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RESEARCH ARTICLE

The higher resting heart rate in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) patients compared to healthy controls: relation with stroke volumes.

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ABSTRACT

Introduction: In patients with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) a higher-than-normal resting heart rate has been reported in a number of studies. As heart rate is linked to stroke volume, the present study explored the relationship between the supine heart rate and stroke volume index in healthy controls and in ME/CFS patients. Moreover, as patients with a postural orthostatic tachycardia syndrome (POTS) during tilt testing, have a higher supine heart rate than patients with a normal heart rate and blood pressure response during tilting, these two patient groups were also compared.

Methods and results: From a database of individuals who had undergone tilt-testing, including supine Doppler measurements for stroke volume index calculation, we selected ME/CFS patients and healthy controls without evidence of hypotension or syncope. 474 ME/CFS patients were analyzed, 314 with a normal heart rate and blood pressure response and 160 with POTS during tilt-testing, and 56 healthy controls. Resting stroke volume indices were similar between the 3 groups. All 3 groups had an inverse relation between the resting stroke volume index and resting heart rate (all $p<0.0001$). The slope of the relation was not significantly different between the 3 groups. Using the upper limit of the 95% prediction interval for the heart rate of healthy controls, 46 (15%) of patients with a normal heart rate and blood pressure response had a resting heart rate above the upper limit, 248 (85%) a heart rate between the upper and lower limit. In 47 (29%) patients developing POTS the resting heart rate was above the upper limit, and in 113 (71%) patients within the upper limit and lower limit. This distribution was significantly different between the two patient groups ($p=0.0001$).

Conclusion: Patients and healthy controls showed a significant and inverse relation between the SVI and heart rate at rest. Already at rest heart rate in patients developing POTS during tilt-testing were higher compared to the patients with a normal heart rate and blood pressure response per unit of SVI, but the heart rate of the majority of all patients fell within the limits of normal of healthy controls. The difference of patients with heart rate above the upper limit versus between the upper limit and lower limit deserves further investigation and may have therapeutic implications.

Keywords: ME/CFS, myalgic encephalomyelitis, chronic fatigue syndrome, healthy controls, postural orthostatic tachycardia syndrome, POTS, stroke volume index, heart rate.

Introduction

A higher resting heart rate is frequently observed in patients with myalgic encephalomyelitis/ chronic fatigue syndrome (ME/CFS) compared to healthy controls [1-13]. The higher heart rate can be explained by an increased sympathetic/decreased parasympathetic activity due to the disease itself [2, 5, 14] or secondary due to a reduced blood volume [15-17], a reduced stroke volume [17-19], and an impaired peripheral oxygen extraction [20].

However, for the assessment of potential circulatory abnormalities also the stroke volume of the heart and the product of the heart rate and stroke volume: the cardiac output has to be taken into account. Already in the sixties Ross et al. investigated the relation between the supine heart rates and stroke volumes in healthy controls. They observed that increasing the heart rate by right atrial pacing resulted in a decreased stroke volume [21] with a net unaltered cardiac output. In a different set-up, using orthostatic stress, Zaidi et al. studied the relation between the decrease in stroke volume and the increase in heart rate at different angles of tilt table testing (different degrees of orthostatic stress) in healthy controls [22]. The decrease in stroke volume was accompanied by an increase in heart rate. In these two studies the participants served as their own control.

We hypothesized that also on a group level there is an inverse relation between stroke volume at rest and heart rate at rest. For this purpose we studied the relation between stroke volume, heart rate, and cardiac output of healthy controls and ME/CFS patients. As resting heart rate is higher in ME/CFS patients who developed a postural orthostatic tachycardia syndrome (POTS) during a tilt test than in ME/CFS patients with a normal tilt test without POTS or hypotension [12], we separately analyzed the relations in these two ME/CFS groups.

Patient, material and methods

We retrospectively reviewed the medical records of 800 ME/CFS patients who visited the out-patient clinic and who underwent a tilt test and where supine measurements of heart rate and stroke volume index were available. The diagnosis of ME/CFS was established using the criteria for CFS [23] and for ME [24], taking the exclusion criteria into account. Specifically, as there is a relation between body mass index (BMI) and resting heart rate and stroke volume [25, 26] we applied a more conservative CFS exclusion criterion of a body mass index (BMI) over 40 kg/m^2 as suggested by Reeves et al. [27]. No other illnesses were present explaining the symptomatology. Patients were selected for analysis when from the tilt test Doppler data for calculation of stroke volume and cardiac index were available in the supine position. Patients using drugs influencing heart rate or blood pressure at the time of the measurements were excluded. Only patients with a normal heart rate and blood pressure response or POTS were selected for the analysis of supine measurements. For comparison healthy controls with available Doppler data were also studied. Healthy controls were recruited from three sources: (a) announcements on ME/CFS patient advocacy websites, (b) posters in the medical clinic's office building, and (c) healthy acquaintances of the ME/CFS participants.

The study was carried out in accordance with the Declaration of Helsinki. All ME/CFS participants and healthy controls gave informed, written consent. The study was approved by the medical ethics committee of the Slotervaart Hospital, Amsterdam, for healthy controls P1450 and for ME/CFS patients P1736.

Doppler echocardiographic measurements:

Time-velocity integral frames were obtained in the resting supine position. The aortic time-velocity integral 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. The time-velocity integral was measured off line by manual tracing of at least 6 cardiac cycles, using the GE EchoPac post-processing software. Stroke volumes were calculated from the time-velocity integral of the aortic valve, corrected for the aortic valve as described previously [28, 29]. Stroke volume index was calculated by the equation: corrected left ventricular outflow tract cross-sectional area * the aortic time-velocity integral, divided by the body surface area (BSA; DuBois formula). Stroke volume index of the separate cycles were averaged.

Disease classification according to the International Consensus Criteria (ICC)

To classify ME/CFS severity, we used the ICC criteria, as follows: "For a diagnosis of ME, symptom severity must result in a significant

reduction of a patient's premorbid activity level. 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)" [24].

Statistical analysis

Data were analyzed using the statistical package of Graphpad Prism version 6.05 (Graphpad software, La Jolla, California, USA). All continuous data were tested for normal distribution using the D'Agostino & Pearson omnibus normality test, and presented as mean and standard deviation (SD) or as median with the interquartile range (IQR) where appropriate. Nominal data were compared using the Chi-square test. Groups were compared using Students T test for unpaired data, or the Mann-Whitney U test, where appropriate. Within group comparison was performed by the paired t-test or by the Wilcoxon signed ranks test, where appropriate. Due to the number of comparisons, we choose a conservative p-value of <0.01 to be statistically significant.

Of the initially reviewed medical records of 800 patients, 76 patients were excluded because of absence of ME/CFS, 157 patients because of orthostatic hypotension or syncope, 16 because of age <18 years, 10 because no stroke volume measurements were available, 10 because of a BMI > 40, 36 for using heart rate and/or blood pressure lowering drugs, and 21 were excluded because of a too poor image quality. This left 474 ME/CFS patients for analysis: 314 ME/CFS patients had a normal heart rate and blood pressure response during a tilt test and 160 ME/CFS patients showed POTS during tilt testing. From 56 healthy controls hemodynamic data of the supine period were available for comparison. Table 1 shows that no differences were present between the baseline characteristics of healthy controls and of the whole group of ME/CFS patients. Table 2 shows the hemodynamic supine measurements: stroke volume index was not significantly different between healthy controls and patients. As heart rate was significantly higher in ME/CFS patients, this resulted in a significantly higher cardiac index (p<0.0001).

Results

Table 1: Baseline characteristics of healthy controls versus ME/CFS patients

	HC (n=56)	ME/CFS (n= 474)	p-value
Male/female *	12/44 (21/79%)	71/403 (15/85%)	0.20
Age (years)	39 (15)	39 (11)	0.99
Height (cm)	173 (8)	172 (8)	0.25
Weight (kg)	73 (15)	72 (15)	0.42
BMI (kg/m^2)	24.3 (4.3)	24.2 (4.7)	0.84
BSA (m^2)	1.87 (0.20)	1.84 (0.19)	0.28
Disease duration (years)	NA	10 (5-18)	

HC: healthy controls; ME/CFS: myalgic encephalomyelitis/chronic fatigue syndrome); BMI: body mass index: BSA: body surface area (formula duBois); * chi-square 2x2 analysis

Table 2: Hemodynamic results of the supine measurements of the tilt-test of healthy controls and ME/CFS patients

	HC (n=56)	ME/CFS (n= 474)	p-value
HR supine (bpm)	62 (10)	71 (11)	<0.0001
SBP supine (mmHg)	134 (16)	135 (16)	0.85
DBP supine (mmHg)	78 (8)	79 (8)	0.50
SVI supine (ml/m^2)	37 (5)	37 (6)	0.96
CI supine (ml/min/m^2)	2.22 (0.34)	2.56 (0.44)	<0.0001

HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; SVI: stroke volume index; HC: healthy controls; CI: cardiac index

Table 3 shows the baseline characteristics of the ME/CFS patients with a normal heart rate and blood pressure response and ME/CFS patients with POTS. Patients with POTS had a shorter duration of disease and were younger (both p<0.0001). Patients with a normal heart rate and blood pressure response were slightly heavier, resulting in a higher BMI (p<0.0001). Fibromyalgia was significantly more present in ME/CFS patients with POTS compared to patients with a normal heart rate and blood pressure response during a tilt test (p=0.001). The distribution of disease severity (mild, moderate, severe disease) was different between patients with a normal heart rate and

blood pressure response and patients with POTS: in patients with POTS more patients had a more severe disease and less mild disease compared to patients with a normal heart rate and blood pressure response (p<0.0001). None of the patients had very severe disease as tilt testing was deemed too taxing for these patients.

Table 3: Baseline characteristics of ME/CFS patients with a normal heart rate and blood pressure during tilt testing (normBPHR) versus patients with postural orthostatic tachycardia (POTS)

	normHRBP (n=314)	POTS (n=160)	p-value
Male/female (n=; %) *	56/258 (18/82%)	15/145 (9/91%)	0.02
Age (years)	42 (11)	34 (10)	<0.0001
Height (cm)	172 (8)	173 (8)	0.09
Weight (kg)	73 (15)	69 (13)	0.008
BMI (kg/m^2)	24.7 (4.8)	23.1 (4.1)	<0.0001
BSA (m^2)	1.85 (0.20)	1.82 (0.18)	0.113
Disease duration (years; IQR)#	12 (6-20)	8 (4-14)	<0.0001
Fibromyalgia yes/no *	100/214 (32/68%)	75/85 (47/53%)	0.001
Severity (mild/moderate/severe) *	154/127/33 (49/40/11%)	56/64/40 (35/40/25%)	<0.0001

ME/CFS: myalgic encephalomyelitis/ chronic fatigue syndrome; BMI: body mass index: BSA: body surface area (formula duBois); normHRBP: ME/CFS patients without hypotension or tachycardia; POTS: postural orthostatic tachycardia syndrome * chi-square 2x2 (gender and fibromyalgia) or 2x3 (disease severity) analysis; # Mann-Whitney test; IQR: interquartile range

Table 4 shows the comparison of the hemodynamic measurements of ME/CFS patients with a normal heart rate and blood pressure response during the tilt test and ME/CFS patients with POTS. Supine heart rate was higher in ME/CFS patients with POTS: p<0.0001. Supine stroke volume was similar between the two patient groups and cardiac index was significantly higher in patients with POTS compared to the patients with a normal heart rate and blood pressure response, p=0.002.

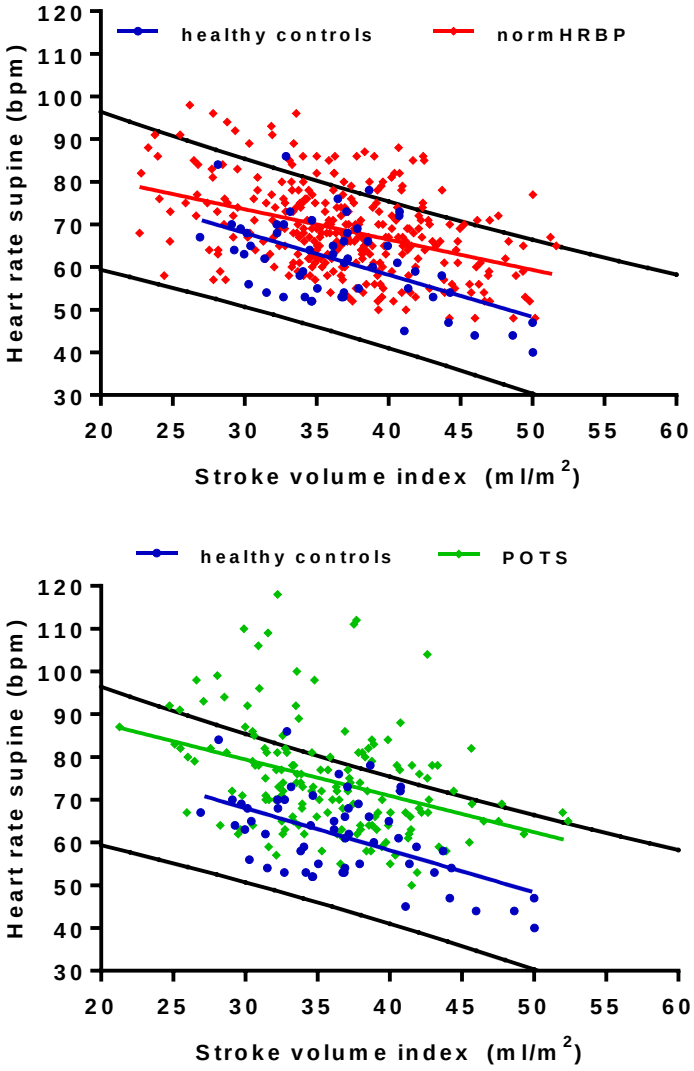
Table 4: Hemodynamic results of ME/CFS patients with a normal heart rate and blood pressure during tilt testing (normBPHR) versus patients with postural orthostatic tachycardia (POTS)

	normHRBP (n=314)	POTS (n=160)	p-value
HR supine (bpm)	69 (10)	74 (13)	<0.0001
SBP supine (mmHg)	136 (17)	132 (15)	0.037
DBP supine (mmHg)	79 (9)	79 (8)	0.796
SVI supine (ml/m^2)	37 (6)	36 (6)	0.054
CI supine (ml/min/m^2)	2.51 (0.42)	2.64 (0.48)	0.002

NormHRBP: patients with a normal heart rate and blood pressure response; POTS: postural orthostatic tachycardia syndrome; HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; SVI: stroke volume index; CI: cardiac index

Figure 1 shows the correlations between heart rate and stroke volume index. In all three studied groups there was a significant and inverse relation between the supine stroke volume index and heart rate (all p<0.0001). The slopes of the regression line in the three groups were not significantly different. Moreover, the 95% prediction intervals of the heart rate per stroke volume index of the healthy controls were calculated, indicated as black lines. No heart rates values of the two patient groups were below the lower limit of the 95% prediction interval of healthy controls. In contrast, in 46 (15%) patients with a normal heart rate and blood pressure response, the heart rate values were above the upper limit of normal and in 47 (29%) patients with POTS. The proportion of heart rate values above the heart rate upper limit of healthy controls was significantly higher in patients with POTS compared to patients with normal heart rate and blood pressure response during tilt testing (p=0.0001).

Figure 1 Correlations between resting heart rate supine and stroke volume index supine for healthy controls (blue), ME/CFS patients with normal heart rate and blood pressure response (red), and ME/CFS patients with postural orthostatic tachycardia syndrome (POTS) (green)



SVI: stroke volume index; normHRBP: normal heart rate and blood pressure response during tilt testing; POTS: postural orthostatic tachycardia syndrome; HC: healthy controls; black lines indicate upper and lower 95% prediction intervals of healthy controls

Discussion

The new finding of this study are that both in healthy controls and in ME/CFS patients there is a significant and inverse relation between the stroke volume index and heart rate at rest: a higher resting stroke volume is accompanied by a lower heart rate. These findings expand the data of Ross et al. showing that in healthy volunteers the induction of a higher heart rate (by atrial pacing) resulted in a lower stroke volume [21]. Thus, not only in an individual subject but also on a group basis the assessment of the relation between stroke volume and heart rate at rest is valid. Interestingly, although the slope of the relation between stroke volume index and heart rate is not different between healthy controls and the two studied patient groups, the heart rate of patients with a normal heart rate and blood pressure response and of patients with POTS are higher for a given stroke volume value, being highest in patients with POTS. The most obvious explanation is that in both patients groups (with tilt

test induced POTS or with a tilt test with a normal heart rate and blood pressure response) have a higher catecholamine drive compared to the healthy controls, even under resting conditions. Increased levels of catecholamines results in a higher heart rate and increased contractility and thus a higher stroke volume [30]. Indeed, the research group of the department of pediatrics of the Akershus hospital in Norway found in multiple studies significant higher levels of epinephrine and norepinephrine in ME/CFS patients compared to patients without CFS and healthy controls [31, 32]. In contrast, others found no differences in catecholamine levels of CFS patients versus healthy controls in the supine position [16, 33].

Our data of an increased resting heart rate and similar stroke volume compared to healthy controls are in line with the data of Timmers et al., and Farquar et al., but contrast with the data of others: Hurwitz et al., Miwa et al., and Newton et al. found a similar resting heart rate compared to healthy controls and a reduced stroke volume [10-13, 17, 18, 34]. Hurwitz et al. not only measured cardiac volumes but also blood volume [17]. When the authors corrected the stroke volume for the blood volume deficit, the stroke volumes differences between the CFS groups disappeared. The association between reduced cardiac volumes and reduced blood volume was confirmed in a later study by Newton et al. [18]. In the present study we did not measure blood volume. It remains to be determined whether the relation between stroke volume and heart rate normalizes to the level of healthy controls when blood volume deficits are corrected and whether differences in resting catecholamine levels in the patients are related to the stroke volume – heart rate relation and to the blood volume deficits. Finally, using the upper limit of the 95% prediction interval for the heart rate of healthy controls, 46 (15%) of patients with a normal heart rate and blood pressure response had a resting heart rate above the upper limit, and 248 (85%) a heart rate between the upper and lower limit. In 47 (29%) patients developing POTS the resting heart rate was above the upper limit, and in 113 (71%) patients within the range of the upper and lower limit. This distribution was significantly different between the two patient groups ($p=0.0001$). The clinical and other differences between ME/CFS patients with a higher-than-normal heart rate for a given stroke volume versus the patients with a heart rate within the normal limits, as determined by the 95% prediction intervals of healthy controls, need to be determined in future and these findings may have therapeutic implications.

Limitations:

The patients included in this study were a subset of ME/CFS patients who underwent a tilt test for quantifying orthostatic intolerance. For this analysis we excluded studied ME/CFS patients with hypotension or syncope during a subsequent tilt test. We analyzed hemodynamic results acquired with Doppler echography and did not include volume measurements of the heart. Finally, supine stroke volume and heart rate measurements were performed in patients prior to a tilt test. The expectation of adverse events during the tilt test may have increased the resting heart rate and stroke volumes. All these factors may have introduced bias and deserve attention in future studies.

Conclusion

This study shows an inverse relation between resting stroke volume index and heart rate. Although the slope of the relation between stroke volume index and heart rate was similar between the healthy controls and the ME/CFS patients with a normal heart rate and blood pressure during a subsequent tilt test and the ME/CFS patients with POTS, the two patient groups showed a higher resting heart rate for a given stroke volume, being highest in patients with POTS. These findings may have clinical and therapeutic implications.

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.

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Author Contributions

CMCVC and FCV conceived the study, CMCVC and FCV collected the data, CMCVC performed the primary data analysis and FCV performed secondary data analyses. All authors were involved in the drafting and review of the manuscript.

Data Availability Statement

The raw data supporting the conclusions of this manuscript will be made available by the authors, without undue reservation, to any qualified researcher

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