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Heart Rate Variability in the Early Period of Tilt Test in Patients with Mitral Valve Prolapse

Zmienność rytmu serca na wczesnym etapie testu pochyleniowego u pacjentów z wypadaniem płatka zastawki mitralnej

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Abstract

Background. Mitral valve prolapse (MPV) is characterized by abnormal contractile dislocation of thickened, degenerative mitral valve leaflets towards the left atrium beyond the surface of the valvular ring. Patients with MPV have been described to reveal high plasma levels of catecholamines, increased reactivity to catecholamines, or abnormal regulation of the baroreceptor reflex. Presyncope and syncope have been often described among the symptoms associated with MPV.
Objectives. Evaluating the effect of the passive upright tilt test in patients with MPV on the activation of the autonomic nervous system.
Material and Methods. The study group comprised 15 patients with MPV, 11 women and 4 men aged 42.3 ± 22.1 years, who were diagnosed for recurrent syncope of unknown etiology, with a positive tilt test. The control group consisted of 42 patients with unexplained syncope, 31 women and 11 men aged 45.1 ± 16.0 years, with a positive result of the tilt test, who did not reveal MPV on echocardiographic examination. Time- and frequency-domain analysis of heart rate variability in two 2-min time intervals (after 30 minutes of lying and between 2 and 4 minutes in upright position) was performed in every patient and the following parameters were evaluated: mRR, SDNN, rMSSD, pNN50, TP, LF, HF, and the B balance index.
Results. No statistically significant differences were found in the parameters of heart rate variability in both the time- and the frequency-domain analysis between the investigated groups when comparing the same phases of the investigation. Analysis of the changes within groups under the effect of the tilt test showed that patients in the study group were characterized by significantly shortened mRR and decreased rMSSD, pNN50, while the remaining parameters did not differ. Patients in the control group revealed a significant decrease in all the investigated parameters of time- and frequency-variability of the heart rate.
Conclusions. Patients with vasovagal syncope and MPV in the early stage of the investigation did not reveal any signs of activation of the sympathetic system manifested by decreased heart rate variability; however they developed statistically significant increases in the diastolic blood pressure, what may point to excessive activation of the sympathetic system. Failure to decrease the heart rate variability parameters is the consequence of central activation of the vagus nerve, the mechanism which counteracts excessive increases in blood pressure (**Adv Clin Exp Med 2006, 15, 6, 1009–1013**).

Key words: vasovagal syncope, heart rate variability, mitral valve prolapse.

Streszczenie

Wprowadzenie. Wypadanie płatka zastawki mitralnej (MPV) charakteryzuje się nieprawidłowym, skurczowym przemieszczaniem pogrubiałych, zmienionych zwyrodnieniowo płatków mitralnych poza płaszczyznę pierścienia zastawki w kierunku lewego przedsionka. U chorych z MPV opisano duże osoczowe stężenia amin katecholowych, zwiększoną reaktywność na aminy katecholowe lub nieprawidłową regulację odruchu z baroreceptorów. Wśród objawów towarzyszących MPV często występują zasłabnięcia i omdlenia.
Cel pracy. Ocena wpływu biernej pionizacji u chorych z MPV na aktywację autonomicznego układu nerwowego.
Materiał i metody. Do grupy badanej należało 15 chorych z MPV, w tym 11 kobiet i 4 mężczyzn w wieku 42,3 ± 22,1 lat, diagnozowanych z powodu omdleń o niejasnej przyczynie, z dodatnim wynikiem testu pochyleniowego. Do grupy kontrolnej włączono 42 chorych z omdleniami o niejasnej przyczynie, 31 kobiet i 11 mężczyzn w wie-

ku 45,1 ± 16,0 lat, z dodatnim wynikiem testu pochyleniowego, u których w badaniu echokardiograficznym nie stwierdzono cech MPV. U każdego chorego przeprowadzono czasową i częstotliwościową analizę zmienności rytmu serca w dwóch 2-minutowych przedziałach czasowych: po 30 min przebywania w pozycji leżącej oraz między 2. a 4. minutą pionizacji, oceniając: mRR, SDNN, rMSSD, pNN50, TP, LF, HF oraz wskaźnik równowagi B.

Wyniki. Nie stwierdzono istotnych statystycznie różnic między wskaźnikami zmienności rytmu serca zarówno uzyskanych w wyniku analizy czasowej, jak i częstotliwościowej między badanymi grupami, porównując wartości w tych samych fazach badania. Analizując zmiany wewnątrzgrupowe pod wpływem pionizacji, stwierdzono u chorych z grupy badanej istotne skrócenie mRR oraz zmniejszenie rMSSD pNN50, a inne wskaźniki nie zmieniły się istotnie. U chorych z grupy kontrolnej stwierdzono istotne zmniejszenie wszystkich ocenianych wskaźników czasowej i częstotliwościowej analizy zmienności rytmu serca.

Wnioski. U chorych z omdleniami wazowagalnymi i MPV we wczesnym okresie badania nie obserwowano aktywacji układu współczulnego objawiającej się zmniejszeniem zmienności rytmu serca, wystąpił jednak istotny statystycznie wzrost ciśnienia rozkurczowego, co może być wyrazem nadmiernej aktywacji układu współczulnego. Brak spadku wskaźników zmienności rytmu serca jest następstwem centralnego pobudzenia nerwu błędnego stanowiącego mechanizm przeciwdziałający nadmiernemu wzrostowi ciśnienia tętniczego (**Adv Clin Exp Med 2006, 15, 6, 1009–1013**).

Słowa kluczowe: omdlenia wazowagalne, zmienność rytmu serca, wypadanie płatka zastawki mitralnej.

Mitral valve prolapse is characterized by abnormal contractile displacement of thickened, degenerative mitral leaflets towards the left atrium beyond the valvular ring. The pathology affects 2–3% of the population and is genetically conditioned [1]. So far, two gene loci have been identified, one being an autosomally dominant trait and the other associated with the X chromosome. In the majority of cases, mitral valve prolapse has a mild or asymptomatic course and only very few patients develop severe complications, such as hemodynamically significant mitral valve insufficiency, tendinous chord rupture, endocarditis, cerebral embolism, arrhythmia, or even sudden cardiac death [2]. Clinically, mitral valve prolapse may manifest itself by heart palpitations, occurring in 56% of patients, tiredness and low tolerance of physical effort (56%), chest pain (50%), dyspnea (30%), dizziness (30%), fainting or syncope (23%), or anxiety neurosis (12%) [2].

Vasovagal syncope is caused by reflex-activated, according to one hypothesis, over-activated mechanoreceptors of the heart muscle [3]. Patients with mitral valve prolapse have been reported to reveal high plasma levels of catecholamines, increased reactivity to catecholamines, abnormal regulation of reflex from baroreceptors, and increased activation of atrial natriuretic peptide secretion [4].

Upright position may increase the degree of mitral valve prolapse. Syncope in patients with mitral valve prolapse may also be caused by disturbed reactivity of the autonomic nervous system to the orthostatic stimulus.

The aim of the study was to evaluate the effect of passive upright tilt in patients with mitral valve prolapse on the activation of the autonomic nervous system.

Material and Methods

The study group (group I) comprised 15 patients with mitral valve prolapse, and included 11 women and 4 men aged 42.3 ± 22.1 years diagnosed for unexplained syncope, with a positive result of the tilt testing. The control group (group II) consisted of 42 patients with unexplained syncope, 31 women and 11 men aged 45.1 ± 16.0 years, with a positive tilt testing result, in whom mitral valve prolapse was not confirmed on echocardiographic examination. The patients of the study group as well as the controls did not receive any cardiovascular medication. Any other pathology that might cause syncope was excluded in both groups on the basis of other examinations, including echocardiography, 24-hour ECG monitoring, and electrocardiographic exercise stress test in some of the patients.

The tilt test was performed according to the Italian protocol with nitroglycerin provocation in case of negative result of the passive phase of the test on a tilt table manufactured by OPiW in Opole, Poland. The patients were provoked with 400 µg of nitroglycerin administered sublingually. The investigation was performed in a quiet room, with dimmed light, in the morning hours. During the examination the patients were secured with safety belts fastened at the level of the chest and the knees. During the tilt test all the patients had ECG Holter monitoring, the tracings then being analyzed by means of a Medilog Optima system manufactured by Oxford. Time- and frequency-domain analysis of heart rate was performed according to ESC recommendations [5] in two 2-min time intervals: after 30 minutes in the lying position and between 2 and 4 minutes in the upright position.

The time-domain HRV parameters included calculation of the mean RR interval (mRR), standard deviation of the normal RR intervals (SDNN), root mean square of the mean sum of squares of the differences between consecutive RR intervals (rMSSD), and the proportion of the differences between consecutive RR intervals exceeding 50 ms (pNN50). The frequency-domain analysis included total power (TP) in the bandwidth 0–0.4 Hz, low-frequency parameters (LF) (0.04–0.15 Hz), and high-frequency components (HF) (0.15–0.4 Hz). The LF/HF ratio, or balance index (B), was also calculated.

The evaluation of hemodynamic parameters included measurement of blood pressure in basic conditions and after two minutes in the upright position.

Statistical Analysis

Continuous variables were presented as their mean values and standard deviations and compared using the Student's *t* test for independent and dependent variables as well as the Mann Whitney *U* and Wilcoxon tests in relation to the distribution of the investigated variables. Discrete changes were compared by means of the chi-squared test. $p < 0.05$ was assumed statistically significant.

Results

NTG provocation was applied in 12 of the study patients with mitral valve prolapse and in 31 subjects from the control group (80% vs. 74%, *p* = n.s). In the study group there were 10 mixed (VASIS I) and 5 cardiodepressive (VASIS II) reactions. In the control group there were 27 mixed and 15 cardiodepressive neurocardiogenic reactions. Table 1 presents the heart rate variability parameters in the investigated time intervals.

Table 2. The increase in blood pressure in the study group and controls at rest and in the early stage of upright position

Tabela 2. Wzrost ciśnienia krwi w grupie badanej i kontrolnej w spoczynku i na wczesnym etapie pionizacji

	RRs (mm Hg)	RRr (mm Hg)
Group I phase I (Grupa I faza I) Group I phase II (Grupa I faza II)	113.0 ± 17.0 NS 118.1 ± 16.5	74.4 ± 13.1 p < 0.02 83.4 ± 9.8
Group II phase I (Grupa II faza I) Group II phase II (Grupa II faza II)	117.5 ± 17.2 NS 117.4 ± 19.4	78.5 ± 13.5 NS 82.1 ± 15.8

Neither time- nor frequency-domain analysis revealed any statistically significant differences between heart rate variability parameters in the same phase of the examination in both groups. Intragroup analysis of changes resulting from the upright position revealed a significant shortening of mRR and decreases in rMSSD and pNN50 in patients of the study group, whereas other parameters did not differ. Patients of the control group revealed a significant decrease in all the investigated parameters of time- and frequency-domain analysis of heart rate variability.

Table 2 presents changes in blood pressure at rest and after 2 minutes of the tilt test.

Discussion

Disturbed functions of the autonomic nervous system may play a significant role in the incidence of syncope and fainting in patients with mitral

Table 1. Heart rate variability parameters in the study group and in controls in the investigated time intervals

Tabela 1. Wskaźniki zmienności rytmu serca w grupie badanej i kontrolnej w analizowanych przedziałach czasu

	mRR (ms)	SDNN (ms)	rMSSD (ms)	pNN50 (%)	TP (ms)	LF (ms)	HF (ms)	B
Group I (Grupa I) Phase I (Faza I) Phase II (Faza II)	1013.4 ± 226.4 *p* < 0.01 829.9 ± 198.8	57.8 ± 34.8 NS 52.1 ± 28.5	60.3 ± 56.0 *p* < 0.05 40.4 ± 31.7	20.6 ± 20.3 *p* < 0.05 13.7 ± 15.4	46.0 ± 24.9 NS 45.9 ± 26.0	28.5 ± 17.0 NS 31.7 ± 20.6	24.6 ± 18.2 NS 20.3 ± 17.1	1.3 ± 0.5 NS 2.1 ± 1.6
Group II (Grupa II) Phase I (Faza I) Phase II (Faza II)	960.5 ± 151.8 *p* < 0.01 789.2 ± 158.9	57.7 ± 28.5 *p* < 0.01 40.4 ± 20.0	48.8 ± 42.6 *p* < 0.01 24.3 ± 14.9	18.2 ± 20.3 *p* < 0.01 5.4 ± 8.7	46.2 ± 23.2 *p* < 0.01 34.7 ± 20.2	26.7 ± 12.4 *p* < 0.01 20.0 ± 14.2	23.1 ± 18.2 *p* < 0.01 11.6 ± 8.0	1.5 ± 0.9 *p* < 0.01 2.1 ± 1.0

valve prolapse. Patients with mitral valve prolapse have been described to develop a hyperadrenergic condition [6] as well as normal, or even decreased sympathetic autonomic system tone [2]. Patients with mitral valve prolapse are characterized by a defect in the autoregulatory mechanism at the level of catecholamine receptor regulation, transient changes in the levels of catecholamines during the day, or simultaneous incidence of both of the above phenomena [2].

In this investigation, no significant differences in heart rate variability parameters in basic conditions as well as after assumption of an upright position were found between patients with mitral valve prolapse and those without this pathology. Lower values of heart rate variability parameters in children with mitral valve prolapse compared with children without this pathology [7] have been reported in literature; however, no significant differences in the parameters were observed in adults [1].

Evaluating the effect of upright position on the heart rate variability parameters in a group of patients with vasovagal syncope and mitral valve prolapse, this study found that the majority of heart rate variability parameters did not differ significantly when the heart rate frequency was increased in a similar way as in patients with vasovagal syncope but without mitral valve prolapse, who in that time revealed a significant decrease in the majority of parameters to the values beyond the sympathetic-parasympathetic balance index, which was found to increase.

A decrease in central volume as a result of upright position together with an increase in adrenergic tone are considered to be triggering factors for vasovagal syncope, which may develop in cases of prolonged upright position. Patients with mitral valve prolapse were found in the early stage of the examination to reveal abnormal reactivity of the autonomic system to tilting. The observation of parasympathetic atonia in the early stage of the tilt test was also reported by Lippmann et al., who found an association between this pattern of heart rate variability parameters and a positive result of the tilt test [8]. However, the majority of reports on heart rate variability parameters describe a similar trend as in the patients of the present study without mitral valve prolapse. HRV findings in patients with vasovagal syncope in the early stage of the tilt test did not give clear results, as some authors found no differences [9] and others reported a lack of decrease in HRV parameters, which are the measure of parasympathetic modulation of the sinoatrial node [10].

Increased heart rate variability in the first 20 minutes after the onset of passive tilt testing in patients with vasovagal syncope treated with upright training compared with values found in the diagnostic tilt test was observed in one study. The changes corresponded to clinical improvement in these patients and seem to point to higher autonomic system reserve in response to orthostatic stress [11].

In the present study the lack of decreases in heart rate variability parameters was observed only in the initial phase of the passive tilt test in the patients with mitral valve prolapse; this was not observed in subjects with negative tests or in patients with a positive tilt test without MVP.

Patients with mitral valve prolapse did not reveal significantly different incidences of positive tilt test results in the passive phase of the examination or different distributions of neurocardiogenic reaction types according to VASIS in comparison with patients without mitral valve prolapse, which suggests a lack of effect of the observed autonomic system dysfunction on the further course of the examination.

In investigations on the effect of the tilt test on heart rate, Chresler et al. found no significant differences between patients with mitral valve prolapse and controls [12]. According to the present authors' knowledge, there have so far been no reports on the effect of passive upright tilting on heart rate variability in patients with vasovagal syncope and mitral valve prolapse.

The analysis of associations between heart rate variability parameters and blood pressure in the investigated time intervals points to a simultaneous activation of both components of the autonomic system in the initial period of passive upright tilting, as was shown before during vasovagal syncope on the basis of changes in the QT interval [13].

The results of this investigation indicate the necessity to consider mitral valve prolapse in the analysis of the effects of the upright tilt test on heart rate variability parameters.

The authors conclude that patients with vasovagal syncope and mitral valve prolapse in the early phase of the examination did not demonstrate decreased heart rate variability; however, they developed a statistically significant increase in diastolic pressure, which may reflect activation of the sympathetic system. Failure to decrease heart rate variability parameters could be the consequence of central stimulation of the vagus nerve, the mechanism which counteracts excessive increases in blood pressure.

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