VIA MEDICA

ORIGINAL ARTICLE

Folia Cardiol.
2006, Vol. 13, No. 7, pp. 578–583

ISSN 1507–4145

Disturbances of blood pressure and spectral heart rate variability during orthostatic stress in patients with type 1 diabetes mellitus

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Abstract

Background: *Orthostatic hypotension in diabetes patients is a sign of autonomic dysfunction. Heart rate variability (HRV) analysis is one of the methods for cardiac autonomic neuropathy assessment. The aim of this study was to assess blood pressure and HRV during 5 minute upright tilting in patients with type 1 diabetes.*

Methods: *We studied 48 normotensive diabetes patients aged 18–28 years, with diabetes lasting 9–23 years. Matched control group consisted of 32 healthy persons. We performed 24 h Holter ECG monitoring (Suprima 12, DMS, USA) and ambulatory blood pressure monitoring (Spacelab 90207, Datex-Ohmeda, USA). Manual measurements were initialized every minute during 5 minute standing, preceded by 15 min rest in supine position. Spectral HRV parameters were analyzed: total power (TP), very low frequency (VLF), low frequency (LF) and high frequency (HF) — in 5-min periods in supine and standing position.*

Results: *Systolic blood pressure fall was noted in 19% of diabetes patients and 3% of the controls ($p = 0.001$) and diastolic blood pressure fall in 23% of diabetes patients and 0% of the controls ($p = 0.001$). During rest diabetes patients with orthostatic hypotension showed significantly lower TP and VLF spectra ($p = 0.001$). After tilting lower TP, VLF, LF and HF in diabetes patients with orthostatic hypotension was observed ($p = 0.001$). In standing position LF (NU, normalized units) decreased in diabetes patients in contrast to healthy people, in which LF spectrum increased.*

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The research was supported by Medical University in Łódź
within the confines of statutory activity No 503-505-2.

Received: 17.10.2005 Accepted: 4.10.2006

Conclusions: *Diabetes patients with orthostatic hypotension have more advanced autonomic dysfunction than diabetes patients without orthostatic hypotension, which manifests as lower spectral HRV components during tilting. Diabetes patients show pathological fall of LF (NU) component during orthostatic stress.* (Folia Cardiol. 2006; 13: 578–583)

Key words: orthostatic hypotension, heart rate variability, diabetes, ambulatory blood pressure monitoring

Introduction

Regardless of its type, diabetes impairs autonomic system regulation. Such pathology is called diabetic autonomic neuropathy (DAN) [1]. Initially it is asymptomatic. As disease progresses, cardiovascular, digestive, ophthalmic and urinary symptoms occur [1]. The loss of function of the autonomic system occurs a few months after diabetes onset and gradually leads to its total impairment [1, 2]. Cardiovascular autonomic neuropathy impairs heart rhythm control, decreases exercise tolerance and causes orthostatic hypotension [1, 2].

Maintaining vertical position is possible owing to the constant adaptation of cardiovascular system based on the autonomic regulation [3]. Assessment of heart rate variability (HRV) by the spectral and time domain analysis is an appreciated method of DAN diagnosis [1, 4, 5]. Reduced parameters of HRV represent an early feature of DAN and appear much earlier than the clinical symptoms [1, 6]. In the diagnosis of DAN, spectral analysis of HRV is used by recording short, a few minute ECG tracing during provocation tests such as orthostatic stress test, deep breathing and Valsalva test [7, 8]. The orthostatic stress test is a stimulus for the autonomic system. When a healthy person changes body position from horizontal to vertical, reduced venous return causes a fall of central venous pressure and arterial pressure. This is a signal for aortic and pulmonary baroreceptors. Centripetal impulses are detected by vasomotor centre in the brain stem. Centrifugal signals reduce the parasympathetic drive and increase sympathetic drive. This causes heart rate increase and also increases heart muscle contractility and venous return, mainly by arterial constriction. Thus, hemodynamic disturbances caused by orthostatic stress are reduced [3]. Diabetic patients with DAN present impaired compensating mechanisms, which leads to orthostatic hypotension. It is often symptomatic with collapses and loss of consciousness in the clinical picture. The quality of life in such cases is considerably decreased.

Because orthostatic hypotension can be diagnosed by blood pressure and heart rhythm measurement it could be considered as a good test for DAN detection. The aim of this study was to assess blood pressure and spectral HRV parameters during 5-minute upright tilting in patients with type 1 diabetes mellitus.

Methods

Forty eight normotensive patients with type 1 diabetes mellitus — 26 men and 22 women aged 18–28 (mean 23 ± 3.5 years) were studied, suffering from diabetes for 9–23 years (mean 16.3 ± 3.8 years). The diagnosis was confirmed by history, medical examination and lab tests — according to current criteria.

All examined patients were on intensive insulin therapy. The control group consisted of 32 healthy people, sex and age matched.

We performed 24-hour ambulatory blood pressure monitoring (Spacelab 90207, Datex-Ohmeda, USA), British Hypertension Society recommendation (http://www.bhsoc.org/bp_monitors/ambulatory.htm) and 24-hour Holter ECG monitoring by DMS 300-6, Suprima 12 system, DMS, USA. Manual measurements were initialized every minute. As inappropriate reaction for supine position we considered systolic blood pressure decrease of 20 mm Hg and diastolic blood pressure decrease of 10 mm Hg as compared to the blood pressure measured just before elevating to standing position after 15 min of rest minimum.

Blood pressure fall satisfying the above conditions accompanied by clinical symptoms: vertigo, scotoma and fainting was considered symptomatic orthostatic hypotension. During 5 min immediately preceding vertical position and during 5 min of the test spectral HRV parameters were also analysed.

We separated the following frequency bands in which spectrum power was assessed:

— total power (TP) — 0–0.4 Hz;
— very low frequency (VLF) — 0.033–0.04 Hz;
— low frequency (LF) — 0.04–0.15 Hz;
— high frequency (HF) — 0.15–0.4 Hz;
— LF/HF ratio.

The parameters were measured and compared in absolute units (ms^2) and normalized units (NU). The normalized units were calculated as below:

— for low frequencies:
LF [NU] = [LF/(TP – VLF)] × 100;

— for high frequencies:
HF [NU] = [HF/(TP – VLF)] × 100.

Statistical analysis

The results are expressed as mean values ± standard deviation (SD). Because Shapiro-Wilk test failed to meet the criteria of the normal distribution of the analysed data, the statistical analysis was carried out with U Mann-Whitney test for independent variables and Wilcoxon test for paired variables at the significance level of 0.05. The differences satisfying a condition of zero hypothesis false rejection with probability of 0.05 or less were considered significant. The Stats Direct v. 1.9.8 programme was used for statistical computation.

Results

The results are given in Tables 1–3. We observed that orthostatic hypotension occurred significantly more frequently in the diabetes group than in the control group.

Twenty percent of diabetes patients had orthostatic hypotension and 10% of them were symptomatic, presenting mainly the systolic blood pressure fall.

In resting conditions (supine position) diabetes patients with orthostatic hypotension had remarkably lower TP and VLF spectrum in comparison to healthy persons and diabetes patients without co-existent orthostatic hypotension. We did not note any significant differences of LF and HF (neither in ms^2 nor in NU) between the groups (Fig. 1).

During tilting we observed lower TP and VLF values and also significantly lower values of LF, HF and LF/HF ratio in diabetes group with orthostatic hypotension.

Table 1. Prevalence of symptomatic or asymptomatic orthostatic hypotension in healthy persons and in diabetes patients.

		Diabetic group		Control group	P (examined *vs.* control group)
		Asymptomatic hypotension	Symptomatic hypotension		
Systolic blood pressure decrease	9 (19%)	5	4	1 (3%)	0.001
Diastolic blood pressure decrease	11 (23%)	9	2	0 (0%)	0.001

Table 2. The values of heart rate variability parameters in frequency-domain measured in supine position and in standing position in healthy persons and diabeties patients with (+) and without (–) orthostatic hypotension (OH).

	Diabetic group		Control group
	OH(–)	OH(+)	OH(–)
Supine			
TP [ms^2]	4356 ± 3251	2979 ± 2313^{AB}	4749 ± 3467
VLF[ms^2]	2746 ± 2936	1319 ± 784^{AB}	3197 ± 2958
LF [ms^2]	1061 ± 794	1180 ± 1142	1093 ± 912
HF [ms^2]	489 ± 314	471 ± 423	503 ± 434
LF/HF ratio	2.96 ± 1.9	3.01 ± 2.7	2.36 ± 1.8
Standing			
TP [ms^2]	3778 ± 2555	2385 ± 1842^{AB}	4398 ± 4009
VLF [ms^2]	1972 ± 1542	789 ± 522^{AB}	2918 ± 2960
LF [ms^2]	1131 ± 863	852 ± 625^{AB}	1320 ± 972
HF [ms^2]	367 ± 214	302 ± 258^{AB}	424 ± 377
LF/HF ratio	3.12 ± 2.7	2.70 ± 2.2^{AB}	3.33 ± 2.6

TP — total power; VLF — very low frequency; LV — low frequency; HF — high frequency; A: $p < 0.005$ *vs.* subgroup without orthostatic hypotension; B: $p < 0.001$ *vs.* control group

Table 3. The values of heart rate variability parameters in frequency-domain measured in normalized units during supine position and in standing position in healthy persons and diabetes patients with (+) and without (–) orthostatic hypotension (OH).

	Diabetic group		Control group
	OH(–)	OH(+)	OH(–)
Supine			
LF [NU]	67.5 ± 11.2	72.3 ± 14.3	70.8 ± 14.8
HF [NU]	31.6 ± 9.7	27.4 ± 8.1	33.5 ± 11.2
LF/HF [NU]	2.17 ± 1.6	2.50 ± 1.5	2.17 ± 1.9
Standing			
LF [NU]	64.2 ± 10.8^{B}	53.2 ± 11.9^{AB}	89.2 ± 13.0
HF [NU]	21.7 ± 8.6	18.9 ± 9.9^{AB}	26.8 ± 11.3
LF/HF [NU]	3.08 ± 2.3	2.73 ± 1.8^{AB}	3.32 ± 2.7

LV — low frequency; HF — high frequency; A: $p < 0.005$ *vs.* subgroup without orthostatic hypotension OH(–); B: $p < 0.001$ *vs.* control group

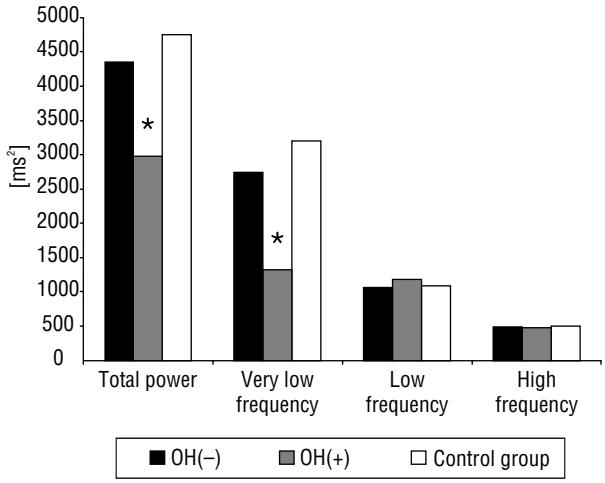

Figure 1. Heart rate variability spectral parameters measured in supine position in healthy persons and diabetes patients with and without orthostatic hypotension; OH(–) — diabetes patients subgroup without orthostatic hypotension; OH(+) — diabetic patients subgroup with orthostatic hypotension; $p < 0.005$ *vs.* OH(–); $p < 0.001$ *vs.* control group.

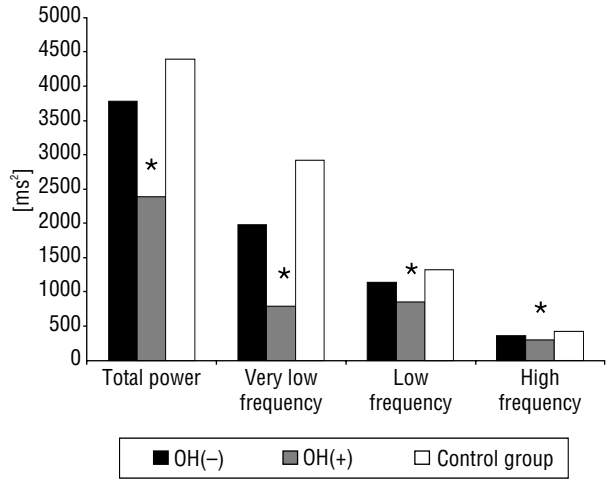

Figure 2. Heart rate variability spectral parameters measured in standing position in healthy persons and diabetes patients with and without orthostatic hypotension; OH(–) — diabetes patients subgroup without orthostatic hypotension; OH(+) — diabetes patients subgroup with orthostatic hypotension; $p < 0.005$ *vs.* OH(–); $p < 0.001$ *vs.* control group.

Moreover, in standing position diabetes patients without orthostatic hypotension had lower LF values (NU) in contrast to the control group (Fig. 2).

After tilting a decrease of LF spectrum component in diabetes group with and without orthostatic hypotension was found, contrary to healthy persons in which LF spectrum increase was noted (Fig. 3).

Discussion

The clinical importance of orthostatic hypotension is not appreciated because the measurement of blood pressure during orthostatic stress is rarely checked. We find orthostatic hypotension as one of the most disturbing symptoms of autonomic dysfunction. It significantly impairs the quality of life. Its occurrence in a group of patients above 70 increases the risk of death twice [10]. The intensity of patients complaints does not always correlate with the degree of blood pressure fall during tilting [11]. The clinical symptoms depend on flow changes in cerebral circulation and occur much earlier than blood pressure fall [12].

The volume changes of blood and blood pressure changes after tilting in healthy persons are

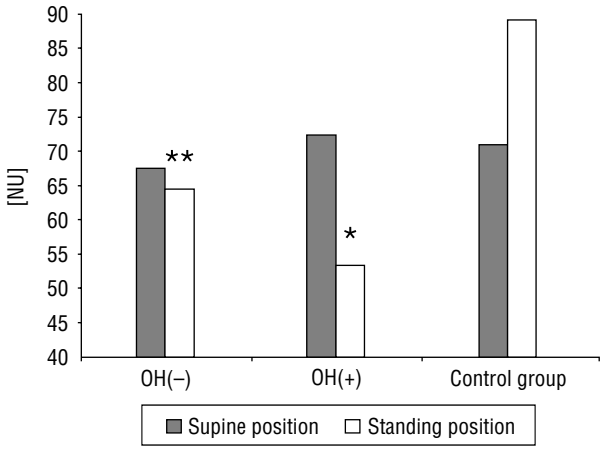

Figure 3. Changes in low frequency spectrum (NU) after tilting in healthy persons and diabetes patients with and without orthostatic hypotension; OH(–) — diabetic patients subgroup without orthostatic hypotension; OH(+) — diabetic patients subgroup with orthostatic hypotension; *p < 0.001 *vs.* control group; **p < 0.005 *vs.* control group.

detected by baroreceptors [13]. Information coming from baroreceptors reaches the centres in the brain stem, which are responsible for cardiovascular regulation. They modulate the activity of efferent sympathetic and parasympathetic fibres. It leads to changes in vascular tension, heart contractility and rhythm. After tilting we can observe orthostatic hypotension in patients with impaired physiological mechanisms of counteracting the results of decreased preload [3].

The impaired function of efferent part of autonomic system often leads to orthostatic hypotension. In diabetes there is peripheral damage of autonomic system leading to the reduction of sympathetic and parasympathetic activity — with sympathetic predominance [1]. Loss of autonomic system function occurs after diabetes onset and progresses thereafter [1, 2]. The main trigger of this pathology is decompensation of diabetes [14, 15]. It is estimated that diabetic neuropathy occurs in 30–66% of diabetes patients [16, 17] and as much as 87% of patients including subclinical cases [18]. So far there are no uniform criteria of the diagnosis of neuropathy, especially in asymptomatic patients. Nowadays the Ewing test and its modifications have only historical value [19, 20]. There are many scales to estimate the extent of neuropathy such as CASS (Composite Autonomic Severity Score) [21]. The analysis of HRV is a recognized method to evaluate cardiac autonomic neuropathy. It is performed as a 24-hour analysis or short-term test, particularly during orthostatic stress test, deep breathing and Valsalva test [7]. Many authors showed that HRV analysis in the preclinical stage of DAN is more sensitive than Ewing test [6]. Along with HRV estimation in a 24-hour registration and short term (5–15 min) recording in stable conditions, specific provocation tests are used for assessment of the components of autonomic system.

The orthostatic stress test is one of them. It causes sympathetic activation and demonstrates its adequacy. The Valsalva test and deep breathing test monitor mainly the parasympathetic component of autonomic system [22]. Healthy persons after tilting demonstrate heart rhythm acceleration and TP and HF decrease. The increase of LF is a sign of adrenergic stimulation and vagal inhibition [7, 23]. In a group of diabetes patients with orthostatic hypotension we registered decreased values of TP and VLF spectrum in stationary conditions. The orthostatic stress test revealed a significant decrease of all spectrum values (TP, VLF, LF, HF) in the group with orthostatic hypotension.

Because physiologic reaction for vertical position is TP [7, 23, 24] decrease we analysed LF and HF in normalized units in order to estimate their absolute changes.

In diabetes group with or without orthostatic hypotension we registered LF (NU) fall, contrary to the control group with LF (NU) increase. LF (NU) fall was particularly excessive in a subgroup with orthostatic hypotension but was also observed in a group without orthostatic hypotension.

Thus the altered response of LF spectrum for vertical position is the evidence of autonomic dysfunction. It occurs much earlier than symptomatic hypotension representing a more serious autonomic disorder.

This study emphasizes the use of HRV analysis during the upright tilt test in the diagnosis of DAN at early stages. Especially it can be helpful in cases where HRV parameters in rest conditions are not suggestive for any pathology.

Conclusions

Orthostatic hypotension is a frequent finding in young patients with long-lasting type I diabetes. Systolic blood pressure fall as an answer for orthostatic stress is a stronger factor causing symptoms of hypotension than diastolic blood pressure fall.

Diabetes patients with orthostatic hypotension have more advanced autonomic dysfunction contrary to diabetes patients without orthostatic hypotension.

It can be observed as the decrease of all components of HRV spectrum during tilting. diabetes patients with orthostatic hypotension have pathologic fall of LF component (in normalized units) of heart variability spectrum. Also, diabetes patients without orthostatic hypotension have inadequate reaction of LF (normalized units) for orthostatic stress but it is less pronounced.

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