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The Abnormal Cardiac Index and Stroke Volume Index Changes During a Normal Tilt Table Test in ME/CFS Patients Compared to Healthy Volunteers, are Not Related to Deconditioning

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Abstract

Background. A small study in ME/CFS (Myalgic Encephalomyelitis/Chronic Fatigue Syndrome) patients undergoing tilt testing, showed that, despite a normal tilt test, stroke volumes and cardiac output were lower than in healthy volunteers. Moreover, it was suggested that this difference was related to deconditioning of patients. Aim of the study. We performed table testing in 150 ME/CFS patients. Stroke volumes and cardiac output were related to the severity of the disease.

Methods and results. In the patients the severity of the disease was clinically evaluated according to the ME criteria and scored as mild, moderate or severe disease. In a subgroup of 109 patients this clinical diagnosis was confirmed by the physical functioning score of the Rand-36 questionnaire. Significantly lower physical functioning scores (indicating worse functioning) were observed in the more severely affected patients. Stroke Volume Index (SVI) and Cardiac Index (CI) were measured by suprasternal aortic Doppler imaging in the supine position, prior to the tilt, and twice during the tilt. Thirty-seven healthy volunteers underwent the same tilt protocol. In all patients and all healthy volunteers, a normal heart rate and blood pressure response was observed during the tilt. The decreases in SVI and CI during the tilt was significantly larger in patients compared to the SVI and CI decrease in HV. The decrease in SVI and CI were similar and not significantly different between the mild, moderate, and severe ME groups.

Conclusions. During a normal tilt table test decreases in SVI and CI decrease are significantly greater in ME/CFS patients than in HV, consistent with previous work. The absence of differences between patients with mild, moderate, and severe ME/CFS suggests that the decreases in stroke volumes and cardiac output are not related to deconditioning. Other factors like decreased blood volumes and autonomic dysfunction may cause this difference in the hemodynamic response between ME/CFS patients and HV.

Keywords: Cardiac Output; Chronic Fatigue Syndrome; Deconditioning; Head-Up Tilt Test; Myalgic Encephalomyelitis; ME Severity; Rand-36 Questionnaire; Stroke Volume

Abbreviations

BMI	:	Body Mass Index
BSA	:	Body Surface Area
CFS	:	Chronic Fatigue Syndrome
CI	:	Cardiac Index
DBP	:	Diastolic Blood Pressure
HR	:	Heart Rate
HUT	:	Head-Up Tilt Test
HV	:	Healthy Volunteers
IOM	:	Institute of Medicine
MAP	:	Mean Blood Pressure

ME	:	Myalgic Encephalomyelitis
NMH	:	Neurally Mediated Hypotension
Normal BPHR Response During HUT	:	normal Blood Pressure and Heart Rate
OI	:	Orthostatic Intolerance
R36 Phys Funct	:	Rand-36 Physical Functioning Score
SBP	:	Systolic Blood Pressure
SVI	:	Stroke Volume Index
SVRI	:	Systemic Vascular Resistance Index
VTI	:	Time-Velocity Integral

Introduction

Myalgic Encephalomyelitis (ME)/Chronic Fatigue Syndrome (CFS) is a chronic, and often disabling disease [1-3]. The disease is multi-systemic, and is characterized amongst others by chronic fatigue/exhaustion, exercise intolerance, memory and concentration disorders, headache, multi-joint and muscle pain, unrefreshing sleep and an abnormally long recovery period after mental or physical exercise, called post-exertional malaise. Disease prevalence is unknown but estimates in the US vary between 1 and 4 million patients, in the Netherlands between 20,000 and 40,000 patients. The disease disproportionally affects women. The onset is typically around the 30th year but may also be present in children. The pathophysiology is complex and is at present incompletely understood. However, recent studies have shown that there is a genetic predisposition [4], that immunological abnormalities are involved [5] and that metabolic abnormalities involving the citric acid cycle might play a role [6]. Moreover, a recent study demonstrated the presence of widespread neuro-inflammation [7].

Due to the absence of objective markers of the disease, a cluster of signs and symptoms are used for the diagnosis. Although a variety of diagnostic criteria sets are available, the most commonly used are the Fukuda criteria for the diagnosis of CFS [3] and the Carruther criteria for the diagnosis of ME [2]. One of the symptoms that was highlighted recently is Orthostatic Intolerance (OI) [1]. The prevalence of orthostatic intolerance is variable in studies of ME/CFS patients, ranging between 28 and 97%, but higher than in healthy controls [1,8-12]. For the diagnosis of orthostatic intolerance usually a Head-Up Tilt Test (HUT) [8] or a standing test [13] is used. Based on heart rate and blood pressure changes during these orthostatic stress tests, predefined abnormalities can be diagnosed, like various forms of orthostatic hypotension, postural orthostatic tachycardia syndrome and various forms of syncope [14].

Although these hemodynamic abnormalities can be demonstrated by orthostatic stress testing, a study of ME/CFS patients with a normal test, i.e. with a normal heart rate and blood pressure response, showed abnormal changes in cardiac output and stroke volumes during the test [9]. The authors compared 26 CFS patients and 30 Healthy Volunteers (HV) and found a larger cardiac output and stroke volume decrease during HUT in the patients compared to the HV. For the determination of stroke volumes, a pulse contour analysis (Model flow) of the Finapres device was used. However, data on the reliability of stroke volume measurements using the pulse contour analysis are conflicting [15-23].

Therefore, the aim of this study was to measure stroke volume and cardiac output changes during HUT in a large group of ME/CFS patients and to compare the data with that of HV. For measurements of stroke volumes/ cardiac output we used a validated technique: suprasternal aortic Doppler echography [24-27]. Moreover, it has been suggested that the larger cardiac output and stroke volume decrease in ME/CFS patients compared to HV was due to deconditioning [9]. As disease severity is inversely related physical functioning [28], the disease severity was correlated with the stroke volume and cardiac output changes.

Material and Methods

Patient Selection

Between November 2012 and August 2018, 636 patients visited the clinic because of the suspicion of ME/CFS. At the first visit, prior to the tilt test, extensive history taking was done, to determine whether patients fulfilled the criteria for ME and CFS. Additionally, the disease severity according to the ME criteria was assessed [2]. The ME severity is scored as mild: (an approximate 50% reduction in pre-illness activity level), moderate (mostly housebound), severe (mostly bedridden) or very severe (totally bedridden and need help with basic functions).

Furthermore, in 109 patients a Rand-36 questionnaire was available. From this questionnaire the physical functioning subscale score was taken [29]. As part of the work-up of ME/CFS, all underwent tilt table testing with heart rate and blood pressure recording and suprasternal aortic VTI measurements for SVI quantification (see below).

We include 150 patients who completed the test without an early tilt back, with a normal heart rate and blood pressure response during the tilt and with a complete and good quality set of three stroke volume measurements. For comparison, 37 HV meeting the same inclusion criteria were studied. The study has been carried out in accordance with Declaration of Helsinki and was approved by the MEC of the Slotervaart hospital, Amsterdam, NL.

Head-Up Tilt Test

Patients and HV were fasted for no more than two hours and instructed to drink enough fluids to avoid confounding effects of relative dehydration. No patients or volunteers used drugs likely to affect intravascular volume (diuretics) and heart rate and blood pressure lowering drugs (beta-blockers, calcium-blockers, ACE inhibitors, AII antagonists, or ivabradine). The test started with a

supine rest period of at least 15 minutes during which the baseline Doppler echocardiographic measurements were performed. The Nexfin device was connected at the start of this resting period. After this resting period, patients were tilted to 70 degrees. Tilt duration from 0 to 70 degrees lasted approximately 30 sec. While in the head up position, the patients and HV were instructed to avoid movement of the lower leg musculature in order to minimize venous return by the skeletal muscle pump. Without any complaints or important discomfort, the test was terminated between the 25th and 30th minute of upright standing.

Nexfin Measurements

An appropriate size Nexfin finger cuff was placed around the mid-phalanx of the middle finger of the left hand. The left arm and hand were positioned alongside the body facilitating stable measurements. During the entire protocol, Heart Rates, Systolic, Diastolic and Mean Blood Pressures (SBP, SBP, MAP) were continuously recorded. Data were stored digitally and transferred to an Excel file. The times of the start of the Nexfin recording and the moment of the start of tilting was noted from an independent radio controlled clock. The start of tilting was set at 0 minutes.

Doppler Echocardiographic Measurements:

The Time-Velocity Integral (VTI) of the aorta was measured using a continuous wave Doppler pencil probe connected to a Vivid I machine (GE, Hoevelaken, NL) with the transducer positioned in the suprasternal notch. A maximal Doppler signal was assumed to be the optimal flow alignment. At least 2 frames of 6 seconds were obtained. Echo Doppler recordings were stored digitally. VTI frames were obtained in the resting supine position, halfway and at the end of the upright period.

From a previously made echocardiogram the diameter of the outflow tract was obtained. Also the times of the VTI recordings were noted and the Vivid-I times were corrected for the times of the radio clock.

Data Analysis:

The aortic VTI was measured by manual tracing of at least 6 cardiac cycles, using the GE EchoPac post-processing software. This was done by one operator (CMCvC). Stroke Volumes Indices (SVI) were calculated from the VTI and the outflow tract area, corrected for the aortic valve area [30,31] and divided by the Body Surface Area (BSA; DuBois formula). SVI's of the separate cycles were averaged. The cardiac index was calculated from the heart rate and SVI. The Nexfin derived Heart Rate and Blood Pressures at the aortic VTI sampling times were averaged. Systemic Vascular Resistance was calculated as: Mean Arterial Pressure (MAP)/ CI*80.

Statistical Analysis:

Data were analyzed using SPSS version 21 (IBM). All continuous data were tested for normal distribution using the K-S test. Normally distributed data are presented as means ± SD, otherwise the median and IQR are given (for BMI). Nominal data (gender) were compared using the Chi-square test. Normally distributed groups were compared using Students T test for unpaired data, median BMI of patients and HV were compared using the median test, distribution using the Mann Whitney U test. Graphs were constructed using Graphpad Prism version 6.00 (Graphpad software, La Jolla California USA).

Results

(Table 1) shows the baseline characteristics of ME/CFS patients and HV. All patients fulfilled the criteria for CFS, 107 (71%) patients fulfilled the criteria for ME, and 43 (29%) had atypical ME. The physical functioning score of the Rand-36 differed significantly between the mild, moderate, and severe ME patients, with lower scores in more affected patients.

	Patients (n=150)	**Healthy volunteers (n=37) P**
Age (years)	41 ± 11	37 ± 15
Gender F/M	124/26 (83/17%)	30/7 (81/19%)
BMI (kg/m^2)	24.2 (21.9-27.7)	23.1 (21.4-26.1)
BSA (duBois; m^2)	1.85 ± 0.18	1.83 ± 0.17
ME/CFS	107/150 (71/100%)	
Disease severity, ME criteria		
Mild	85 (57%)	
Moderate	54 (36%)	
Severe	11 (7%)	
R36 Phys Funct (n=109)	50 ± 22	
R36 Phys Funct Mild ME (n=63)	59 ± 19****	
R36 Phys Funct Moderate ME (n=39)	39 ± 19	
R36 Phys Funct Severe ME (n=7)	26 ± 9*	
Disease duration (years)	13 ± 8	
****: p<0.0001 mild ME vs moderate and severe ME; *: p<0.05 severe ME vs moderate ME.		

Table 1: Baseline characteristics of ME/CFS patients and HV undergoing HUT.

(Table 2) shows the hemodynamic data of the tilt test. VTI recording were made a mean of 2.1 ± 1.2 min before start of the tilt and at 14.5 ± 4.1 min and 26.4 ± 3.3 min after start of the tilt. VTI recording lasted mean 0.8 ± 0.9 min. Heart rates of patients

were all significantly higher than that of HV, both supine and at the 2-time points during the tilt period. During the tilt systolic and diastolic blood pressures were significantly higher in patients than in HV. MAP's of patients were also significantly higher than of HV. SVI's were all significantly lower than that of HV. The CI index was significantly lower in patients at the end of the tilt period. As the consequence of the higher MAP and lower CI, SVRI was significantly higher in patients than in HV.

	Patients Normal BPHR	**Healthy volunteers**
	N=150	**N=37**
HR (bpm) supine	68 ± 10**	62 ± 9
HR (bpm) mid study	81 ± 11*	76 ± 15
HR (bpm) end study	85 ± 12*	79 ± 16
SBP (mmHg) supine	136 ± 18	130 ± 12
SBP (mmHg) mid study	135 ± 18*	129 ± 12
SBP (mmHg) end study	133 ± 18*	126 ± 13
DBP (mmHg) supine	79 ± 9	77 ± 6
DBP (mmHg) mid study	86 ± 11***	81 ± 8
DBP (mmHg) end study	86 ± 10**	81 ± 7
MAP (mmHg) supine	102 ± 12*	97 ± 8
MAP (mmHg) mid study	105 ± 13*	100 ± 9
MAP (mmHg) end study	104 ± 13**	98 ± 9
SVI (ml/m^2) supine	35 ± 5*	37 ± 5
SVI (ml/m^2) mid study	24 ± 4****	28 ± 5
SVI (ml/m^2) end study	23 ± 4****	27 ± 5
CI (l/min/m^2) supine	2.38 ± 0.36	2.28 ± 0.37
CI (l/min/m^2) mid study	1.97 ± 0.35	2.09 ± 0.31
CI (l/min/m^2) end study	1.90 ± 0.34*	2.05 ± 0.28
SVRI (dyne*s/cm5*m^2) supine	3485 ± 587	3481 ± 575
SVRI (dyne*s/cm5*m^2) mid study	4359 ± 808***	3867 ± 704
SVRI (dyne*s/cm5*m^2) end study	4475 ± 885****	3867 ± 634
*,**,***,****: p<0.05, p<0.01, p<0.005, p<0.0001 ME/CFS patients versus HV		

Table 2: Hemodynamic data of ME/CFS patients and HV during HUT.

(Figures 1A,B) show the absolute and relative changes during the tilt period compared to the supine HR, SVI and CI data of patients and HV. HR changes were not different between patients and HV. The decreases in SVI and CI were all significantly larger in patients than in HV. The percent SVI decrease at mid tilt was 31 ± 10% in patients and 25 ± 10% in HV (p<0.005) and at end tilt 35 ± 9% in patients and 28 ± 10% in HV (p<0.0001). The CI decrease mid tilt was 17 ± 10% in patients and 8 ± 7% in HV (p<0.0001), and at the end tilt it was 20 ± 9% in patients and 10 ± 6% in HV (p<0.0001).

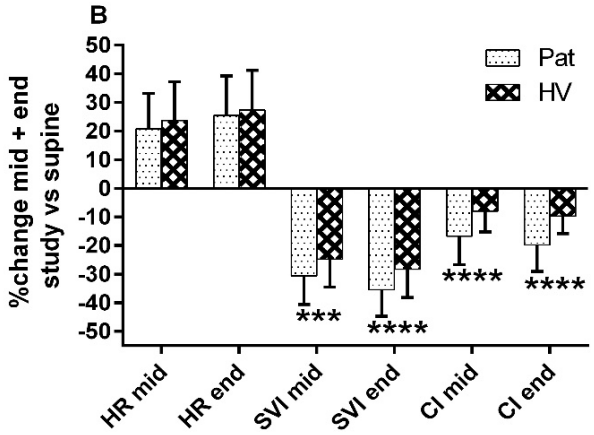

Figure 1A

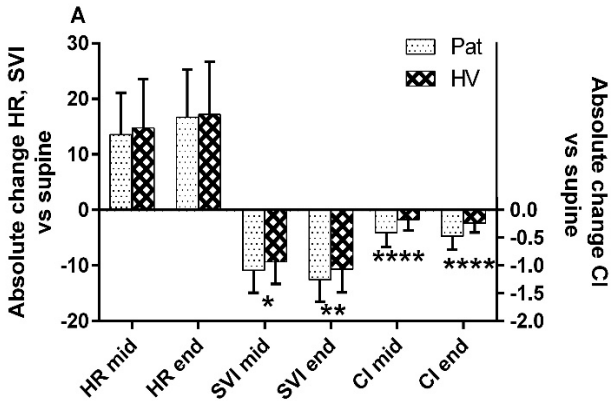

Figure 1B

Figures 1A and **B:** show the absolute (Figure A) and relative changes (Figure B) of heart rate, stroke volume index and cardiac index in ME/CFS patients and healthy volunteers halfway the tilt period (mid) and at the end of the tilt period. *, **, ***, ****: p<0.05, p<0.01, p<0.005, p<0.0001 ME/CFS patients versus HV.

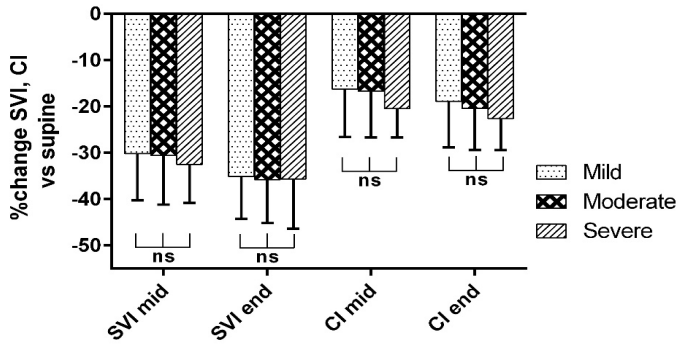

Figure 2

Figure 2: shows the percent change of the stroke volume and cardiac index in ME/CFS patients with mild, moderate and severe disease according to the ME criteria. There are no significant differences between the three groups.

(Figure 2) shows the relation between the disease severity and SVI and CI changes during the tilt. There were no significant differences in SVI and CI changes during the tilt between patients with mild, moderate, and severe ME.

There were no significant differences in SVI, CI and the relative changes of SVI and CI between ME and atypical ME patients (data not shown).

Discussion

The present study shows that in ME/CFS patients who have a normal heart rate and blood pressure response to tilt testing, a significantly lower stroke volume and cardiac output was observed compared to HV. These data confirm the previous findings of Timmers, et al. [9]. When comparing the magnitude of change of cardiac output and stroke volumes of the present and the aforementioned study several differences are observed. In the present study the stroke volume decrease in HV at the end of the study was 28%, versus a mean 40% reduction in the study of Timmers et al. Moreover, in HV cardiac output decreased 10% in the present study compared to a mean reduction of 19% in the study of Timmers, et al. However, in published studies on healthy subjects, there a very large differences in the hemodynamic response during tilt testing, ranging from a decrease in stroke volume of 11% in the elderly [32] to a decrease of 63% in healthy young women [33], with a typical response around a 30% decrease in stroke volume [34-38]. As the decrease in stroke volume during tilt testing in HV is, amongst others, related to age, gender, training status, fluid filling status, used technology, and tilt duration, the differences of stroke volume and cardiac output data of the present study versus the study of Timmers, et al. fall within the variability spectrum of the hemodynamic measurements during tilting and may therefore not be different.

Despite the differences in decrease in cardiac output and stroke volume between the 2 studies, both suggest that the decrease is significantly more robust in ME/CFS patients than in healthy volunteers. Timmers, et al. suggested that the differences between CFS patients and HV in stroke volume and cardiac output changes during the tilt was due to deconditioning [9]. For this purpose, we explored the relation between the disease severity and the changes in stroke volume and cardiac output. Intuitively, it is assumed that more severe patients are more deconditioned than less affected patients. Although specific data on physical functioning/deconditioning are missing, questionnaires like the Rand-36, show that the self- reported physical functioning scores are lower in more severe ME/CFS patients compared to patients with a milder expression of the disease [28]. This observation was confirmed in a subset of patients of the present study in whom the Rand-36 scores were available. The difference between the groups with mild, moderate and severe ME were all significantly different, with lower values in the more affected patients (Table 1).

However, there are differences in the physical functioning scores between the study of Pendergrast, et al [28] and the present study. In the study of Pendergrast patients were classified as housebound and not housebound based on the DePaul Symptom Questionnaire (DSQ) [39]. In the housebound patient group, the mean Rand-36 physical functioning score was 17 and in the not housebound group 42. In the present study the severity was assessed by history taking during the first visit. The mean Rand-36 physical functioning score in patients with mild ME was 59, in moderate ME 39 and in severe patients 26 (Table 1). For comparison with the data of Pendergrast, et al. the ME severity criterion of mild can be classified as not house bound and the combined severity of moderate and severe as housebound. The mean physical functioning score of moderate and severe ME was 37 ± 19. It may therefore be concluded that the physical functioning scores are higher than reported by Pendergrast, et al. [28]. These differences are unexplained except for the methodology used (questionnaire vs history taking) to assess housebound vs not housebound and possibly differences in patient selection and severity.

(Figure 2) shows that the decrease in stroke volumes and cardiac output are not significantly different between mild, moderate, and severe ME patients. The data therefore suggest that deconditioning does not explain the larger decrease in stroke volumes and cardiac output in ME/CFS patients compared to HV. Other suggested mechanisms are reduced blood and erythrocyte volumes [40-42], possibly due to a blunted erythropoietin response [43] and an abnormal sympathetic and parasympathetic response in ME/CFS patients, leading to excessive venous pooling while standing [44-46].

In the studied patients heart rate and blood pressure were maintained albeit at the expense of an increased peripheral resistance (Table 1). It can be hypothesized that in case of a further reduction

of stroke volumes, compensatory mechanisms for maintaining blood pressure fail, leading to hypotension and (near)-syncope. Indeed, Rowe, et al. [47] and Bou-Holaigah, et al. [8] observed an increased incidence of neurally mediated hypotension (NMH) in CFS patients during HUT. This concept of an excessively reduced cardiac output as one of the pathophysiological mechanism of NMH in ME/CFS patients' needs to be assessed prospectively.

Limitations

Measurement of stroke volumes and cardiac output by suprasternal aortic Doppler is operator dependent and the calculation of stroke volumes is time-consuming. Therefore, stroke volume determination during complete HUT study is not practical.

Conclusions

During a HUT with a normal Heart Rate and Blood Pressure response, Stroke Volumes and Cardiac Output in ME/CFS patients decrease significantly more than in HV. The data are consistent with a previous study. The absence of a difference in the decreases of stroke volume and cardiac output between patients with mild, moderate, and severe disease suggests that the decrease of stroke volumes and cardiac output is not related to deconditioning. Other mechanisms like decreased blood volumes and autonomic dysfunction may explain the differences between patients and healthy volunteers.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contributions

CMCvC, and FCV conceived the study and collected the data, CMCvC performed the primary data analysis and FCV performed secondary data analyses. The authors were involved in the drafting and review of the manuscript. Both approved the final version.

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Submission Elsewhere

This manuscript is not under consideration elsewhere.

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