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Changes in QT Interval During Tilt-Induced Vasovagal Syncope

Ocena okresu repolaryzacji komór serca u chorych z omdleniami wazowagalnymi w czasie testu pochyleniowego

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Abstract

Background. Orthostatic stress causes changes in the activity of the components of the autonomic nervous system. In patients with neurally mediated syncope (NMS), the balance between the sympathetic and parasympathetic parts of this system is disturbed, which can be the cause of bradycardia and/or asystole and significant fall in blood pressure. The QT interval, reflecting the repolarization period of the ventricles, can be altered by the neurocardiogenic reaction because its duration depends mainly on the heart rate and autonomic nervous system activity.
Objectives. Assessing the influence of head-up tilt testing on the duration of the QT interval in patients with NMS.
Material and Methods. Fifty-seven patients (group I), aged 46.5 ± 17.9 years (39 women and 18 men) with NMS induced by the tilt test conducted according to the two-phases Raviele protocol, and 33 patients (group II), aged 41.3 ± 16.3 years (18 women and 15 men) diagnosed for unexplained syncope without neurocardiogenic reaction, were evaluated. Durations of the RR, QT, and QTc intervals were assessed after the syncope in group I during the sinus or junctional rhythm, and in group II immediately after the test, five minutes after the test, and during sleep between 4:00 and 4:15 AM.
Results. The duration of the RR interval after the tilt test was significantly longer in group I than in group II ($p < 0.001$) and the QT interval five minutes after the test was significantly longer in group I than in group II ($p < 0.05$). In group I the RR interval after syncope was significantly longer than at five minutes after the test ($p < 0.01$) and during sleep ($p < 0.05$). The QT intervals after syncope and five minutes after the test did not differ and were significantly shorter than during sleep ($p < 0.05$). In group II, the RR intervals immediately after the tilt test and five minutes after the test did not differ and were significantly shorter compared with the values during sleep ($p < 0.001$). QT after the test and five minutes after the test did not differ and were significantly shorter than during sleep ($p < 0.001$).
Conclusions. Slowing of the heart rate during neurocardiogenic reaction is not accompanied by adequate QT interval prolongation immediately after stopping the tilt test. The results point to the concomitant activation of sympathetic and parasympathetic components of the autonomic nervous system in the human heart during neurally mediated syncope (**Adv Clin Exp Med 2006, 15, 4, 613–618**).

Key words: QT interval, vasovagal syncope, tilt test.

Streszczenie

Wprowadzenie. Zmiana aktywności składowych układu autonomicznego wpływa na czas trwania okresu repolaryzacji komór serca mierzonego jako odstęp QT. Jest to zależne nie tylko od zmian częstotliwości serca, ale także od bezpośredniego wpływu mediatorów układu autonomicznego.
Cel pracy. Ocena okresu repolaryzacji komór u chorych z omdleniami wazowagalnymi.
Materiał i metody. Badanie wykonano u 57 chorych w wieku 46,5 ± 17,9 lat (39 kobiet i 18 mężczyzn), u których w czasie testu pochyleniowego według protokołu włoskiego wystąpiło omdlenie wazowagalne (grupa I). Grupę kontrolną stanowiły 33 osoby w wieku 41,3 ± 16,3 lat (18 kobiet, 15 mężczyzn), u których omdlenie nie wystąpi-

ło (grupa II). Czas trwania odstępu RR, QT i QTc oznaczano u chorych po omdleniu wazowagalnym w czasie bradykardii zatokowej lub zastępczego rytmu węzłowego. U osób bez omdlenia w czasie testu pochyleniowego badane wskaźniki oznaczano po opuszczeniu stołu pionizacyjnego do poziomu. Ponownej oceny badanych wskaźników dokonywano 5 minut po zakończeniu badania oraz w czasie snu, między godz. 4:00 a 4:15.
Wyniki. Czas trwania odstępu RR po zakończeniu testu i czas trwania odstępu QT po 5 minutach od zakończenia badania były istotnie dłuższe u badanych chorych w porównaniu do grupy kontrolnej (odpowiednio $p < 0,001$ i $p < 0,05$). W grupie chorych z omdleniem wazowagalnym odstęp RR po omdleniu był istotnie statystycznie dłuższy niż 5 minut po badaniu ($p < 0,01$) oraz w czasie snu ($p < 0,05$). Odstęp QT w okresie po omdleniu oraz 5 minut później nie różnił się istotnie i był istotnie krótszy niż w czasie snu ($p < 0,05$). W grupie osób bez omdlenia odstępy RR bezpośrednio po teście pochyleniowym oraz 5 minut po badaniu nie różniły się istotnie między sobą, ale były krótsze od odstępu RR w czasie snu ($p < 0,001$). Odstęp QT po teście pochyleniowym oraz 5 minut później nie różnił się istotnie i był krótszy niż odstęp QT w godzinach nocnych ($p < 0,001$).
Wnioski. W czasie omdlenia wazowagalnego nie ma wydłużenia czasu trwania odstępu QT adekwatnego do zwolnienia częstości serca. Wyniki badania wskazują na jednoczesną aktywację obu składowych układu autonomicznego w czasie omdlenia wazowagalnego (**Adv Clin Exp Med 2006, 15, 4, 613–618**).

Słowa kluczowe: odstęp QT, omdlenie wazowagalne, test pochyleniowy.

The relationship between the duration of the QT interval and heart rate is an indispensable property of the ventricular repolarization process. Changes in the activity of the autonomic system and circulating catecholamines may be reflected by the relationship between the RR and OT intervals [1]. The effect of parasympathetic system activity on the QT interval duration has not yet been fully established, as the observed QT interval prolongation with decreased heart rhythm may be an indirect consequence of changes in the heart rate and not the direct effect of the activity of the parasympathetic system on the heart muscle [2]. A prolonged QT interval with unchanged heart rate indicates an increase in vagus nerve tone or inhibited activity of the parasympathetic system, which was observed at night compared with the resting period during the day when the patient is alert [3]. On vasovagal syncope, the vagus nerve is activated, which is manifested by bradycardia or even inhibition of heart activity; moreover, strong activation of the sympathetic system is manifested by an increased plasma catecholamine level, especially of adrenalin [4].

Evaluation of changes in the QT interval immediately after vasovagal fainting gives the unique possibility of assessing the effect of the sympathetic and parasympathetic system activation on the QT interval and the relationship between the QT and RR intervals [5]. This is a model which can be used to investigate the effect of autonomic system mediators directly on the heart muscle.

The aim of the study was to evaluate the effect of neurocardiogenic reaction on the activation of both components of the autonomic system on the basis of an analysis of the relationship between the duration of the QT and RR intervals immediately after vasovagal syncope in patients diagnosed for syncope.

Material and Methods

The investigation was performed in 57 patients aged 46.5 ± 17.9 years (39 women and 18 men) who had vasovagal syncope induced by the tilt test according to the Italian (Raviele) protocol (group 1). In 15 patients, syncope occurred in the passive phase of the tilt test, while in 42 patients it was provoked by sublingual administration of 400 μg nitroglycerin. According to the VASIS classification, 23 patients developed type 1 (mixed), 31 patients type 2 (cardio-depressive), and 3 subjects type 3 (vasodepressive) neurocardiogenic reaction.

The control group consisted of 33 subjects aged 41.3 ± 16.3 years (18 women, 15 men) diagnosed for presyncope or fainting who did not develop syncope (group 2). The reasons for the reported complaints were established on the basis of history and further studies. Analysis of the clinical picture, accessory investigations, and further observation revealed that 8 subjects who reported faintness did not develop the typical vasovagal reaction; the reaction was found possible on the basis of history findings in 11 patients. The possibility of psychogenic fainting was taken into consideration in 5 patients. Epileptic seizures were found on further observation in 3 patients; the number of such episodes decreased after institution of anti-epileptic treatment. Three patients were diagnosed with situational syncope, and in a further three patients loss of consciousness was found to be caused by hypoglycemia, migraine, and vertebral syndrome.

The tilt test was performed in all of the investigated subjects in order to diagnose the episodes of syncope. The durations of the RR, QT, and QTc intervals were assessed in the patients after vasovagal syncope after two preceding sinus or junctional rhythms in the case of the RR interval or during sinus bradycardia or junctional rhythm. In

patients without syncope during the tilt test, the investigated parameters were assessed after bringing the tilt table to the horizontal position. Assessment of the investigated parameters was repeated five minutes after termination of the investigation and during sleep from randomly selected evolutions of the sinus rhythm between 4:00 and 4:15 a.m.

Statistical Analysis

The values of the investigated parameters in corresponding time ranges were compared by means of the Student's t test for unpaired variables following evaluation of the normality of the distribution and the equality of variation of the investigated variables. The values of the investigated parameters in the groups were compared by means of parametric variation analysis following evaluation of the normality of their distribution. The differences were then assessed by the NIR test.

Results

The investigated parameters are presented in Table 1 taking into account statistical deviations in the form of arithmetic means and their standard deviations.

The investigated parameters changed significantly in the course of the examination in a similar degree in the patient and control groups. The duration of the RR interval after termination of the test and the duration of the QT interval five minutes after the test were significantly longer in the patients than in the controls ($p < 0.001$ and $p < < 0.05$, respectively).

In the patients with vasovagal syncope, the RR interval after fainting was statistically significantly longer than at five minutes after the test ($p < 0.01$) and during sleep ($p < 0.05$). The QT intervals immediately after fainting and five minutes after fainting did not differ and were statistically significantly shorter than during sleep ($p < 0.05$). In patients who did not faint, the RR intervals immediately after the tilt test and five minutes after the test did not differ significantly and were statistically significantly shorter that the RR intervals during sleep ($p < 0.001$). Likewise, the QT intervals immediately after the tilt test and five minutes later did not differ, but they were significantly shorter than the QT interval at night ($p < 0.001$).

A graphic presentation of the relationship is shown in Figure 1.

It is difficult to interpret the values and changes in the correlated QT interval as the heart rates in the patients of cardiodepressive type during vasovagal syncope were below the values which could be assessed by Bazett's formula [6]. Hence the values presented in Table 1 were calculated but not discussed.

Discussion

The QT interval in the electrocardiogram reflects the repolarization of the heart ventricles, and its duration in individual layers of the heart muscle is responsible for the initiation, peak, and termination of the T wave [7]. In physiological conditions, changes in the QT interval duration are mainly brought about by changes in the heart rate, which may be attributable to the effect of the parasympathetic system on the activity of pace-

Table 1. RR, QT, and QTc interval durations immediately after the tilt test, five minutes after the test, and during sleep in vasovagal patients and the control group

Tabela 1. Czas trwania odstępu RR, QT i QTc po zakończeniu testu, po 5 minutach od zakończenia badania i w czasie snu u pacjentów, u których wystąpiło omdlenie i w grupie kontrolnej

Interval (Odstęp)		Studied group (Grupa badana)	Control group (Grupa kontrolna)	*p*
RR		1097.7 ± 241.1	921.2 ± 169.5	< 0.001
QT	after	409.3 ± 36.8	394.6 ± 39.1	ns.
QTc		0.395 ± 0.037	0.413 ± 0.037	< 0.05
RR		984.9 ± 240.3	906.6 ± 143.1	ns.
QT	5 min. after	412.6 ± 38.5	397.1 ± 25.9	< 0.05
QTc		0.421 ± 0.029	0.418 ± 0.024	ns.
RR		1018.1 ± 162.9	1031.0 ± 182.3	ns.
QT	night	423.5 ± 33.2	426.2 ± 35.1	ns.
QTc		0.421 ± 0.026	0.422 ± 0.031	ns.

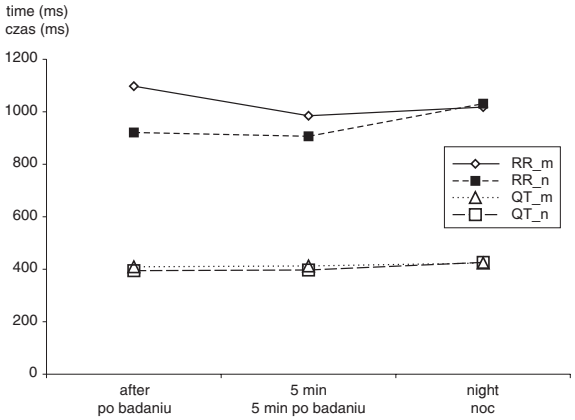

Fig. 1. RR and QT interval duration in the studied time periods in vasovagal patients and the control group

Ryc. 1. Czas trwania odstępów RR I QT w badanych przedziałach czasu u pacjentów, u których wystąpiło omdlenie wazowagalne I w grupie kontrolnej

RR_m – RR interval in vasovagal patients.
RR_n – RR interval in the control group.
QT_m – QT interval in vasovagal patients.
QT_n – QT interval in the control group.

RR_m – odstęp RR u pacjentów, u których wystąpiło omdlenie wazowagalne.
RR_n – odstęp RR u pacjentów z grupy kontrolnej.
QT_m – odstęp QT u pacjentów, u których wystąpiło omdlenie wazowagalne.
QT_n – odstęp QT u pacjentów z grupy kontrolnej.

maker cells of the sinoatrial node [1]. The effect of physical effort on the duration of the QT interval is a complex process which involves not only changes in the heart rate by the inhibition of parasympathetic activity, but also a direct effect of increased sympathetic activity on the repolarization of the ventricular muscle. Although this response results from a number of processes, including presynaptic inhibition of the vagal activity, the effect of circulating and locally secreted catecholamines, and decreased presence of parasympathetic fibers within the heart ventricles, it largely resembles the response observed after administration of atropin [1]. The effect of fluctuations in sympathetic-parasympathetic activity on the duration of the action potential of cardiomyocytes in various layers of the heart muscle, which determines the duration of repolarization and thus the QT interval of the surface electrocardiogram, is not yet fully understood. The various experimental models and a variety of betamimetics (with various effects on the parasympathetic activity) in the performed trials preclude any clinical conclusions [1, 7]. Despite a significant effect of the heart rate, it seems that the duration of the QT interval is a relatively constant parameter, not only in the physiological range determined by Bazett's formula [6], but also in relation to markedly lower frequencies, including paroxysmal ones [2].

Although the vasovagal reflex seems to be a physiological phenomenon, vasovagal syncope is believed to be caused by a disturbed sympathetic-parasympathetic balance in response to orthostatic position. The most commonly accepted and well-documented concept of the induction of the neurocardiogenic reaction which leads to syncope assumes excessive sympathetic activation which, by the stimulation of cardiac mechanoreceptors and hypotensive cardiopulmonary region, leads to the activation of vagus nerve centers with inhibition of the tonic sympathetic activity of the hypothalamus [8]. The reaction produces significant hypotonia and bradycardia, controlled by the vagus nerve, including episodes of asystole. The clinically described sequel manifests as paroxysmal presycope or complete loss of consciousness of reflex character [9].

The neurocardiogenic reaction proceeds in several phases which differ in the activity of different components of the autonomic nervous system. The reaction is preceded by potent sympathetic activation occurring on different pathways manifested by increased levels of both noradrenaline and adrenaline [10]. Increased levels of the latter are believed by some authors to play the key role in inducing reflex reaction [4, 11], although this has not been confirmed by others [12]. The onset of the neurocardiogenic reaction is characterized by an inhibition of sympathetic activity with a relative dominance of parasympathetic activity. The next phase involves the response of the autonomic system to hypotonia and bradycardia and/or asystole, which probably results in sympathetic stimulation.

The above-described phases of the neurocardiogenic reaction are reflected in changes in the duration of the QT interval on the electrocardiograms of patients with vasovagal syncope in the tilt test. Sympathetic activation is associated with a shortening of the ventricular refraction period and the QT interval on the patients' electrocardiograms. The relative shortening of the QT interval observed in our trial in the phase of heart rate slowing during vasovagal syncope seems to confirm the simultaneous activation of both components of the autonomic system or, what is more probable, parasympathetic activation manifested by bradycardia/asystole and the effect of adrenaline secreted in the presyncopal phase or evoked by the RR pause. Adrenergic stimulation, mainly through the effect on the components of outward potassium currents (I_k), results in shortening of the ventricular repolarization time with shortening of the QT interval on the electrocardiogram [13]. The

answer to the question about the separation of the effect of the autonomic system components at the level of the heart ventricles should be sought in the differentiated autonomic innervation of the atria and ventricles of the heart, with the majority of sympathetic nerves in the latter area. The effect of circulating adrenaline, secreted from the adrenal medulla, cannot be overlooked.

Described observation is consistent both with the study on a similar group of patients suffering from vasovagal syncope reported by Jaeger et al. [5] and with the already quoted study by Castellanos et al. in a group of patients with paroxysmal atrio-ventricular block [2]. On this basis one can assume that the effect of the autonomic system, though significant, still merely acts secondarily on the electrophysiological properties of the cardiomyocytes, including the effect on the duration of the action potential, and modulates changes in the QT interval. In presented patients, the interpretation of the lack of a significant prolongation of the QT interval despite prolonged RR interval may give insight into the sympathetic-parasympathetic balance at the level of the ventricular muscle during vasovagal syncope. The findings by Kowallik et al. in healthy men during sleep suggest a similar distribution of sympathetic and parasympathetic effects on the sinoatrial node and ventricular muscle [3].

The described phenomenon, apart from cognitive value, may reflect the complexity of the pathomechanism of the neurocardiogenic reaction and give insight into the autonomic regulation of the heart muscle itself. The potential arrhythmogenic effect of bradycardia and/or asystole associated with vasovagal syncope is abolished by the relative shortening of the QT interval. However, this observation concerns only patients without any structural heart disease, as only these patients were investigated in presented study. Similar reservations concern the earlier mentioned report by Magnano et al. [1]. The presence of severe atherosclerotic lesions in coronary arteries, a history of myocardial infarction, or a significant hypertrophy of the cardiac muscle may significantly modify the response of the QT interval to the described changes in sympathetic-parasympathetic activity. Patients with prolonged QT interval syndrome, in whom the shortening of the QT interval in conditions of raised catecholamine levels is disturbed, constitute a similar group. These are patients in whom episodes of vasovagal syncope are at least as common as in the general population, and their loss of consciousness may be a significant prognostic factor. In patients with syncope and severe anginal episodes and/or confirmed atherosclerotic lesions in the coronary arteries, the decision for a tilt test may be taken after carefully considering the individual risks and expected diagnostic advantages.

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