). In physiological state the prefrontal cortex has inhibitory impact over sympathoexcitatory subcortical circuits resulting in high cardiac vagal control. Reversely, diminished prefrontal activity is associated with disruption of its inhibitory functioning leading to dominance of sympathoexcitatory subcortical circuits (Park and Thayer 2014). Moreover, amygdala is one of the most consistently identified subcortical regions of hyperactivity in anxiety (Holzschneider and Mulert 2011). Thus, disruption of prefrontal cortex inhibitory control linked to emotional dysregulation could represent an important pathomechanism leading to increased cardiovascular-sympathetic activity associated with decreased cardiovascular control in MVP (Bona Olexova et al. 2020). This is also in accordance with neurovisceral integration model which interconnect increased sympathetic nervous activity with anxiety disorders (Thayer and Lane 2000). Taken together, altered inhibitory control of prefrontal cortex associated with hyperactive flow from vasomotor center can together lead to increased sympathetic activity in young MVP patients.

From a developmental aspect, physiological maturation of the cardiac ANS in healthy children and adolescents aged 0.5 to 20 years performs as follows: the cardiac parasympathetic activity followed an exponential increase from infancy associated with a plateau phase during middle childhood, followed by a slight decrease to adolescence, the cardiac sympathetic activity showed a more linear trend, with a gradual decrease from infancy to adolescence (Harteveld et al. 2021). In this aspect, a recent study assumed that insufficient maturation of cardiovagal regulation during adolescence can be associated with development of psychopathology and other diseases (Koenig 2020). Therefore, we suggest that adolescents with MVP has altered vagal maturation during growing up, comparing to their healthy peers, resulting in predominance of resting sympathetic cardiovascular activity, as we revealed in our study. It is questionable whether altered MVP-linked sympathetic cardiovascular dysregulation reflects only abnormalities in the central autonomic regulatory network or it is more associated with MVP-linked psychophysiological/developmental characteristics. Further research to elucidate this important question is needed.

**Limitations of the study**

The findings of this study need to be validated in a larger sample with respect to gender. Moreover, the cardiovascular control was assessed only in the rest phase, thus, the autonomic response to other physiological, emotional, cognitive or social stressors might bring more information about autonomic regulatory mechanisms in MVP.

**Conclusions**

This study revealed sympathetically-mediated cardiovascular overactivity in adolescent MVP evaluated by using non-invasive complex assessment of the conceivable markers of sympathetic vasomotor and cardiac chronotropic regulation. Further studies are needed to elucidate pathways linking MVP and sympathetic dysregulation as a potential pathomechanism leading to higher cardiovascular risk in adolescent patients suffering from MVP.

**Conflict of Interest**

There is no conflict of interest.

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