SYMPATHETIC NERVOUS SYSTEM AND CARDIOVASCULAR RISK IN MITRAL VALVE PROLAPSE

BONA OLEXOVA L^{1,2*}, MESTANIK M^{2,1}, JURKO A JR³, SEKANINOVA N^{1,2}, SLAVIKOVA M^{1,2},
TONHAJZEROVA I^{1,2}

¹Department of Physiology, Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava, Martin, Slovak Republic

²Biomedical Center Martin, Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava, Martin, Slovak Republic

³Pediatric Cardiology, Martin, Slovak Republic

Abstract

Mitral valve prolapse (MVP) represents a frequent cardiovascular condition associated with increased cardiovascular risk, which may have progressive course and become malignant. Dysregulation of autonomic nervous system - especially sympathetic overdrive - is one of the factors considered to play a key role in its aetiology and development. There is a growing evidence of a large impact of sympathetic system on the development of MVP. Exaggerated sympathetic activity may lead to morphologic changes in valves tissue such as thickening and redundancy. Nowadays, few investigative methods are known for evaluation of the regulatory state of sympathetic nervous system, which could be, theoretically, used to identify the subjects with sympathetic overactivity associated with an increased cardiovascular risk. Electrodermal activity or blood pressure variability represent promising non-invasive methods for evaluation of the regulatory outputs of sympathetic nervous system. There is a possibility to extend a set of investigative methods in MVP and include the monitoring of sympathetic activity in the assessment of cardiovascular risk. This article summarizes knowledge about pathogenesis, diagnostic and therapeutic approaches of MVP, and brings some novel insights on the parameters of autonomic nervous regulation, which haven't yet been used in cardiovascular risk assessment in MVP.

Key words: mitral valve prolapse, cardiovascular risk, sympathetic nervous system, electrodermal activity, blood pressure variability

INTRODUCTION

Mitral valve prolapse (MVP) represents a frequent cardiovascular condition associated with an increased cardiovascular risk. Multifactorial aetiology is assumed in the pathology of MVP; however, the principal underlying origin of this disease has still not been identified (1). A dysregulation of autonomic nervous system with exaggerated sympathetic activity could represent one of the pathological mechanisms involved in aetiology and leading to the development of this disorder. MVP has a progressive course and may finally become malignant (2). From this perspective, the evaluation of sympathetic activity might be of help.

Normal healthy tissue of mitral valve consists of three layers: inner ventricular layer, the middle spongiosa, and the outer fibrosa layer (1). Morphological abnormalities like thickening and redundancy of the leaflet with chordal elongation and dilatation of annulus are also known as myxomatous degeneration (1). In MVP the expansion of the middle - spongiosa layer was documented with an increased number of interstitial cells, which featu-

Corresponding author: Lucia Bona Olexova, MD; e-mail: olexova10@jfmf.uniba.sk; lucia.olexova@gmail.com

© 2019 Bona Olexova L et al.

This work is licensed under the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 License (<https://creativecommons.org/licenses/by-nc-nd/4.0/>)

re by signs of activated myofibroblasts (1). Morphology of the cells is also altered. Interstitial cells of valve in MVP have elongated shape and manifest increased contraction, striking stress fibers, and some other contractile features typical for myofibroblasts (3).

The autonomic nervous system (ANS) imbalance turns out to be a considerable indicator of MVP; thus, autonomic dysregulation may be a common way leading to increased morbidity and mortality from cardiovascular diseases and other conditions (4). It points to a significant role of ANS dysregulation as a cardiovascular risk factor. Therefore, the assessment of sympathetic activity may be of interest for better prediction of later complications and targeted preventive and therapeutic interventions. In general, it is very important to know the real origin of this disorder, which allows early identification and monitoring of the patients requiring medical intervention. Nowadays, few investigative methods are known for evaluating the state of ANS. This study focuses on the function and non-invasive assessment of the sympathetic nervous activity in patients with MVP with respect to cardiovascular risk.

Sympathovagal dynamic balance – function

Sympathetic and parasympathetic nervous systems coordinate the functions of the organism at rest and maintain appropriate allostatic response during stress (5). Allostasis represents achievement of stability conveyed by physiological and behavioural alteration, whereas homeostasis ensures physiological stability by maintaining the functions of the organism at the basal level (6). Usually, these two systems, sympathetic and parasympathetic system, act like antagonists – *i.e.* where one system causes activation, the other system inhibits this function. However, this is not absolute true for all organs (*e.g.*, the parasympathetic branch doesn't influence smooth muscles of most vessels, while the sympathetic part causes their constriction). In general, parasympathetic nervous system plays a key role at rest and sympathetic nervous system is dominant in stress and endurance situations. Under physiological conditions these two systems are in dynamic balance (7). Regarding the pathophysiology of MVP, the sympathetic hyperactivity is in the centre of interest as its overactivity may lead to a development of several diseases (*e.g.* hypertension) and, thereby, be associated with a higher cardiovascular risk (8). The role of sympathetic activity in the aetiology and its extensive impact on the development of MVP is discussed below.

Mitral valve prolapse

MVP, also known as Barlow's syndrome, is a common defect which afflicts 2–3% of the world population (9). This valvular abnormality characterised by one or both abnormal mitral leaflets in the left atrium redounds to mitral regurgitation manifested by late systolic murmur (2). The mitral regurgitation is caused by a morphological abnormality of one or more components of a complex mitral valve apparatus, *i.e.* leaflets, chordae tendineae, papillary muscles, or mitral annulus. Nevertheless, except for anatomical abnormalities of other mitral apparatus parts, the thickness of mitral valve alone turned out to be not associated with significant mitral regurgitation (10). Patients diagnosed with MPV usually present with concomitance of various symptoms including palpitations, orthostatic rhythm disorder, exertional dyspnoea, anomalous chest pain, and neuropsychiatric symptoms. They are summarily called "mitral valve prolapse syndrome". This syndrome includes the symptoms which are not the primary consequences of valvular regurgitation alone.

MVP can be caused by familial, sporadic, or other, less common causes (fibroelastic deficiency, Marfan's syndrome, bacterial endocarditis, acute ischemia, etc.) (11, 12). Despite the fact that MVP is the most frequent cause of isolated mitral regurgitation leading to surgical repair, knowledge about genetic factors underlying the pathogenesis and progression of MVP is poor (11). The key determinant responsible for the complex of these symptoms has been supposed to be abnormal autonomic regulation with elevated concentrations of catecholamines in circulation and enhanced β receptor affinity, indicating the presence of

hyperadrenergic state, lowered vagal tone, and other autonomic dysfunctions (2). Most of the patients with MVP were diagnosed with initial increased sympathetic activity and excessive autonomic responsiveness (13). In addition, sympathetic nervous system is influenced by circadian rhythm – the sympathetic overactivity is typical for the morning and *vice versa* – the sympathetic underactivity is presented during the night (14). Thus, the probability of occurrence of MVP symptoms is the highest in the morning.

Sympathetic nervous system could affect the tissue of mitral valve via its neurotransmitter – norepinephrine. Thus, coupling between neurotransmitters and specific receptors triggers a sequence of reactions, which results in modified physiological function within cells. Sympathetic neurotransmitters could play a key role in dysfunction of nerve terminals in the valve because of their reaction with adrenergic receptors (ARs). The regulatory state of sympathetic control can be reflected by expression of ARs in mitral valves, which was amplified in MVP. Immunochemistry analysis of $\beta 1$ -ARs, $\beta 2$ -ARs and $\alpha 1$ -ARs in MVP tissue has shown dense deposits of these receptors (3). Under physiological conditions the expression of adrenergic receptors is controlled through the mechanism of down-regulation – a decrease in number of binding sites in membrane – which is induced by excessive and prolonged exposition of receptors to ligands (15). Based on the evidence of increased sympathetic activity in MVP with increased plasma levels of catecholamines (16) and findings of enhanced expression of ARs in mitral valve tissue in patients with MVP on the other side (3) we can suggest possible dysfunction of the regulation of ARs receptors expression in MVP patients.

This autonomic imbalance is hypothesized to be a crucial determinant at the beginning and also in progression of MVP. Autonomic dysregulation is an indicator of MVP pathogenesis and seems to be a very good predictor of miserable prognosis in MVP because of negative cases associated with congestive heart failure, progressive mitral insufficiency, thromboembolism, bacterial endocarditis, and even sudden cardiac death (2, 17). These events, which appear at the terminal state in the course of aging, show up more frequently in patients with MVP (2). Regarding the sex differences, according to Framingham study, females seem to be more vulnerable to MVP than men (2).

In patients with secondary mitral regurgitation increased levels of muscle sympathetic nervous activity were found (18); however, less is known about the non-invasive indices of sympathetic neural regulation in patients with MVP, and, particularly, in paediatric patients. The early identification of patients with MVP is of major importance since MVP could be therapeutically affected. Therefore, we suggest that early management of this potentially malignant entity could help to decrease the number of patients with a dramatic impact of the advanced states. Natural course of MVP is not homogenous, it varies across benign and malignant conditions with increased morbidity and mortality caused by progressive regurgitation of the mitral valve (2). Currently, the gold standards in diagnostics of MVP are physical examination and two-dimensional (2D) echocardiography (11). Other methods which allow more detailed imaging of mitral valve in MVP include three-dimensional (3D) echocardiography (19) and 2D transoesophageal echocardiography (TEE), which represent very good identifiers of accurate localization of MVP (20). Nowadays, cardiac magnetic resonance imaging belongs to useful non-invasive methods for identifying MVP itself and MVP-related regurgitation (21). Non-invasive examination of sympathetic nervous system state could extend the diagnostic methods in future, improve early diagnostics, and allow the follow-up of clinically silent forms.

Therapeutical approaches in MVP may be firstly medical (beta-blockers e.g. propranolol) in patients with symptoms of dysautonomia like chest pain or palpitations. Individuals suffering from severe mitral regurgitation can undergo a repair or replacement of mitral valve (22). Reparation of mitral valve involves subvalvular, valvular, and annular interventions (23). Solution for mitral regurgitation represents transcatheter mitral valve interventions. This is a safer way for patients because transcatheter therapy is mini invasive and avoids risks accompanied with open heart surgery. These techniques are developed for interventions on many parts of mitral valve apparatus (24).

Assessment of sympathetic nervous activity

The examination methods of sympathetic nervous system activity are:

a) *Blood pressure variability (BPV)*

Regulation of blood pressure (BP) is under control of sympathetic nervous system (25). It has been documented that BP is not constant but is under influence of profound and spontaneous oscillations during short-term and long-term sessions. This results in variations within 24 hours (i.e. short-term variability: beat-to-beat, minute-to minute, hour-to-hour, and day-to-night changes) and also during days and months (i.e. long-term variability: days, weeks, months, seasons) (26). Spectral analysis of BPV is composed of two bands:

- High-frequency (HF) band of BPV 0.15-0.40 Hz (27). Oscillations of systolic and diastolic BP in this frequency band is markedly affected by breathing with its mechanic effect. Systolic BP is influenced by heart rate; thus, respiratory sinus arrhythmia takes part in the emergence of HF band of systolic BPV. Therefore, the HF band of systolic and diastolic BPV is mainly the result of non-autonomic effects of breathing and its complexity (7).
- Low-frequency (LF) band of BPV 0.075-0.15 Hz (27). Baroreceptor mechanism and central mechanisms are responsible for the origin of this band of BPV Mayer waves (7). The primary aim of the arterial baroreflex is to sustain BP homeostasis (28). Baroreflex loop consists of baroreceptors, ANS, heart, and vessels (29). Arterial baroreflex plays the major role in short-term BP control and production of BP oscillations with periods from seconds to minutes (28). The baroreflex modulates sympathetic outcome to the vessels and, thereby, peripheral resistance. Therefore, arterial baroreflexes play a pivotal role in producing slow oscillations in BP via reflex loop, involving sympathetic nervous activity and vessels (30). Thus, low frequency band of systolic BPV is considered as a marker of sympathetic activity.

In summary, high-frequency band of BPV results mainly from the mechanical effect of breathing on intrathoracic pressure, while low-frequency band of BPV is predominantly under influence of sympathetic nervous activity (7).

b) *Electrodermal activity (EDA)*

Electrodermal activity (EDA) is an index of sympathetic branch of ANS. It is used to evaluate conductance of the upper corneal layer of skin and its changes influenced by activity of sweat glands, which are exclusively under sympathetic control (31,32). Under standard conditions, e.g. thermoneutral zone, EDA in these areas represents the reactions to psychological rather than thermoregulatory stimuli (33).

EDA is characterized by two major parameters – tonic part and phasic part (32). Tonic part of EDA – skin conductance level (SCL) – depends on the degree of wetness in the upper corneal layers of skin. The phasic EDA – skin conductance response (SCR), depends to a great extent on the number of sweat gland ducts that are actually filled with sweat, resulting in electric shunts between the upper skin layer and the conductive deeper tissue. The principle is based on measurement of skin conductance – with/without application of electrical potential between two electrodes on skin surface and measuring the final current flow between them (31,32).

EDA represents a non-invasive examination method frequently used in psychophysiology – for example in biofeedback training. A modern management of the disorders, which are known to be connected with emotional distress like hypertension and functional bowel disorders, involves application of EDA-biofeedback as a part of treatment (34). In psychophysiological research EDA can be evaluated as an index of stress, arousal, and emotion, and, potentially, it could be used for monitoring of sympathetic nervous regulation in patients with MVP, characterized by sympathetic overactivity.

It seems that a complex approach for measurement of sympathetic activity is important for diagnosis of early abnormalities in autonomic nervous system in MVP patients, espe-

cially in children and adolescents characterized by dynamic developmental processes which may result in greater vulnerability to autonomic dysregulations.

Cardiovascular risk

For a long time it was questionable how to identify the individuals at risk of developing cardiovascular disease. Currently, several algorithms exist for the estimation of cardiovascular risk, *e.g.* SCORE (Systematic Coronary Risk Evaluation) risk charts presenting the 10-year risk of fatal cardiovascular disease. This estimator is based on the evaluation of following major risk factors: gender, age, systolic blood pressure (mmHg), cholesterolaemia (mmol/L), and smoking status (35). Since sympathetic overdrive participates in the aetiology and development of specific cardiovascular diseases, it may be expected that it could be included in already known risk factors for a more detailed assessment of cardiovascular risk. Thus, non-invasive and sensitive methods like BPV or EDA could be used for early diagnosis of sympathetic overactivity and help to find out patients in latent state of cardiovascular disease. Noted investigative methods - EDA, BPV - can represent the possibility to assess early abnormalities of ANS regulation associated with higher cardiovascular risk in MVP. From this point of view, these methods could provide precious information about the pathological mechanisms leading to higher cardiovascular risk.

CONCLUSION

Mitral valve prolapse nowadays represents a major problem, especially in paediatric cardiology. Sympathetic excitation could be one of the pathological mechanisms leading to development and sustaining of MVP and, simultaneously, it is associated with increased cardiovascular risk. Therefore, non-invasive monitoring of sympathetic activity using electrodermal activity or blood pressure variability could be helpful in modern effective management of preventive and therapeutical interventions in patients with MVP.

REFERENCES

1. Hayek E, Gring CN, Griffin BP. Mitral valve prolapse. *Lancet*. 2005; 365 (9458): 507–518.
2. Hu X, Zhao Q. Autonomic dysregulation as a novel underlying cause of mitral valve prolapse: a hypothesis. *Med Sci Monit*. 2011;17 (9): 27–31.
3. Hu X, Wang H-Z, Liu J, Chen A-Q, Ye X-F, Zhao Q. A novel role of sympathetic activity in regulating mitral valve prolapse. *Circ J*. 2014; 78 (6): 1486–1493.
4. Thayer JF, Yamamoto SS, Brosschot JF. The relationship of autonomic imbalance, heart rate variability and cardiovascular disease risk factors. *Int J Cardiol*. 2010; 141 (2): 122–131.
5. McEwen BS. Stress, Adaptation, and Disease: Allostasis and Allostatic Load. *Ann N Y Acad Sci*. 1998; 840: 33–44.
6. Tonhajzerova I, Mestanik M. New perspectives in the model of stress response. *Physiol Res*. 2017; 66 (Suppl 2): 173–185.
7. Tonhajzerová I, Mešťaník M. *Psychofyziológia: od stresovej odpovede po biofeedback*. Martin: VEGA; 2016. 164 pp.
8. Brook RD, Julius S. Autonomic imbalance, hypertension, and cardiovascular risk. *Am J Hypertens*. 2000; 13 (6 Pt 2): 112–122.
9. Ma JI, Igata S, Strachan M, Nishimura M, Wong DJ, Raisinghani A, DeMaria A. Predictive Factors for Progression of Mitral Regurgitation in Asymptomatic Patients With Mitral Valve Prolapse. *Am J Cardiol*. 2019; 123 (8): 1309–1313.
10. Sénéchal M, Michaud N, Machaalany J, Bernier M, Dubois M, Magne J, Couture C, Mathieu P, Bertrand OF, Voisine P. Relation of mitral valve morphology and motion to mitral regurgitation severity in patients with mitral valve prolapse. *Cardiovasc Ultrasound*. 2012; 10: 3.

11. Delling FN, Vasan RS. Epidemiology and pathophysiology of mitral valve prolapse: new insights into disease progression, genetics, and molecular basis. *Circulation*. 2014; 129 (21): 2158–2170.
12. Shah PM. Current concepts in mitral valve prolapse—Diagnosis and management. *J Cardiol*. 2010; 56 (2): 125–133.
13. Beketova G V, Soldatova O V, Gan R V, Horiacheva IP, Aleksieienko NV, Nekhaienko MI, Zborshchik MV. Daily Profile Of Blood Pressure In Children With Mitral Valve Prolapse. *World Med Biol*. 2018; 14: 009.
14. Grassi G, Bombelli M, Seravalle G, Dell'Oro R, Quarti-Trevano F. Diurnal blood pressure variation and sympathetic activity. *Hypertens Res*. 2010; 33 (5): 381–385.
15. Tsao P, von Zastrow M. Downregulation of G protein-coupled receptors. *Curr Opin Neurobiol*. 2000; 10 (3): 365–369.
16. Pasternac A, Tubau JF, Puddu PE, Król RB, De Champlain J. Increased plasma catecholamine levels in patients with symptomatic mitral valve prolapse. *Am J Med*. 1982; 73 (6): 783–790.
17. Han H, Ha FJ, Teh AW, Calafiore P, Jones EF, Johns J, Koshy AN, O'Donnell D, Hare DL, Farouque O, Lim HS. Mitral Valve Prolapse and Sudden Cardiac Death: A Systematic Review. *J Am Heart Assoc*. 2018; 7 (23): e010584.
18. Öztürk C, Schueler R, Weber M, Welz A, Werner N, Nickenig G, Hammerstingl C. Sympathetic Activity in Patients With Secondary Symptomatic Mitral Regurgitation or End-Stage Systolic Heart Failure. *JACC Cardiovasc Interv*. 2016; 9 (19): 2050–2057.
19. Antoine C, Mantovani F, Benfari G, Mankad S V, Maalouf JF, Michelena HI, Enriquez-Sarano M. Pathophysiology of Degenerative Mitral Regurgitation. *Circ Cardiovasc Imaging*. 2018; 11 (1): e005971.
20. Monin J-L, Dehant P, Roiron C, Monchi M, Tabet J-Y, Clerc P, Fernandez G, Houel R, Garot J, Chauel C, Gueret P. Functional Assessment of Mitral Regurgitation by Transthoracic Echocardiography Using Standardized Imaging Planes: Diagnostic Accuracy and Outcome Implications. *J Am Coll Cardiol*. 2005; 46 (2): 302–309.
21. Delling FN, Kang LL, Yeon SB, Kissinger K V, Goddu B, Manning WJ, Han Y. CMR Predictors of Mitral Regurgitation in Mitral Valve Prolapse. *JACC Cardiovasc Imaging*. 2010; 3 (10): 1037–1045.
22. Shah SN, Oliver TI. Mitral Valve Prolapse. *StatPearls*. StatPearls Publishing; 2018.
23. Mohty D, Orszulak TA, Schaff H V, Avierinos J-F, Tajik JA, Enriquez-Sarano M. Very Long-Term Survival and Durability of Mitral Valve Repair for Mitral Valve Prolapse. *Circulation*. 2001; 104 (12 Suppl 1): 1–7.
24. Markham R, Kyranis S, Aroney N, Lau K, Poon K, Scalia G, Walters D. Transcatheter mitral valve intervention: an emerging treatment for mitral regurgitation. *Intern Med J*. 2018; 48 (4): 382–390.
25. Henry DP, Luft FC, Weinberger MH, Fineberg NS, Grim CE. Norepinephrine in urine and plasma following provocative maneuvers in normal and hypertensive subjects. *Hypertension*. 1980; 2: 20–28.
26. Grassi G, Bombelli M, Brambilla G, Trevano FQ, Dell'Oro R, Mancia G. Total Cardiovascular Risk, Blood Pressure Variability and Adrenergic Overdrive in Hypertension: Evidence, Mechanisms and Clinical Implications. *Curr Hypertens Rep*. 2012; 14 (4): 333–338.
27. Stauss HM. Identification of blood pressure control mechanisms by power spectral analysis. *Clin Exp Pharmacol Physiol*. 2007; 34 (4): 362–368.
28. Di Rienzo M, Parati G, Radaelli A, Castiglioni P. Baroreflex contribution to blood pressure and heart rate oscillations: time scales, time-variant characteristics and nonlinearities. *Philos Trans A Math Phys Eng Sci*. 2009; 367 (1892): 1301–1318.
29. Coupé M, Fortrat JO, Larina I, Gaugein-Koch G, Gharib C, Custaud MA. Cardiovascular deconditioning: From autonomic nervous system to microvascular dysfunctions. *Respir Physiol Neurobiol*. 2009; 169 (Suppl 1): 10–12.
30. Malpas SC. Neural influences on cardiovascular variability: possibilities and pitfalls. *Am J Physiol Circ Physiol*. 2002; 282 (1): 6–20.
31. Visnovcova Z, Mestanik M, Gala M, Mestanikova A, Tonhajzerova I. The complexity of electrodermal activity is altered in mental cognitive stressors. *Comput Biol Med*. 2016; 79: 123–129.
32. Stanton N, Hedge A, Brookhuis K, Salas E, Hendrick HW, editors, editors. *Handbook of Human Factors and Ergonomics Methods*. CRC Press; 2004. 764 pp.

33. Boucsein W. *Electrodermal activity*. New York: Springer Science+Business Media, LLC; 2012. 618 pp.
34. Yucha C, Montgomery D, Association for Applied Psychophysiology and Biofeedback. *Evidence-based practice in biofeedback and neurofeedback*. AAPB; 2008. 81 pp.
35. Conroy RM, Pyörälä K, Fitzgerald AP, Sans S, Menotti A, De Bacquer D, Ducimetriére P, Jousilahti P, Keil U, Njølstad I, Oganov RG, Thomsen T, Tunstall-Pedoe H, Tverdal A, Wedel H, Whincup P, Wilhelmsen L, Graham IM. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. *Eur Heart J*. 2003; 24 (11): 987–1003.

Acknowledgements: This work was supported by the Slovak Scientific Grant Agency under grant VEGA 1/0044/18, Ministry of Health of the Slovak Republic under the project registration number 2018/20-UKMT-16, Minister of Education, Science, Research and Sports, Slovak Republic under grant ITMS 26220220187, the project is co-financed from European Union (EU) sources, and Slovak Research and Development Agency under grant APVV-15-0075.

Received: April, 18, 2019

Accepted: May, 30, 2019