RESEARCH ARTICLE

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Patients with Joint Hypermobility Show Larger Cerebral Blood Flow Reductions during Orthostatic Stress Testing Than Patients without Hypermobility: A Case Control Study

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Abstract

Aims: An abnormal reduction in cerebral blood flow (CBF) during orthostatic stress is common in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), a condition with more prevalent joint hypermobility than in the healthy population. As one of proposed underlying mechanisms of orthostatic intolerance in hypermobile patients is vessel laxity, reducing the normal return of blood to the heart during orthostatic stress, we hypothesized that the CBF reduction during tilt-testing would be larger in ME/CFS patients with joint hypermobility than in patients without hypermobility.

Methods: In this case-control study, 100 female ME/CFS cases with joint hypermobility, who had undergone tilt-testing with CBF measurements, were compared to 100 female ME/CFS patients without joint hypermobility, matched by age and disease duration.

Results: No differences in baseline characteristics were found between groups. The hypermobile patients had significantly more postural orthostatic tachycardia syndrome (POTS) during tilt testing than the non-hypermobile ones. Compared to supine CBF, the degree of CBF reduction during the tilt was significantly larger in hypermobile cases than in the non-hypermobile controls: -32 (6)% vs -23 (7)% ($p<0.0001$) The larger CBF reduction in hypermobile patients was not only present in POTS patients: -33 (6)% vs -24 (4)%, but also in patients with a normal heart rate and blood pressure response to tilt testing: -31 (6)% vs -22 (9)%: (both $p<0.0001$).

Conclusions: ME/CFS patients with joint hypermobility syndromes have larger CBF reductions during orthostatic stress testing than patients without hypermobility. This larger CBF reduction is independent of the heart rate and blood pressure results of the orthostatic stress test.

Keywords: Orthostatic intolerance, cerebral blood flow, POTS, hypermobility, Ehlers-Danlos syndrome, tilt table testing, ME/CFS, extracranial Doppler echography

Introduction

Orthostatic intolerance (OI) is a well-established symptom in patients with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) [1-11]. Previous publications have shown that disorders associated with joint hypermobility, such as Ehlers-Danlos Syndrome (EDS), are more common in ME/CFS compared to healthy controls [12-14]. In drawing attention to the overlap of ME/CFS, orthostatic intolerance, and EDS, Rowe and colleagues proposed that connective tissue laxity in blood vessels results in increased pooling of blood, leading to reduced venous return to the heart when upright, and thus to hemodynamic abnormalities [1]. Others have proposed that neuropathy and hyper-responsiveness of the alpha- and beta-adrenergic system may play a mechanistic role in the orthostatic intolerance associated with joint hypermobility [15-18].

We have recently demonstrated that 90% of ME/CFS patients have an abnormal reduction in cerebral blood flow (CBF) during head-up tilt table testing, explaining the presence of OI symptomatology [9]. We hypothesized in view of the assumed vessel laxity in hypermobility syndromes, that CBF during orthostatic stress, is more

compromised in ME/CFS patients with hypermobility compared to those without hypermobility. Therefore, the aim of this case-control study was to compare the CBF reduction during tilt testing in these two patient groups.

Methods

Participants

The study was conducted in the outpatient clinic of the Stichting CardioZorg, a cardiology clinic in the Netherlands that specializes in diagnosing and treating adults with ME/CFS. Cases and controls were identified from the charts of ME/CFS patients who visited our clinic between November 2017 and December 2020, in whom a head-up tilt test was performed for quantification of OI. The diagnosis of ME/CFS was made according to the ME/CFS criteria [19, 20], and we excluded those with any other illnesses that could explain the symptomatology. Cases were eligible if they satisfied criteria for ME/CFS and had joint hypermobility; the latter was considered present if the diagnosis of joint hypermobility or hypermobile Ehlers-Danlos Syndrome (hEDS) had been made by a geneticist, rheumatologist, or specialized rehabilitation physician. In all other patients, seen during the study period in whom a formal diagnosis of hypermobility had not been established, we asked whether they were highly flexible or were hypermobile. In the event of a positive answer, the Beighton score was obtained (Beighton et al., 1973). For this study, we chose a conservative, elevated Beighton score of 6 or higher as the threshold for confirming the diagnosis of hypermobility [21, 22].

Controls without hypermobility were identified from the clinic database, first matching on gender and age. We then selected the individual with the closest ME/CFS disease duration in years (+/- 1 year). The ME/CFS controls who underwent tilt-testing because of OI symptoms were selected without knowledge of their CBF or hemodynamic responses to tilt testing.

In all participants, the examining clinician (FCV) ascertained for the presence of orthostatic intolerance symptoms in daily life, such as dizziness/light-headedness, prior (near)-syncope, nausea, etc., as well as triggering events like standing in a line [8, 9]. ME/CFS disease severity was graded using the International Consensus Criteria (ICC) with severity scored as mild (an approximately 50% reduction in the patient's premorbid activity level), moderate (mostly housebound), and severe (which combined severe [mostly bedbound] and very severe [bedbound and dependent on help for physical functions]) [20]. We noted whether study participants were using medications that could alter heart rate (HR) or blood pressure (BP). Finally, we documented whether patients had fibromyalgia as an additional symptom of ME/CFS according to the widespread pain index $\geq$ 6 of the American College of Rheumatology questionnaire, or if the diagnosis had been made elsewhere by a rheumatologist or rehabilitation physician [23].

The study was carried out in accordance with the Declaration of Helsinki. All ME/CFS participants gave informed, written consent. The use of descriptive clinical data of patients was approved by the medical ethics committee of the Slotervaart Hospital, Amsterdam, the Netherlands, P1450.

Head-up tilt test with CBF measurements

Measurements were performed as described previously [9, 24]. Briefly, all participants were positioned for 20 min supine before being tilted head-up to 70 degrees for a maximum of 30 minutes. The process of tilting took approximately 30 seconds. HR, systolic BP (SBP), and diastolic BP (DBP) were continuously recorded by finger plethysmography. HR and BP were

extracted from the device and imported into an Excel spreadsheet. Internal carotid artery and vertebral artery Doppler flow velocity frames were acquired by one operator (FCV), using a Vivid-I system (GE Healthcare, Hoevelaken, the Netherlands) equipped with a 6–13 MHz linear transducer. High resolution B mode images, color Doppler images and the Doppler velocity spectrum (pulsed wave mode) were recorded in one frame. At least two consecutive series of six frames per artery were recorded. Image acquisition for all 4 vessels at each time point (supine and end-tilt) lasted 3 (1) min. Blood flow of the internal carotid and vertebral arteries was calculated offline by an investigator (CMCvC) who was unaware of the patient case or control status. Blood flow in each vessel was calculated from the mean blood flow velocities x the vessel surface area and expressed in ml/min. Flow in the individual arteries was calculated in 3-6 cardiac cycles and data were averaged. Total cerebral blood flow was calculated by adding the flow of the four arteries. End-tidal PCO_2 ($P_{ET}CO_2$) was monitored using a Lifesense device (Nonin Medical, Minneapolis USA).

Doppler measurements for determination of CI .

CI is the cardiac output corrected for body surface area (BSA). Measurements were performed as described previously [25]. Briefly, 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, and at the end of tilt test phase. From an echocardiogram performed earlier, the diameter of the outflow tract was obtained. 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 [26, 27] and divided by the BSA (Du Bois formula). SVI's of the separate cycles were averaged. The cardiac index was calculated from the HR and SVI. We have previously validated this methodology by a direct comparison with CI measurements using transthoracic VTI images from the apical 4-chamber view [25].

Hemodynamic classification of HR and BP changes during tilt testing

The changes in HR and BP during the tilt were classified according to the consensus statement and guidelines [28-30] as follows: (a) normal HR and BP response, (b) classic orthostatic hypotension (cOH), defined as a >20 mm Hg reduction in SBP and/or >10 mm Hg reduction in DBP within 3 minutes of the start of standing. In the event of a baseline SBP over 160 mm Hg a reduction of over 30 mm Hg was used [31]. (c) Delayed orthostatic hypotension (dOH) was defined by the same criteria as for cOH, but with an onset after 3 minutes of the start of standing, (d) postural orthostatic tachycardia syndrome (POTS) was defined as a sustained increase in HR of 30 bpm or more within 10 minutes of standing, without an abnormal BP response, and (e) syncope or near-syncope.

Statistical analysis

Data were analyzed using Graphpad Prism version 8.4.2 (Graphpad software, La Jolla, California, USA) and SPSS version 21 (IBM USA). All continuous data were tested for normal distribution using the D'Agostino-Pearson omnibus normality test, and presented as mean (SD) or as median with the

IQR, where appropriate. Nominal data were compared using the Chi-square test (up to a 2x3 table). Groups were compared using the unpaired t test, or the Mann-Whitney U test, where appropriate. Due to the multiple comparisons we considered a p-value of <0.01 to be statistically significant.

Results

During the study period, 503 patients were diagnosed with ME/CFS. One hundred and one ME/CFS patients were classified as being hypermobile (20%), only one of whom was male. To improve the homogeneity of the study sample, this individual was excluded from the study group, leaving 100 female patients with hypermobility. The diagnosis of hypermobility was previously made by a geneticist, rheumatologist or a specialized rehabilitation physician in 80 patients. In the remaining 20 patients we measured the Beighton score, which was 7 (6-8). Demographic and tilt test data were not different between the 80 patients with a previous diagnosis of hypermobility and the 20 patients in whom we assessed the Beighton score (data not shown).

From the same study period, we identified 100 female ME/CFS controls, matched by age and disease duration, but without hypermobility. Baseline demographic and clinical characteristics of the two groups are reported in table 1. The distribution of mild, moderate, and severe ME/CFS was similar between the two groups. Daily life OI symptoms in the two patient groups were reported by all 200 (100%) ME/CFS patients. The prevalence of fibromyalgia was 46 (46%) in the hypermobile group and 47 (47%) in the non-hypermobile group. There were no differences between groups in other baseline characteristics.

Table 1. Demographic and clinical data of the study population

	Hypermobility present (n=100)	Hypermobility absent (n=100)	p-value
Age (years)	35 (11)	35 (10)	0.92
Mild/moderate/severe	16/63/21	32/47/21	0.02ǂ
Fibromyalgia present	46 (46%)	47 (47%)	0.89ǂ
Height (cm)	170 (6)	170 (7)	0.30
Weight (kg)	69 (16)	73 (18)	0.12
BMI (kg/m^2)	23.8 (5.2)	25.3 (6.0)	0.05
BSA (Du Bois; m^2)	1.79 (0.19)	1.82 (0.20)	0.27
Disease duration (years)*	11 (5-19)	11 (7-20)	0.26#

Daily life OI symptoms	100	100	1

BMI: body mass index; BSA: body surface area, formula of Du Bois; OI: orthostatic intolerance; * median (IQR); # Mann-Whitney U test; ǂ Chi-square test.

Table 2. Hemodynamic tilt test data of ME/CFS patients with and without hypermobility

	Hypermobility present (n=100)	Hypermobility absent (n=100)	p-value
NormHRBP/dOH/POTS	38/3/59	60/9/31	0.0002ǂ
HR supine (bpm)	75 (13)	77 (13)	0.33
HR end-tilt (bpm)	105 (21)	100 (19)	0.09
SBP supine (mmHg)	134 (16)	134 (16)	0.98
SBP end-tilt (mmHg)	129 (21)	127 (18)	0.48
DBP supine (mmHg)	80 (10)	79 (9)	0.49
DBP end-tilt (mmHg)	88 (15)	85 (12)	0.19
$P_{ET}CO_2$ supine (mmHg)	37 (3)	37 (3)	0.97
$P_{ET}CO_2$ end-tilt (mmHg)	26 (5)	28 (5)	0.005
CI supine (L/min/m^2)	2.63 (0.47)	2.64 (0.46)	0.92
CI end-tilt (L/min/m^2)	2.02 (0.50)	1.99 (0.37)	0.59
CBF supine (ml/min)	626 (98)	612 (105)	0.32
CBF end-tilt (ml/min)	425 (78)	469 (82)	0.0001

CBF: cerebral blood flow; CI: cardiac index; HR: heart rate; normHRBP: normal heart rate and blood pressure; DBP: diastolic blood pressure; $P_{ET}CO_2$: end tidal CO_2 pressure; SBP: systolic blood pressure; dOH: delayed orthostatic hypotension; POTS: postural orthostatic tachycardia syndrome; ǂ Chi-square test.

Table 2 shows the tilt test data of HR, BP, $P_{ET}CO_2$, CI, and CBF. In the hypermobile group there were more patients with POTS and fewer with a normal HR and BP response (p=0.0002). In the group of hypermobile ME/CFS patients, $P_{ET}CO_2$ at end-tilt and the CBF at end-tilt were significantly lower than in the control group (p respectively 0.005 and 0.0001). Figure 1 shows the graphic representation of the percent CBF reduction between supine and end-tilt for the total group of hypermobile and non-hypermobile ME/CFS patients: CBF reduction was significantly greater in the hypermobile patients (p<0.0001).

Figure 1. CBF reduction in patients with and without hypermobility.

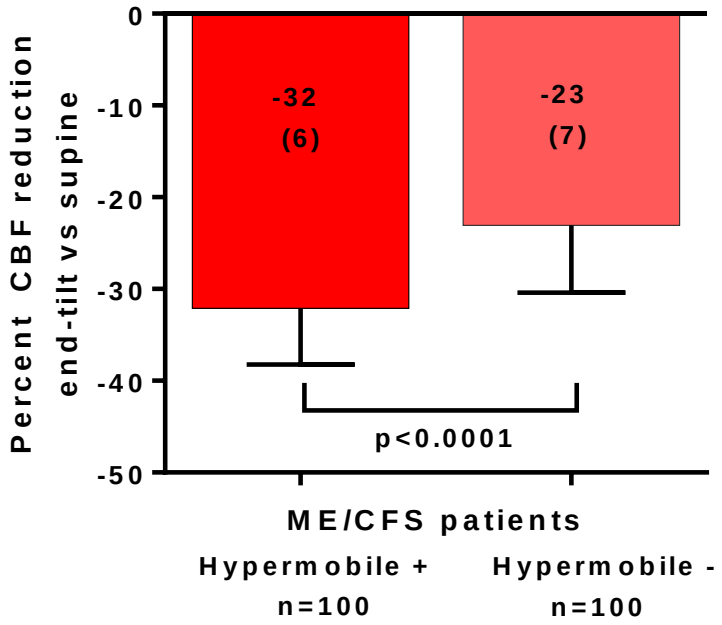

Figure 1. CBF: cerebral blood flow; CFS: chronic fatigue syndrome; ME: myalgic encephalomyelitis. Cerebral blood flow reduction between supine and end-tilt for ME/CFS patients with hypermobility (left column) and without hypermobility (right column).

Table 3. Hemodynamic tilt test data of the subset of ME/CFS patients with POTS

	Hypermobility present with POTS (n=59)	Hypermobility absent with POTS (n=31)	p-value
HR supine (bpm)	78 (15)	79 (13)	0.57
HR end-tilt (bpm)	116 (20)	117 (19)	0.81
SBP supine (mmHg)	132 (14)	133 (13)	0.60
SBP end-tilt (mmHg)	125 (18)	128 (18)	0.54
DBP supine (mmHg)	80 (9)	80 (8)	0.89
DBP end-tilt (mmHg)	87 (14)	88 (13)	0.70
$P_{ET}CO_2$ supine (mmHg)	37 (4)	36 (4)	0.50
$P_{ET}CO_2$ end-tilt (mmHg)	25 (5)	26 (6)	0.38
CI supine (L/min/m^2)	2.67 (0.50)	2.78 (0.51)	0.33
CI end-tilt (L/min/m^2)	2.14 (0.56)	2.12 (0.44)	0.86
CBF supine (ml/min)	635 (98)	599 (91)	0.09
CBF end-tilt (ml/min)	425 (73)	453 (77)	0.09

CBF: cerebral blood flow; CI: cardiac index; HR: heart rate; DBP: diastolic blood pressure; $P_{ET}CO_2$: end tidal CO_2 pressure; SBP: systolic blood pressure; POTS: postural orthostatic tachycardia syndrome.

POTS was identified in 59 hypermobile patients compared to 31 non-hypermobile patients (p = 0.0002). Baseline characteristics between POTS patients with and without hypermobility were not significantly different (data presented in the supplementary material: table 1S). As shown in Table 3, there were no significant differences in the tilt test results between the POTS groups with and without hypermobility.

A normal HR and BP response to tilt testing was present in 38 hypermobile patients and in 60 non-hypermobile patients. Baseline characteristics between those two groups were not significantly different (data presented in the supplementary material: table 2S). Table 4 shows the tilt results for these ME/CFS patients with a normal HR and BP response for hypermobile and non-hypermobile patients. The CBF end-tilt was significantly lower in the hypermobile patients vs the non-hypermobile patients (p=0.003). Figure 2 shows the percent CBF reduction in hypermobile and non-hypermobile patients with POTS and patients with a normal HR and BP response. In both hemodynamic groups the CBF reduction was significantly larger in the hypermobile patients than in the non-hypermobile patients (all p<0.0001).

Three patients with hypermobility and 9 without hypermobility had a dOH response during the tilt. The CBF reductions were -35 (7)% and -25 (4)%, respectively; p=0.001.

Table 4. Hemodynamic tilt test data of ME/CFS patients with a normal heart rate and blood pressure response

	Hypermobility present normHRBP (n=38)	Hypermobility absent normHRBP (n=60)	p-value
HR supine (bpm)	72 (10)	77 (13)	0.11
HR end-tilt (bpm)	90 (12)	92 (14)	0.42
SBP supine (mmHg)	138 (18)	134 (17)	0.34
SBP end-tilt (mmHg)	138 (22)	131 (17)	0.07
DBP supine (mmHg)	81 (11)	79 (10)	0.47
DBP end-tilt (mmHg)	90 (15)	85 (10)	0.11
$P_{ET}CO_2$ supine (mmHg)	37 (3)	37 (3)	0.73
$P_{ET}CO_2$ end-tilt (mmHg)	28 (5)	30 (5)	0.08
CI supine (L/min/m^2)	2.60 (0.41)	2.56 (0.41)	0.61
CI end-tilt (L/min/m^2)	1.85 (0.32)	1.91 (0.30)	0.37
CBF supine (ml/min)	606 (91)	612 (109)	0.78
CBF end-tilt (ml/min)	422 (82)	473 (82)	0.003

CBF: cerebral blood flow; CI: cardiac index; HR: heart rate; normHRBP: normal heart rate and blood pressure; DBP: diastolic blood pressure; $P_{ET}CO_2$: end tidal CO_2 pressure; SBP: systolic blood pressure.

Figure 2. Percent CBF at end-tilt in patients with POTS (panel A) and in patients with a normal HR and BP response (panel B)

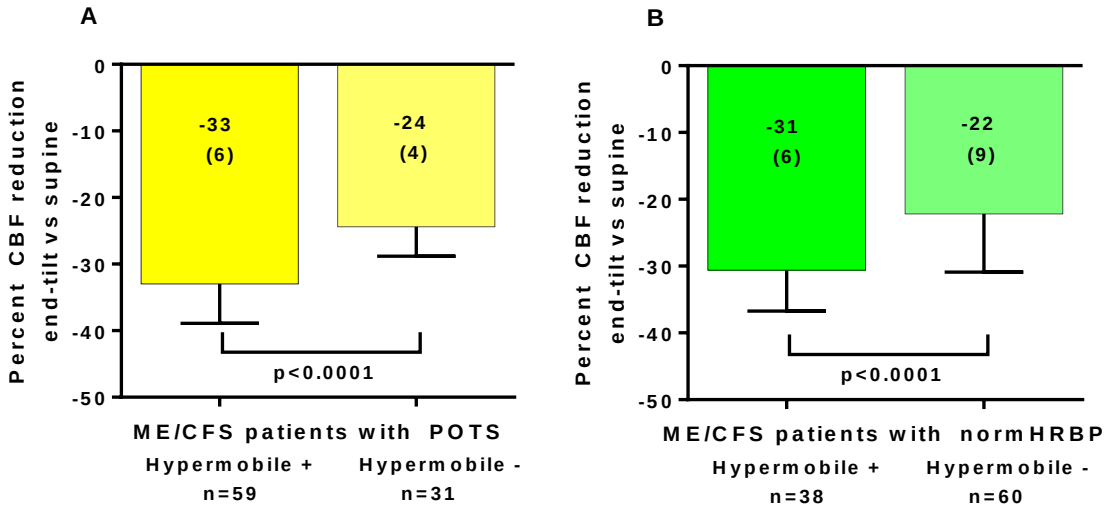

Figure 2A Cerebral blood flow reduction between supine and end-tilt for ME/CFS patients having POTS at end-tilt with hypermobility (left column) and without hypermobility (right column).
Figure 2B Cerebral blood flow reduction between supine and end-tilt for ME/CFS patients having normHRBP at end-tilt with hypermobility (left column) and without hypermobility (right column).

CFS: chronic fatigue syndrome; ME: myalgic encephalomyelitis; normHRBP: normal heart rate and blood pressure; POTS: postural orthostatic tachycardia syndrome.

Discussion

The main finding of this study is that all ME/CFS patients with OI complaints, with and without hypermobility, have a significant CBF reduction during tilt testing, and that hypermobile ME/CFS patients have a larger CBF reduction than non-hypermobile patients. Importantly, the larger CBF reduction among hypermobile patients was independent of the blood pressure and heart rate responses to tilting.

Several points of this study need emphasis. Although fatigue is a prominent feature in the various EDS syndromes [15, 32-35] and although many symptoms of EDS are similar to the symptoms of ME/CFS [35], there is limited data on both the prevalence of ME/CFS in hypermobile patients and the prevalence of hypermobility in ME/CFS patients. Three research groups have studied the prevalence of hypermobility in the ME/CFS population. Rowe and co-authors found a prevalence of hypermobility of 60% in ME/CFS children [14], while Nijs and co-authors found a hypermobility prevalence of 21% in adult ME/CFS patients [12] and Bragee and coworkers found a prevalence of 49% [13]. In our adult patient population with symptoms both fulfilling the ME and CFS criteria, the prevalence of a hypermobility syndrome was 20% in female patients. The differences in prevalence between the study of Bragee et al. and our study may be related to methodology used to classify patients as being hypermobile or not. We used a Beighton cut-off value of ≥ 6, while Bragee et al used a cut-off value ≥ 4 for the diagnosis of hypermobility. In the 80% of the hypermobile

ME/CFS patients in our cohort who had their hypermobility diagnosis established elsewhere, Beighton scores were not known, and were not repeated as part of the study protocol. However, our prevalence is in line with the prevalence data of Nijs et al. The diagnostic criteria of ME are more extensive and more complex than the CFS criteria. The ME symptom criteria, including the cardinal symptom of post-exertional malaise, have not been assessed in various studies of EDS patients. More studies are needed in the EDS population to determine the prevalence of ME/CFS and in ME/CFS patients whether the prevalence of criterial symptoms are different between ME/CFS patients with and without hypermobility.

Most studies of OI in hypermobile patients have focused on POTS [15, 17, 35-40]. Our data extend these findings, as the higher prevalence of POTS in hypermobile ME/CFS patients was confirmed in our study. We have previously shown in healthy controls that the reduction in CBF during tilt testing in these controls is 7% [9]. Our present study clearly shows that the CBF reduction is over 3-fold more severe in ME/CFS patients than in the controls, in both CFS patients with and without hypermobility, and is present irrespective of the type of hemodynamic response to tilt testing. The finding that the hemodynamic results (POTS, dOH or a normal HR and BP response) of a tilt test do not reflect the degree of CBF velocity abnormalities, measured by transcranial Doppler, has been shown in other patient groups than ME/CFS patients [41-43]. Our data therefore suggest that for management/treatment of patients with hypermobility more attention should be paid to OI symptomatology and diagnostic procedures, rather than focusing only on POTS.

Factors causing CBF reduction remain a topic to be studied, but may involve changes in cardiac output [44-46] and the presence of hypocapnia [44-50]. Our data show similar changes in cardiac output and hypocapnia between the hypermobile and non-hypermobile patient groups, suggesting that other factors must be responsible for the abnormal CBF reductions. Endothelial dysfunction [51, 52], and the presence of antibodies against beta-adrenergic receptors [53-56], may limit cerebral flow. As cerebral flow is tightly coupled to the cerebral metabolic demands [57], a reduction in CBF may also be due to a temporarily reduced metabolic demand of the brain.

Limitations

We acknowledge that patients evaluated in our specialized cardiology clinic may have been more likely to be referred for evaluation of their orthostatic symptoms, and so the prevalence of CBF abnormalities might be different than in the general population of ME/CFS patients. We have previously shown that those with no orthostatic symptoms in daily life have CBF reductions during tilt testing similar to controls.

We accepted the diagnoses of joint hypermobility syndromes or EDS made in other clinics. In patients without this diagnosis we tested patients for joint hypermobility using the Beighton score if they reported being highly flexible or hypermobile. Controls who did not report being flexible did not have a Beighton score measured, so it is theoretically possible that some in the control group might be re-classified as hypermobile if the Beighton score had been assigned. We think this is unlikely, and in any event would have mitigated against finding a difference between groups. Nonetheless, a prospective study in which all ME/CFS patients undergo Beighton scoring, independent of their self-reports of hypermobility, or prior diagnoses of hypermobility by others, would provide a more definitive proof of this concept.

Our main focus was on the prevalence of CBF reductions in a study population comparing hypermobile and non-hypermobile ME/CFS patients, and therefore investigations of cerebral autoregulation and regional cerebral blood flow were beyond the scope of this study. The mechanisms of the greater reduction in CBF during tilt testing in the hypermobile patients will be important to investigate in the future. We only studied ME/CFS patients with OI symptoms. Whether patients with hypermobility but without OI show the same differences compared to non-hypermobile patients need to be studied in future.

Clinical implications

Individuals with ME/CFS and comorbid hypermobility experience a more profound CBF reduction during an orthostatic stress than non-hypermobile ME/CFS patients. This finding suggests that joint hypermobility is a risk factor for a greater orthostatic symptom burden. Stratifying ME/CFS patients by the degree of joint hypermobility will be important in clinical trials, particularly those evaluating the response to medications directed at orthostatic intolerance. An unbalanced assignment of patients with hypermobility to one intervention group could result in uneven baseline degrees of reduction in CBF. The relation between the degree of CBF reduction and symptom burden, however, needs to be studied further.

Conclusions

The main findings of this study are that all CFS patients with OI complaints, with and without hypermobility, have a significant CBF reduction during tilt testing, and that hypermobile patients have a larger CBF reduction than non-hypermobile patients. Although the CBF reduction is similar in the various hemodynamic outcomes (POTS, dOH and a normal HR and BP response), the underlying mechanisms (vessel laxity, limited vessel contractility, and hyper-responsiveness of the beta adrenergic receptors, and others) remain to be studied.

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IRB Approval

The study was carried out in accordance with the Declaration of Helsinki. All ME/CFS participants gave informed, written consent. The use of descriptive clinical data of patients was approved by the medical ethics committee of the Slotervaart Hospital, Amsterdam, the Netherlands, P1450.

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

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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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Supplementary Material

Table 1S. Demographic data of ME/CFS patients with POTS

	Hypermobility present with POTS (n=59)	Hypermobility absent with POTS (n=31)	p-value
Age (years)	33 (10)	30 (8)	0.11
Mild/moderate/severe	7/35/17	7/16/8	0.41ǂ
Fibromyalgia present	22 (37%)	18 (58%)	0.06ǂ
Height (cm)	171 (6)	171 (7)	0.84
Weight (kg)	68 (14)	70 (16)	0.58
BMI (kg/m^2)	23.2 (4.5)	23.9 (5.8)	0.48
BSA (Du Bois; m^2)	1.79 (0.18)	1.80 (0.19)	0.70
Disease duration (years)*	10 (4-17)	10 (5-12)	0.60#

BMI: body mass index; HR: heart rate; BSA: body surface area, formula of Du Bois; POTS: postural orthostatic tachycardia syndrome. * Median (IQR); # Mann-Whitney U test; ǂ Chi-square test..

Table 2S. Demographic data of ME/CFS patients with a normal heart rate and blood pressure response

	Hypermobility present in normHRBP (n=38)	Hypermobility absent in normHRBP (n=60)	p-value
Age (years)	39 (12)	38 (10)	0.46
Mild/moderate/severe	8/26/4	22/27/11	0.08ǂ
Fibromyalgia present	22 (58%)	24 (40%)	0.08ǂ
Height (cm)	169 (7)	168 (6)	0.38
Weight (kg)	70 (17)	74 (17)	0.40
BMI (kg/m^2)	24.6 (5.8)	26.1 (6.1)	0.25
BSA (Du Bois; m^2)	1.80 (0.20)	1.82 (0.19)	0.57
Disease duration (years)*	11.5 (5-20.3)	13.5 (9-22.5)	0.35#

BMI: body mass index; BSA: body surface area, formula of Du Bois; normHRBP: normal heart rate and blood pressure during the tilt test; * Median (IQR); # Mann-Whitney U test; ǂ Chi-square test.

