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Clinical improvement in patients with orthostatic intolerance after treatment with bisoprolol and fludrocortisone

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Orthostatic intolerance **is the development of disabling symptoms upon assuming an upright posture that are relieved partially by resuming the supine position. Postural tachycardia syndrome (POTS) is an orthostatic intolerance syndrome characterized by palpitations because of excessive orthostatic sinus tachycardia, lightheadedness, tremor, and near-syncope. Patients usually undergo extensive medical, cardiac, endocrine, neurologic, and psychiatric evaluation, which usually fails to identify a specific abnormality. The authors investigated the autonomic and hemodynamic profile of patients with POTS and the effectiveness of bisoprolol and fludrocortisone. The authors evaluated 11 female patients with POTS before and after medical treatment with a cardioselective bisoprolol β-blocker or fludrocortisone, or both, and 11 age-matched control patients. Variability of heart rate and systolic blood pressure was assessed by fast Fourier transform, and spontaneous baroreceptor gain was assessed by use of the temporal sequences slope and α index. Modelflow was used to quantify hemodynamics. Symptoms in all patients improved greatly after medication. The autonomic and hemodynamic impairment observed in patients with POTS, particularly after orthostatic stress, is treated effectively with bisoprolol or fludrocortisone or both. These results need further confirmation in a controlled double-blind study. Proper medical treatment improves dramatically the clinical and autonomic–hemodynamic disturbances observed in patients with POTS. The data support the hypothesis that POTS is the result of a hyperadrenergic activation or hypovolemia during orthostasis.**

Key words: POTS, orthostatic intolerance, noninvasive hemodynamics, autonomic activity, bisoprolol, fludrocortisone.

Orthostatic intolerance is the development of disabling symptoms (palpitations because of excessive sinus tachycardia, lightheadedness, tremor, syncope, or near-syncope) when assuming an upright posture, which are partly relieved by resuming the supine position [1]. The condition predominantly affects younger persons, and women more than men [2]. Onset can be sudden and have a dramatic impact on patient well-being and work capacity. The condition almost always is misdiagnosed as a psychiatric disorder [2].

In persons with orthostatic intolerance, heart rate increases excessively during standing, resulting in increased stress on the cardiovascular system to maintain adequate blood pressure and blood flow to the brain [1,2]. Arterial baroreceptors play an important role in the regulation of blood pressure and hemodynamic response to postural changes. Any disruption can result in an inappropriate response to assuming the upright position and can lead to several symptoms, including syncope or near-syncope. The best-characterized syndrome of orthostatic intolerance is postural tachycardia syndrome (POTS), which is disabling [1–4]. Patients usually undergo expensive and extensive medical, cardiac, endocrine, neurologic, and psychiatric evaluation, which often does not identify a specific abnormality. The aim of the current study was to evaluate the clinical, autonomic, and hemodynamic profile of patients with POTS and the effectiveness of pharmacologic treatment with a cardioselective β-blocker (bisoprolol) or fludrocortisone or both.

Patients and methods

Patients

We studied 11 female patients (age range, 17–57 y; mean age ± SD, 31 ± 11 y) with overt POTS–at least with orthostatic grade by symptoms (OGS) grade 3, with severe limitation in activities of daily living but able to stand more than one minute on most occasions (1). Patients were taken from a sample of 310 new patients with unexplained syncope or near-syncope who were evaluated in the Autonomic Laboratory between January 1997 and December 1998. Patients were enrolled in the study if they met the following criteria (OGS > 3): (1) an increase in heart rate of more than 30 beats per minute and a decrease in blood pressure of less than 20/10 mm Hg when assuming the upright position; (2) at least a daily occurrence of disabling orthostatic symptoms (excessive palpitation, light-headedness, tremor, syncope, or near-syncope) that do not occur while in the supine position; (3) an ability to stand for more than 1 minute on most occasions and; (4) limitations in normal daily activities. Eleven age-matched healthy females served as control patients. Routine examination, including electrocardiography, echocardiography, Holter monitoring, 24-hour

ambulatory blood pressure monitoring, and plasma thyroid hormone levels, was performed for all patients and showed no abnormalities. All patients were nonsmokers and were not prescribed any medication, except for birth control pills. Patients were asked not to drink coffee on the day before testing, and to fast for at least 8 hours before the administering of tests. All patients gave informed consent. The study was approved by the local institutional ethics committee.

Study protocol

Room temperature in the Autonomic Laboratory was approximately 22°C. The tests always began at 10 AM. After a 30-minute bed rest, data were recorded during a 10-minute period with the patient in the supine position. Patientr then were tilted (70° head-up, with an electrically-driven table), with footboard support for a maximum of 45 minutes. A hand support was used to permit the acquisition of Finapres waves at heart level in the supine and tilted positions. If a patient met the OGS grade of more than 3 for POTS criteria [1], with reproduction of the postural symptoms, he or she was asked to undergo at least a 3-minute test to enable the acquisition of data. During tilt, continuous recording of electrocardiogram and blood pressure, beat-by-beat, was registered and stored simultaneously.

Bisoprolol (5 mg one time daily) was prescribed to patients with POTS, with the exception of one patient who was asthmatic and was prescribed fludrocortisone (0.1 mg twice daily). All patients were instructed to increase salt intake. Patients were examined for signs of clinical improvement 6 weeks later. If orthostatic symptoms still were apparent, fludrocortisone was added to the bisoprolol. All patients were re-evaluated at 12 weeks. The study had no placebo arm.

Noninvasive arterial pressure and electrocardiogram signal monitoring

The digital arterial pressure was obtained noninvasively with use of a commercial Finapres device (model 2300; Ohmeda, Englewood, CO, USA). With this technique, a plethysmographic finger-stall is placed around the medium phalanx of the third finger, and the pressure of this finger-stall is modulated in such a manner that the transmural pressure effectively remains zero. Therefore, the variations of the pressure of the stall vary simultaneously with the variations of the arterial pressure of the finger. All Finapres recordings were made at the heart level [5].

The automatic calibrations generated by the "servo-reset" of the device were turned off during the recordings to allow the acquisition of continuous beat-by-beat data; calibrations were generated in the intervals between the maneuvers. The analog pressure curve from the Finapres and the electrocardiogram were digitized, with a sampling rate of 500 Hz (Dataq model DI-420; Data 9 Instruments, Inc., Akron, OH, USA) and stored for later processing and analysis.

Calculations of R-R intervals and systolic arterial pressure were performed with use of software that uses an algorithm (Dataq calculation package, version 3.14) that allows the detection of the peaks of the R wave of the electrocardiogram and the peaks of the simultaneous Finapres arterial wave. The recordings were edited manually for correction of mistakes as a result of artifacts, T-wave detection, and ectopic beats [6].

Analysis of heart rate and systolic pressure variability

The spectrum analysis of heart rate variability and systolic blood pressure variability was performed with use of Matlab software (MathWorks Inc., South Natick, MA, USA) in a Pentium (Intel Corp., USA) computer system [6,7] specifically developed to provide a flexible analysis system. Spectral analysis was performed by use of the nonparametric Welch method [8]. The 256 R-R intervals and systolic pressure values were divided into seven blocks of 64 points with 50% overlap. For each block, the data were detrended (the mean value and the linear trend were estimated and removed), and a Hanning data window was applied. The spectrum was decomposed after normalization of the frequency axis by the average mean heart rate or systolic pressure for the 256 series in two bands: (the high-frequency (HF) component, between 0.15 and 0.40 Hz and the low-frequency (LF) component, between 0.05 and 0.15 Hz. We also used, in heart rate variability analysis, the normalized units of LF and HF components that are calculated by dividing the LF or HF power by the total power above 0.05 Hz and multiplying by 100 to quantify the so-called sympathovagal balance [9,10].

Calculation of spontaneous gain of arterial baroreceptor

We calculated the spontaneous arterial baroreceptor gain in two ways:

(1) The method that uses the temporal sequences is based on the analysis of the occurrence of sequences in which successive variations of the values of the systolic arterial pressure correlated with the duration of the (barosequences). The software automatically chose the sequences when variations were higher than 3.3 msec per unit of pressure (mm Hg). The regression line relating all these sequences was calculated and represented the gain of the arterial baroreflex. The average of all sequences gives the overall measure of the gain of the baroreceptor [11]; for example, a hypothetical sequence of systolic pressures of 122 mm Hg, 124 mm Hg, 127 mm Hg, and 129 mm Hg, accompanied by changes in the R-R interval of 700 msec, 742 msec, 775 msec, and 806 msec, will generate a slow sequence (decrease of heart rate) with a correlation coefficient of 0.992 and a sensibility or gain of the baroreceptor of 14.5 msec/mm Hg. In this type of analysis, only sequences with a correlation coefficient (R) more than 0.80 are used [11].

(2) The method that uses the spectral coherence (α index) is based on the assumption that oscillations of the arterial pressure in the band centered at 0.10 Hz, obtained by spectral analysis of systolic blood pressure variability, represent rhythmic fluctuations of vasomotor activity mediated by the arterial baroreflex (also known as Mayer waves). This band in the spectrum of heart rate variability seems to correspond to the sympathetic and vagal

adjustments mediated by the baroreflex [12]. From the spectral analysis of heart rate variability and systolic blood pressure variability, the cross-correlation between them is calculated. The baroreflex gain is estimated by the gain of the transfer function in the spectral bands when good coherence exists (more than 50%) between the spectra of the systolic pressure and R-R interval. The baroreceptor sensitivity is calculated by the module of the cross-spectra of the R-R interval and systolic blood pressure between 0.04 and 0.15 Hz.

The spontaneous-gain method (temporal or spectral) correlates well with pharmacologic methods [13], which are less convenient because they necessitate the introduction of external stimuli and drugs with direct vascular effects, such as phenylephrine.

Calculation of noninvasive hemodynamics

To estimate cardiac output and total peripheral resistance, we chose a method developed by Wesseling [14] because of its simplicity, low cost, and noninvasive nature. This method uses the analysis of the wave of digital arterial pressure obtained by Finapres, Portapres, or intra-arterial recordings for calculation of the various hemodynamic parameters, after applying the beat-to-beat modelflow software interpretation, BMI. Several studies have shown the application of this trielementary model of arterial impedance for describing the relation between aortic pressure and flow [15]. After model parameters are detected, flow can be computed from measured pressure by simulating the model [15]. This flow provides a continuous measure of cardiac output. Integrated over one heartbeat, it provides stroke volume. The nonlinear trielementary model represents the three main characteristics of the aortic impedance and allows a precise calculation of stroke volume and cardiac output. Wesseling [14] reports a very good correlation between absolute values obtained by this technique and by thermodilution invasive techniques (with errors <2%). However, this method is usually used for assessing changes (by percent) in the hemodynamic data from normal controls. The estimation of stroke volume by modelflow applied to the Finapres arterial pressure wave rather than intraarterial recordings, and is already validated [16,17].

Statistical analysis

Results are presented as the mean ± standard deviation. For statistical analysis, nonparametric methods were used. For comparisons of mean among all patients and all control patients, the Kruskall-Wallis test was used. For comparison of changes in paired samples, the Wilcoxon rank sum test was used. A p value <0.05 was considered to be significant.

Results

Patients were examined for subjective orthostatic improvement of symptoms after 6 weeks. The 10 patients who were undergoing β-blocker therapy all improved. Seven of the 10 became asymptomatic, as did the patient treated with fludrocortisone. The three patients who still had symptoms (two with mild orthostatic symptoms, namely dizziness, and one with fatigue) were prescribed fludrocortisone, 0.1 mg, one time daily and β-blocker therapy.

All 11 patients were asymptomatic at 12 weeks from the start of initial therapy and were reassessed with use of the

Table 1. Autonomic and hemodynamic variables in the three groups in the supine position (basal) and after the first 5 minutes of tilt

	Basal			Tilt		
	Patients with POTS	Patients with POTS (after treatment)	Control patients	Patients with POTS	Patients with POTS (after treatment)	Control patients
CO	5.38 (2.20)	4.15 (2.09)§	5.03 (0.84)	4.17 (2.08)	3.48 (1.66)§	3.75 (0.47)
SV	58.1 (21)	60.6 (26.7)	69.2 (11.5)	34.0 (11)	41.6 (14.9)§	46.8 (5.1)⩽
TPR	1409 (551)	1733 (793)	1424 (288)	2284 (1073)	2241 (834)	2166 (370)
HR	92.5 (13.8)	69.5 (9.8)§	75.0 (8.3)⩽	121.4 (14.2)	81.9 (10.2)§	87.7 (7.3)⩽
SBP	115.5 (26.1)	101.2 (19.1)	120.3 (10.6)*	136.1 (34.1)	110.6 (20.9)§	129.6 (9.6)*
DBP	66.8 (18.1)	58.3 (7.7)	65.9 (8.7)	87.8 (26.4)	71.0 (8.2)	80.2 (8)
BRG-α	15.2 (8.6)	22.8 (14.7)§	16.9 (6)	4.4 (2.8)	11.8 (7.6)§	9.0 (3.1)⩽
BRG-t	11.4 (5.5)	20.7 (11.1)§	16.4 (8.1)	6.4 (3.8)	10.7 (6.9)§	8.9 (3.4)
LF (RR)	523 (475)	951 (930)	821 (544)	540 (848)	546 (478)	750 (426)⩽
LF (ν)	41.3 (7.1)	40.1 (16.1)	43.0 (18.3)	55.8 (25.2)	51.1 (22.1)	67.1 (17.7)
HF (RR)	775 (1028)	1407 (1290)§	1128 (983)	203 (366)	923 (1586)	340 (340)
HF (ν)	45.8 (15.6)	50.9 (17.2)§	50.4 (18.6)	18.0 (7.4)	35.1 (16.1)§	27.8 (14.7)
LF (SBP)	2.4 (1.0)	3.5 (2.6)	3.8 (3)	23.1 (14)	7.4 (5.4)§	10.1 (5.9)⩽
HF (SBP)	1.7 (1.3)	1.6 (1.0)	1.3 (1)	5.5 (3.7)	3.5 (2.7)	4.1 (2.3)

§p <0.05 for changes between patients with POTS before and after treatment, in basal and tilt position.
⩽p <0.05 for changes between patients with POTS before treatment and normal controls, in basal, and in tilt position.
*p <0.05 for changes between patients with POTS after treatment and normal controls, in basal, and in tilt position.
Data are means (SD); CO = cardiac output in L/min; SV = stroke volume in ml; TPR = total peripheral–+ resistance in dyn.s.cm^{-5}; HR = heart rate in beats per minute; SBP = systolic blood pressure in mm Hg; DBP = diastolic blood pressure in mm Hg; BRG = baroreceptor gain (as α index or temporal sequences) in ms/mm Hg; LF (R-R) = absolute low-frequency component of HRV in ms2; LF (ν)-relative low-frequency component of HRV in ν; HF (RR)-absolute high frequency component of HRV in ms2; HF (ν) = relative high frequency component of HRV in ν; LF (SBP) = absolute low-frequency component of SBPV in mm Hg2; HF (SBP) = absolute high-frequency component of SBPV in mm Hg2.

same protocol as in the initial study (Tables 1 and 2). No significant side effects were observed in any patient (one patient had mild hypokalemia). Heart rate was higher in patients before treatment when in either position. Orthostasis provoked an increase in heart rate in patients before treatment, and, in treated patients, the heart rate response to orthostasis was similar to that in control patients (see Fig. 1). As expected, β-blocker therapy reduced significantly systolic blood pressure. After treatment, patients had lower values of systolic blood pressure than did healthy control patients when in any position. Patients with POTS before treatment had more of an increase (by percent) in systolic blood pressure when compared with the other two groups. No difference in diastolic blood pressure was found between groups in any situation.

Patients with POTS had lower cardiac output after therapy, both in the supine and in the upright position. Tilting provoked a higher decrease (by percent) in cardiac output in healthy patients than in patients with POTS who were treated. There were no statistical differences in stroke volume between the groups when the patients were in the supine position; however, untreated patients with POTS had a greater decrease in stroke volume during tilting than did either control patients or treated patients. In the supine position, patients had more of a baroreceptor gain after treatment than before treatment that was probably caused by the β-blocker effect. Patients with POTS before treatment had less of a baroreceptor gain when compared with the same patients after treatment (in any position) and with healthy patients (only in tilted position).

The only difference in the LF component of the R-R interval variability, absolute or normalized, between groups was a blunted response to tilt in patients with POTS patients before treatment when compared with controls. After treatment, patients with POTS had higher values of the HF component of the R-R interval variability than before treatment. No differences in the HF component of systolic blood pressure variability were found between any groups when in any position. The LF component of systolic blood pressure variability showed that patients with POTS had a significant increase of this component when they experienced orthostatic stress, when compared with the other two groups (Fig. 2). There were no differences between POTS patients after treatment and healthy control patients in the LF component of systolic blood pressure variability.

Table 2. Differences in autonomic and hemodynamic variables in first 5 minutes of tilt (∇ tilt/basal) in the three groups

	Patients with POTS	Patients with POTS (after treatment)	Control patients
CO	−1.21 (1.32)	−0.67 (0.87)	−1.29 (0.54)*
SV	−24.2 (10.9)	−19.1 (18)	−22.5 (11.4)
TPR	875 (769)	507 (758)	742 (327)⋞*
HR	28.8 (17)	12.4 (7.2)§	12.7 (6.8)⋞
SBP	20.7 (17.7)	9.4 (6.7)§	9.3 (9.2)⋞
DBP	21 (11.1)	12.7 (6.7)	14.3 (7)
BRG-α	−10.8 (8.1)	−11.2 (10)	−7.9 (4.5)*
BRG-t	−5.0 (3.8)	−10.0 (8.7)§	−7.6 (6.6)
LF (RR)	−17 (682)	−405 (743)	−70 (498)
LF (ν)	14.6 (28.8)	11.0 (17.7)	24.1 (9.9)⋞
HF (RR)	−573 (711)	−484 (702)	−787 (912)
HF (ν)	−27.8 (14.5)	−15.8 (12.5)	−22.6 (9.7)
LF (SBP)	20.7 (14.2)	3.9 (3.9)§	6.3 (4.7)⋞
HF (SBP)	3.8 (2.8)	1.9 (2.9)	2.8 (2.1)

§$p < 0.05$ for changes between POTS before and after treatment.
⋞$p < 0.05$ for changes between POTS before treatment and normal controls.
*$p < 0.05$ for changes between POTS after treatment and normal controls.
Data are mean (SD), CO = cardiac output in L/min; SV = stroke volume in ml; TPR = total peripheral resistance in dyn.s.cm^{-5}; HR = heart rate in beats per minute; SBP = systolic blood pressure in mm Hg; DBP = diastolic blood pressure in mm Hg; BRG = baroreceptor gain (as α index or temporal sequences) in ms/mm Hg; LF (RR) = absolute low-frequency component of HRV in ms2; LF (ν) = relative low frequency component of HRV in normalized units; HF (RR) = absolute high-frequency component of HRV in ms2; HF (ν) = relative high-frequency component of HRV in normalized units; LF (SBP) = absolute low-frequency component of SBPV in mm Hg2; HF (SBP) = absolute high-frequency component of SBPV in mm Hg2.

Discussion

The main finding of this study was that postural tachycardia syndrome can be treated effectively, with great improvements in orthostatic symptoms and in autonomic and hemodynamic disturbances. Treatment with sodium-loading [18] but not with erythropoietin, which enhances blood cell volume and slightly increases blood pressure [19], seems to improve the quality of life in the patients. This suggests that the cause of POTS symptoms is not decreased red blood cell volume but is more likely related to a duration-dependent sympathetic neuropathy [20], which causes orthostatic venous pooling in the leg and is aggravated by idiopathic hypovolemia [21]. Idiopathic orthostatic tachycardia responds well to saline infusion to correct underlying hypovolemia [22]. The favorable response of patients with POTS to midodrine administration supports the suggestion of some type of autonomic dysfunction with loss of adequate lower extremity vascular tone [22]. This study reports for the first time the usefulness of a selective β1-blocker, bisoprolol, combined when needed with a salt-retaining drug (fludrocortisone), in the treatment of hemodynamic and autonomic disturbances in patients with POTS. Therefore, reversal of an abnormal sympathetic vasomotor response is necessary for the prevention of postural symptoms. Low [1] proposed that in patients with florid POTS, such as the patients in this study, a β-blocker is the preferred treatment because it is in a hyperadrenergic state. We chose bisoprolol because of the fewer side effects, namely fatigue, when compared with propranolol because it is given once a day, and because it is lipophylic.

The autonomic and hemodynamic findings in this study are similar to recently published data by Novak *et al.* [23]. In that study, the effectiveness of the treatment of patients has not been evaluated. Novak *et al.* [23] refer to clinical, autonomic, and hemodynamic indexes that could improve the diagnosis of POTS in the wide range of orthostatic

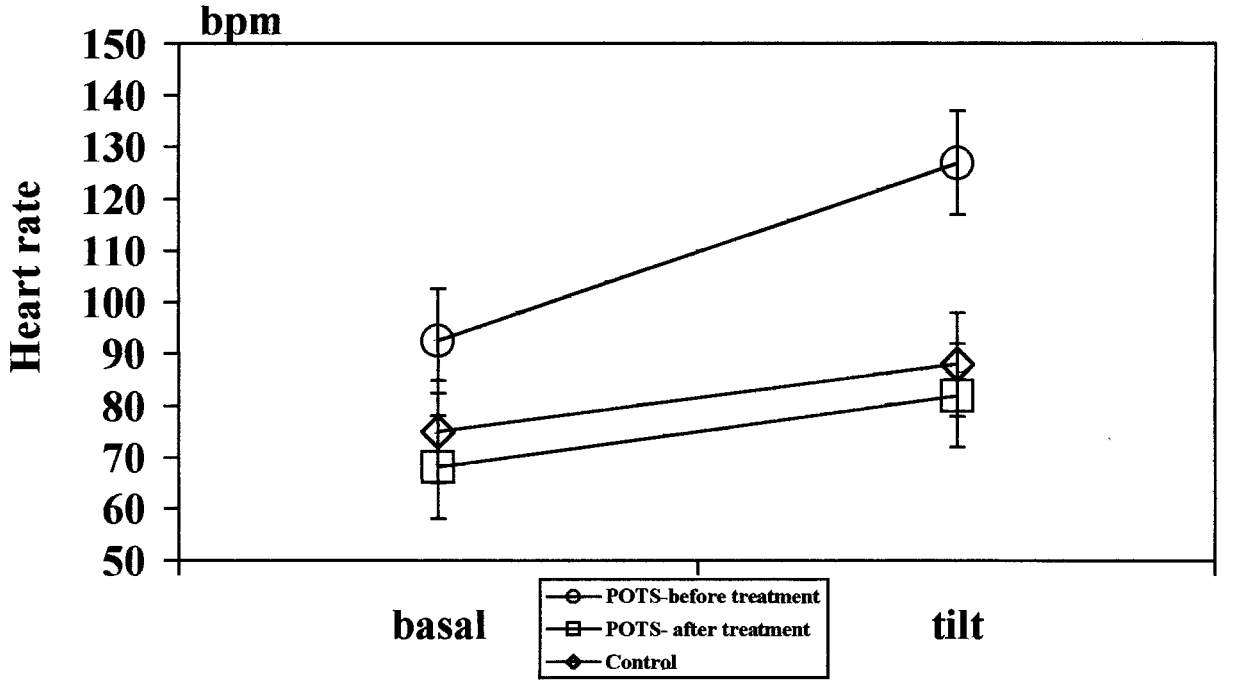

Figure 1. Heart rate before and after tilt in patients with POTS, before and after treatment, and in healthy controls.

intolerance and chronic fatigue syndromes [24]. A hyperadrenergic state and distal neuropathy, affecting adrenergic sympathetic cardiovagal fibers, seem to be involved in the pathophysiology of POTS [22,23], which may explain the effectiveness of our treatment.

Furlan *et al.* [25] had similar results as Novak *et al.* [23]. Furlan *et al.* [25] performed muscle sympathetic nerve activity measurements to evaluate the sympathetic dysfunction. The patients with orthostatic intolerance had a blunted muscle sympathetic nerve activity response to tilting, and the authors concluded that there was a cardiac compensatory sympathetic overactivity and a blunted postganglionic sympathetic vasoconstrictory response to standing. Again, effectiveness of treatment was not assessed.

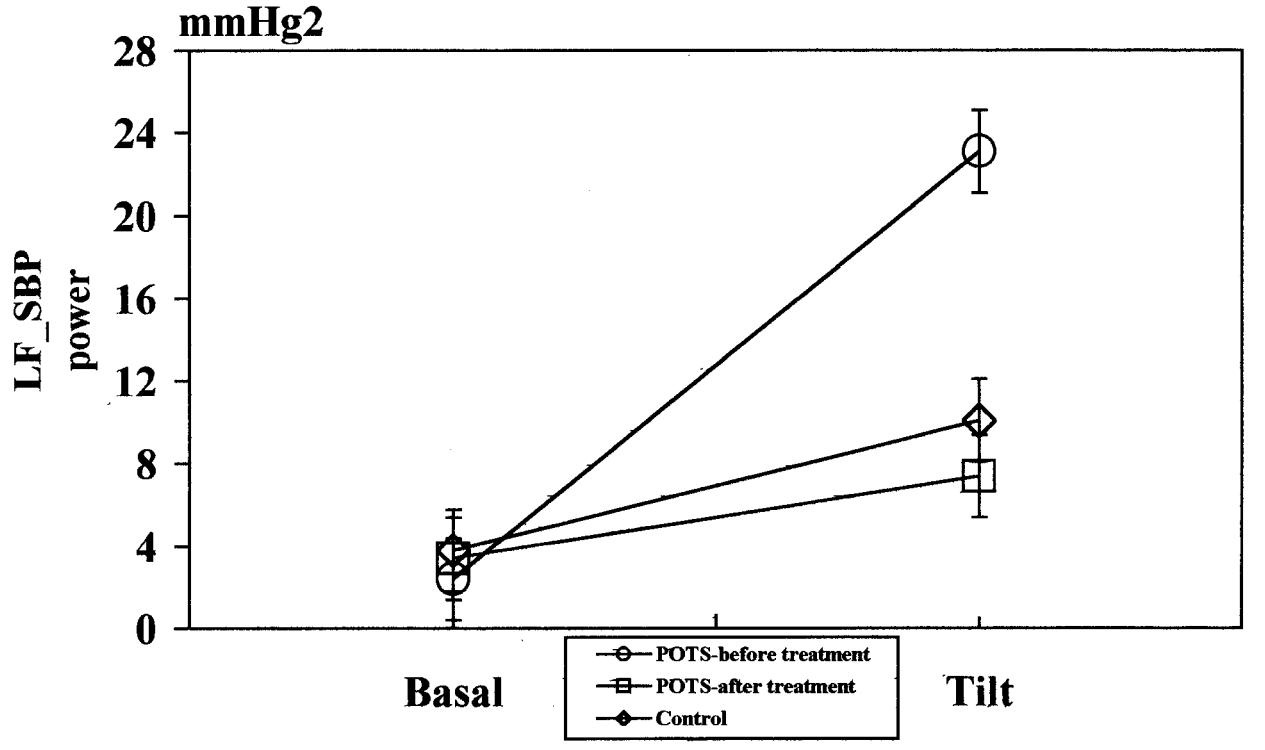

Figure 2. Low-frequency sympathetic vasomotor component before and after tilt in patients with POTS, before and after treatment, and in healthy controls.

Jacob [22] evaluated heart rate and systolic blood pressure in patients with orthostatic intolerance and the effects of saline loading, clonidine, and midodrine. This study showed that saline infusion was the most effective treatment in stopping the increase in heart rate and the systolic blood pressure disturbances in patients with POTS. Clonidine, but not midodrine, worsened the orthostatic symptoms. Some authors argue that the orthostatic symptoms in patients with POTS partially may be a result of an increase in cerebrovascular resistance in the orthostatic position because of an increase in depth of respiration, which results in hypocapnic cerebrovascular constriction and impaired autoregulation, in contrast with patients with orthostatic hypotension where the autoregulated control typically is expanded [26].

The autonomic indices observed in our study confirm the suggestions of Novak *et al.* [23] and Eckeberg [10] that the HF spectral component of the R-R interval is a good marker of vagal tonic activity and that the LF component of the R-R interval is not an index of sympathetic activity, even after normalization because even in healthy persons it does not increase with orthostatic stress. There was a good correlation of sympathetic vasomotor activity with the LF component of systolic blood pressure variability, with a sharp increase when in the tilted position, particularly in patients with POTS. The HF component of blood pressure variability does not have an autonomic origin; it depends instead on the mechanical effects of respiration because it increases in any group after assuming the tilted position [27].

Study limitation

Limitations of the study include the short follow-up period, the small number of patients, and the absence of male patients older than 18. Muscle sympathetic nerve activity and beat-to-beat recording of blood flow velocity with use of transcranial Doppler imaging have not been performed. A placebo arm was not used because previous published data showed a significant clinical improvement with β-blocker therapy in these patients [1,28]; however, these results need further confirmation in a controlled double-blind study.

Conclusion

Patients with POTS had only a slightly higher heart rate and lower heart rate variability when in the recumbent position than did control patients. Hemodynamic and autonomic parameters in the patients with POTS before treatment showed significant modifications in the upright position during head-up tilt. Treatment with bisoprolol or fludrocortisone, or both, normalized these hemodynamic and autonomic disturbances during orthostatic stress. Because this syndrome is often misdiagnosed and can be treated easily, resulting in marked clinical improvement, more attention should be paid to its correct and timely diagnosis. Long-term randomized double-blind studies with more patients and male participants will be necessary to confirm the findings of this observational study.

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