

Variability of postural orthostatic tachycardia in patients with myalgic encephalomyelitis and orthostatic intolerance

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Abstract Central nervous system dysfunction with myalgic encephalomyelitis (ME) has been suggested as the main cause of chronic fatigue syndrome. Fluctuation of the symptom severity and hierarchy is a characteristic feature in ME patients. The characteristics of the sympathetic activation may differ between the “good days” and “bad days” in them. Twenty-four ME patients with orthostatic intolerance underwent a conventional 10-min active standing test and echocardiography both on a “good day” and a “bad day”, defined according to the severity of their symptoms. The mean heart rate at rest was significantly higher on the “bad days” than on the “good days”. During the standing test on a “bad day”, 5 patients (21 %) failed to maintain an upright posture for 10 min, whereas on a “good day” all the 24 patients maintained it. Postural orthostatic tachycardia (POT) (increase in heart rate ≥ 30 beats/min) or severe POT (heart rate ≥ 120 beats/min) was observed on the “bad days” in 10 patients (43 %) who did not suffer from the severe tachycardia on the “good days”, suggesting the exaggerated sympathetic nervous activation. In contrast, POT did not occur or severe POT was attenuated on the “bad days” in 5 patients (21 %) who developed POT or severe POT on the “good days”, suggesting the impaired sympathetic activation. Echocardiography revealed significantly lower mean values of both the left ventricular end-diastolic diameter and stroke volume index on the “bad days” compared with the “good days”. In conclusion, in ME patients with orthostatic intolerance, the exaggerated activation of the sympathetic nervous system while standing appears to

switch to the impaired sympathetic activation after the system is loaded with the additional accentuated stimuli associated with the preload reduction.

Keywords Chronic fatigue syndrome · Myalgic encephalomyelitis · Orthostatic intolerance · Postural orthostatic tachycardia · Sympathetic nervous system

Introduction

Chronic fatigue syndrome (CFS) characterized by severe disabling fatigue, which is not resolved by rest, causes a marked reduction in the activities of daily living and impairs the quality of life [1–3]. Recently, dysfunction of the central nervous system associated with myalgic encephalomyelitis (ME) has been suggested as the main cause of CFS [4]. The International Consensus Criteria for ME differentiate the ME patients from those who are depressed and identify the patients who are more physically debilitated and have greater physical and cognitive impairments [4].

Orthostatic intolerance (OI) is a hallmark symptom of CFS or ME that restricts the daily functional capacity [5–9]. OI is characterized by the inability to maintain an upright posture without signs and symptoms such as hypotension, tachycardia, light-headedness, pallor, fatigue, weakness, dizziness, tremulousness, and nausea [10–12]. A vast majority of CFS patients experience symptoms related to OI, which strongly predicts the functional capacity, and in turn, the quality of life [8, 9, 13]. Most symptoms of OI are related to the reduced cerebral blood flow. In addition, the sympathetic activation via carotid sinus and aortic arch receptors, as a physiologic compensatory response, appears to be exaggerated in association with tachycardia, secondary to low stroke volume and cardiac output which is caused by venous

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pooling in the legs and buttocks while adopting an upright posture. This exaggerated response results in the development of symptoms of OI in the ME patients [8, 9, 14]. Both ME and OI affect many young individuals, predominantly women. Similar to the general symptoms of ME, the severity of the symptoms of OI also characteristically fluctuates between the “good days” and the “bad days”, possibly as a result of the changes in the sympathetic activation [4].

In the present study, hemodynamic alterations during OI were investigated using a conventional standing test, and left ventricular (LV) size and functions were echocardiographically evaluated to determine the differences in the characteristics of the sympathetic activation between the “good days” and “bad days” in the ME patients.

Materials and methods

Study population

Consecutive patients who were diagnosed with ME at our clinic and followed up regularly for at least 6 months were included in this study. The patients who were unable to stand up quickly were excluded. ME was diagnosed according to the International Consensus Criteria proposed in 2011 [4]. The study population comprised 24 ME patients, including 7 men and 17 women, with a mean age of 30 ± 9 years (range 15–47 years). All the patients had mild or more severe symptoms of OI, which was defined as instability in maintaining the normal consciousness while standing, without the significant symptoms such as disabling fatigue, dizziness, faintness, palpitation, diminished concentration, tremulousness, sweating, light-headedness, visual disturbances, and nausea [6]. All the study patients gave informed consent, and the ethics committee of our institution approved the study protocol.

Symptom grading

All the patients underwent standard M-mode echocardiography followed by the conventional active standing test every 1 or 2 months, and the performance status (PS) was graded as below, according to the severity of the symptoms. Both the “good day” and “bad day” were determined by the patients based on their symptoms either prospectively or retrospectively.

- PS 0 The patient can perform the usual activities of daily living and social activities without malaise.
- PS 1 The patient often feels fatigue.
- PS 2 The patient often needs to rest because of general malaise or fatigue.
- PS 3 The patient cannot work or perform usual

activities for a few days in a month.

- PS 4 The patient cannot work or perform usual activities for a few days in a week.
- PS 5 The patient cannot work or perform usual activities but can perform light work.
- PS 6 The patient needs daily rest but can perform light work on a “good day”.
- PS 7 The patient can take care of himself/herself but cannot perform usual duties.
- PS 8 The patient needs help to take care of himself/herself.
- PS 9 The patient needs to rest the whole day and cannot take care of himself/herself without help.

Conventional active standing test

All the patients were asked to undergo a conventional active standing test. The test was performed either in the morning or in the afternoon. No specific restrictions concerning the daily activities, such as meals, intake of caffeine, or smoking, were imposed prior to the test. After a 5-min rest period in the supine position, the patients were asked to stand up by themselves and to remain standing for 10 min. Hemodynamics, including the systolic and diastolic blood pressures and heart rate, were measured using a digital cuff pressure monitor (HEM-907, Omron; Kyoto, Japan) on the right arm, before standing, immediately after standing, and after 1, 3, 5, 7, and 10 min of standing and then in the recumbent position immediately after the end of the standing test and during any episode of the symptoms. Postural orthostatic tachycardia (POT) was diagnosed as an increase in the heart rate of ≥ 30 beats/min and severe POT was diagnosed as a heart rate of ≥ 120 beats/min, during the 10-min standing test. Instantaneous or delayed orthostatic hypotension was diagnosed as a decrease in the systolic blood pressure of ≥ 20 mmHg or in the diastolic pressure of ≥ 10 mmHg and/or a systolic pressure of ≤ 90 mmHg during the test. Neurally mediated hypotension was diagnosed as orthostatic hypotension with a decrease in the heart rate of ≥ 20 beats/min during the test.

Echocardiography

The LV dimensions were measured according to the recommendations of the American Society of Echocardiography [15]. The LV volume was calculated using the Teichholz formula [16] and the ejection fraction was determined [17].

Statistical analysis

The values are presented as the mean \pm standard deviation. Comparisons of the echocardiographic values or the

parameters between the “good days” and “bad days” or between the study subgroups were performed using analysis of variance followed by Student’s paired or unpaired *t* test. Comparison of PS grading scores between the “good days” and “bad days” or between the study groups were performed using Wilcoxon’s rank sum test. The proportional data were analyzed using the Chi-squared test with Yates’ correction. The value for significance was set at $p < 0.05$.

Results

The PS grading score was at least one higher on the “bad day” (PS: 3–6) than on the “good day” (PS: 2–5) for each patient. The score was significantly ($p < 0.01$) higher on the “bad days” compared with that on the “good days”. Comparative data between the “good days” and “bad days” for both the 10-min active standing test and echocardiographic examination are shown in Tables 1, 2, and 3.

The mean heart rate was significantly higher on the “bad days” than on the “good days” (Table 1), but both the mean systolic and diastolic blood pressures were comparable between the “good days” and “bad days”. All the patients complained of more severe symptoms of OI during the 10-min active standing test on the “bad days” than that on the “good days”. All the 24 ME patients (100 %) maintained an upright posture in the standing test on the “good days”, whereas 5 (21 %) of them failed to complete the test because of severe symptoms of OI (Table 1). POT occurred in 7 patients (29 %), including severe POT in 1 (4 %), on a “good day”. In these patients, the heart rate increased from 63 ± 7 (before standing) to 103 ± 15 (the maximal

Table 1 Comparison of conventional 10-min active standing test results between a “good day” and “bad day” in the 24 ME patients

	“Good day”	<i>p</i> value	“Bad day”
Number of patients	24		24
Inability to complete the test	0 (0 %)	0.06	5 (21 %)
Hemodynamics at rest			
Heart rate (beats/min)	63 ± 6	<0.001	73 ± 9
Systolic blood pressure (mmHg)	111 ± 9	0.42	113 ± 9
Diastolic blood pressure (mmHg)	65 ± 8	0.84	65 ± 8
Hemodynamics during an upright posture			
Normal	14 (58 %)	0.25	10 (42 %)
POT	6 (25 %)	0.53	8 (33 %)
Severe POT	1 (4 %)	ND	3 (13 %)
Sum of POT and severe POT	7 (29 %)	0.23	11 (46 %)
Orthostatic hypotension	3 (13 %)	ND	3 (13 %)
Neurally mediated hypotension	0 (0 %)	ND	1 (4 %)

ND analysis not done, POT postural orthostatic tachycardia

Table 2 Comparison of hemodynamic appearance during a conventional 10-min active standing test between a “good day” and “bad day” in the 24 ME patients

“Good day”	“Bad day”	Number of patients
Exaggerated sympathetic activation in the “bad day”		
Normal	POT	7
Normal	severe POT	1
POT	severe POT	1
POT	severe POT → NMH*	1 (1)
Total		10 (42 %)
Impaired sympathetic activation in the “bad day”		
POT	Normal	4 (2)
Severe POT	POT	1
Total		5 (21 %)
Others		
Normal	OH	1
OH	OH	2 (1)
Normal	Normal	5 (1)
OH	Normal	1
Total		9 (38 %)

The number of the patients who failed to complete the test on the “bad day” is shown in parentheses

ME myalgic encephalomyelitis, POT postural orthostatic tachycardia, NMH neurally mediated hypotension, OH orthostatic hypotension

* The patient gave up standing after 9 min because of NMH following POT

Table 3 Comparison of the echocardiographic findings between a “good day” and “bad day” in the 24 ME patients

	“Good day”	<i>p</i> value	“Bad day”
Number of patients	24		24
Heart rate (beats/min)	64 ± 8	0.03	69 ± 10
LVEDD (mm)	44 ± 4	<0.01	41 ± 6
Stroke volume index (ml/m ²)	35 ± 6	0.02	31 ± 7
Cardiac index (l/min/m ²)	2.3 ± 0.5	0.06	2.1 ± 0.5
LV ejection fraction (%)	68 ± 6	0.41	69 ± 8

ME myalgic encephalomyelitis, LV left ventricular, EDD end-diastolic diameter

rate) during the test. In the other 17 patients, the heart rate increased from 61 ± 5 to 81 ± 7 during the test. On a “bad day”, 11 patients (46 %) developed POT, including severe POT in 3 (13 %), during the standing test. In these patients the heart rate increased from 77 ± 9 to 114 ± 9 during the test. In the other 13 patients, the heart rate increased from 70 ± 10 to 88 ± 11 during the test. In 9 patients (38 %), POT or severe POT was not observed during the test either on a “good day” or “bad day”.

The comparison of the observed hemodynamic appearance while maintaining an upright posture between the

41F (ME) Conventional active standing test

2014/1/7		Good day (PS: 2) Normal						ECG
	Before	Stand up	1	3	5	7	10 min	
								HR:51
								EDD:49
P (beats/min)	59	67	79	70	66	70	69	SI:47
BP (mmHg)	113/63	113/70	125/78	125/79	117/69	119/72	117/76	CI:2.4
								mild faintness
2013/6/21		Bad day (PS: 3) POT						
	Before	Stand up	1	3	5	7	10 min	
								HR:68
								EDD:46
P	65	93	98	101	100	101	102	SI:38
BP	109/59	116/76	112/78	109/80	108/81	104/78	116/84	CI:2.6
								hot flushing, sweating and severe fatigue

Fig. 1 The conventional 10-min active conventional standing test recorded for a 41-year-old female ME patient, suggesting the exaggerated sympathetic activation on the “bad day”. On the “good day”, she felt mild faintness but showed normal hemodynamics throughout the test (*upper*). In contrast, on the “bad day”, she had severe symptoms of hot flushing, sweating, and severe fatigue associated with

POT (*lower*). ME myalgic encephalomyelitis, POT postural orthostatic tachycardia, PS performance status, HR heart rate (beats/min), BP blood pressure (systolic/diastolic: mmHg), ECG echocardiogram, EDD left ventricular end-diastolic diameter (mm), SI stroke volume index (ml/mm²), CI cardiac index (l/min/mm²)

“good days” and “bad days” is shown in Table 2. Eight patients with the normal hemodynamics on the “good day” developed POT, including severe POT in 1, on the “bad day”. Two patients who developed POT on the “good day” developed severe POT on the “bad day”. Therefore, in these 10 patients (42 %, group E), sympathetic activation was exaggerated more on the “bad day” than that on the “good day”. In contrast, 4 patients who developed POT on the “good day” had normal hemodynamic appearance on the “bad day”. Another patient who developed severe POT on the “good day” developed less severe POT on the “bad day”. Therefore, in these 5 patients (21 %, group I), sympathetic activation was impaired on the “bad day” with apparently improved or normalized hemodynamics. Typical cases are shown in Figs. 1 and 2.

The comparison between the echocardiographic findings on the “good days” and “bad days” is summarized in Table 3. At the time of echocardiographic examination, the mean heart rate was significantly higher on the “bad days” compared with that on the “good days”. The mean values for LV end-diastolic diameter (EDD) and stroke volume index were significantly lower on the “bad days” compared with those on the “good days”. The mean value of the cardiac index was lower on the “bad days” than that on the “good days”, but the difference was not significant. The echocardiographic parameters were also compared between

the groups E and I. The mean values for LVEDD (43 ± 2 vs 46 ± 3 mm, $p = 0.04$) and stroke volume index (31 ± 7 vs 37 ± 5 ml/m², $p = 0.03$) were significantly lower in the group I than those in the group E on the “good days”, although the mean cardiac index (2.2 ± 0.4 vs. 2.4 ± 0.2 , $p = 0.23$ l/min/m²) was not significantly different between the groups I and E. The mean heart rate (73 ± 4 vs. 65 ± 9 beats/min, $p = 0.04$) was significantly higher in the group I than that in the group E on the “good days”. The difference was not significant on the “bad days” (I: 74 ± 7 vs. E: 68 ± 8 beats/min, $p = 0.08$).

Discussion

The symptom severity and hierarchy frequently fluctuate in the patients with ME or CFS, although the precise mechanism is unknown [4]. In the present study, the exaggerated sympathetic activation, as suggested by the development of POT, was observed during the conventional active standing test on a “bad day” in majority of the ME patients. Conversely, the impaired sympathetic activation, as suggested by a failure to develop POT, was observed in the other patients who had developed POT on a “good day”. This unexpected finding has not been reported previously. Echocardiography revealed that the LV was diminished in

Fig. 2 The conventional 10-min active standing test recorded for a 25-year-old female ME patient, suggesting the impaired sympathetic activation on the “bad day”. On the “good day”, she felt mild faintness associated with POT but kept standing throughout the test (*upper*). In contrast, on the “bad day”, she had to lie down after 3 min because of severe symptoms of fainting, despite apparently normal hemodynamics. The abbreviations are the same as those in Fig. 1

25F (ME) Conventional active standing test

2010/6/5	Good day (PS: 3) POT			ECG
	HR	BP	Symptoms	
	(beats/min)	(mmHg)		
Before	55	100/49		HR: 60
Stand up	93	97/57	mild faintness	EDD: 38
3 min	84	103/60	mild faintness	SI: 29
			keep standing	CI: 1.7
2010/7/22	Bad day (PS: 5) Normal			
Before	67	108/67		HR: 64
Stand up	77	102/70	fainting	EDD: 34
3 min	75	105/72	fainting (severe)	SI: 22
			lying down on the bed	CI: 1.4

size, in association with the worse cardiac performance, based on a lower stroke volume index on the “bad days” compared with that on the “good days”. Hydration status or preload seemed to be linked to the fluctuation in the symptoms. The observed heart rate at rest was significantly higher on the “bad days” than that on the “good days” in the ME patients, suggesting generally accentuated sympathetic activation on the “bad days”. In several previous reports, a clear correlation was found between the levels of fatigue sensation and muscle sympathetic nerve activity during the static contraction [17, 18]. Furthermore, exhausting incremental exercise provokes sustained increases in the plasma noradrenaline levels, which outlast the termination of exercise by several hours [19]. Inappropriate sympathetic overactivity at rest might represent a neural functional correlate of fatigue [18, 19].

Alterations in the autonomic functions have recently been reported in the patients with ME or CFS, including orthostatic tachycardia, coldness of the extremities, hypothermia, episodes of sweating, profound pallor, sluggish pupillary responses, constipation, and frequent micturition [20]. The feeling of fatigue and exhaustion experienced by the ME patients has been attributed to their difficulty in maintaining an erect posture [17]. ME has features in common with a type of chronic OI that is accompanied by the exaggerated postural tachycardia and the enhanced sympathetic activity, linked to decreased plasma volume, sparing cardiac innervation [8, 9, 14, 20, 21]. Echocardiographic evaluation demonstrated that cardiac function was actually impaired with a low cardiac output secondary to a small

LV in many CFS patients [22–24]. Impaired activation of the renin–angiotensin–aldosterone system, which regulates the circulatory blood volume, may also have a role in the pathophysiology of ME and OI [25, 26].

The marked orthostatic tachycardia observed in majority of the ME patients in this study seems to be a physiologic compensatory response to a smaller stroke volume on the standing. In a previous study using impedance cardiography by Peckerman et al. [27], a reduced cardiac output was observed in the patients with severe CFS both in the supine and in the standing positions. In another study, the impaired cerebral oxygenation related to the altered cerebral hemodynamics in young CFS patients with OI during an active standing test was suggested based on the continuous measurement of cerebral oxygenated hemoglobin using near-infrared spectroscopy [28]. In that study, OI with the impaired cerebral oxygenation occurred, even with apparently preserved hemodynamics with a normal heart rate and blood pressure, suggesting the dysfunctional cerebral circulatory autoregulation.

In the present study, the patients with a resting sympathetic overactivity were even exaggerated on the “bad days” with reduced stroke volume secondary to diminished LV size. Sympathetic activity could be augmented when adopting upright posture even in the “bad days” if the residual sympathetic modulation was maintained in some patients with ME. In contrast, the exaggerated sympathetic overactivity at rest might result in the impaired sympathetic responsiveness to stimulation on standing, exacerbating symptoms of orthostatic intolerance in the

other ME patients. The residual sympathetic modulation appeared to be extremely limited in the latter patients. The mean values of LVEDD and stroke volume index were lower in these patients in the “good days”, suggesting poorer cardiac performance with preload reduction compared with that of the patients with additional sympathetic responsiveness. It is possible that the therapeutic effects by medication with adrenergic β blocking agents [29] or sinus node blocker ivabradine [30, 31] for relieving symptoms of OI are different between the “good days” and “bad days”. Reportedly, CFS patients have a slower acceleration of exercise heart rate and significantly less total exercise capacity, compared with that of the normal control subjects [32, 33]. Few of the patients in those studies achieved target heart rates during exercise. The apparent chronotropic incompetence observed during exercise may be related to the impaired sympathetic activation.

In conclusion, the condition of the prevailing sympathetic modulation at rest and reduced responsiveness to the excitatory stimuli, as shown by failure to develop POT on standing on the “bad days” when it did occur on the “good days”, has been suggested in some ME patients. In many other ME patients, the sympathetic activation was preserved, as shown by the development of POT on the “bad days” when it did not occur on the “good days”. The relatively small heart with impaired cardiac function secondary to a decreased preload observed in the ME patients may be an important potential target for the treatment of this disabling disease.

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Compliance with ethical standards

Conflict of interest The author declares that there is no conflict of interest.

Ethical standard This study is in compliance with the standards in the 1964 Declaration of Helsinki and its later amendments.

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