Chronic fatigue syndrome, orthostatic intolerance and the effect of compression stockings on hemodynamics: a retrospective study.

Master thesis

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ONDERGETEKENDE

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Samenvatting (Dutch)

Achtergrond: Mylagische encephalomyelitis/chronisch vermoeidheidssyndroom (ME/CVS) is een klinisch gedefinieerd syndroom waarbij patiënten ernstig geïnvalideerd kunnen zijn. Alhoewel de etiologie van ME/CVS nog onbekend is, is orthostatische intolerantie een welbekend pathofysiologisch mechanisme. Eerdere studies hebben aangetoond dat de met orthostatische intolerantie gepaard gaande abnormaliteiten in de hemodynamiek effectief behandeld kunnen worden, en specifiek dat compressie applicatie op het onderlichaam ook effectief is. Bij gezonde personen zijn compressiekousen al effectief gebleken in het verbeteren van de veneuze flow. Echter, tot op heden is het effect van compressiekousen op de hemodynamiek bij patiënten gediagnosticeerd met ME/CVS nog niet onderzocht.

Doelstelling: Bepalen wat het effect van graduele compressiekousen (18-24 mmHg) is op de hemodynamiek tijdens orthostatische stress bij patiënten met ME/CVS.

Methodes: De studie betreft een retrospectief studiedesign. Data van hemodynamiek tijdens dubbele kanteltafel tests (met en zonder compressiekousen) van patiënten met ME/CVS (Fukuda 1994 criteria) vergaard tijdens standaard zorg in de periode tussen November 2012 en April 2013 werd verzameld. Hemodynamische uitkomstvariabelen waren bloeddruk, hartslagfrequentie, stroke volume index en cardiac index.

Resultaten: 15 geschikte cases zijn gevonden en geïncludeerd. Een consistente maar niet-significante verhoging van de stroke volume index en de cardiac index werd geobsereerd. Een trend ($p<0.10$) werd echter gevonden voor een verhoging van de stroke volume index door compressie tijdens ruglig in vergelijking met de test zonder compressie. Voor de bloeddruk en de hartslagfrequentie werden geen significante resultaten gevonden.

Conclusies: Graduele compressiekousen van 18-24 mmHg lijken geen verbetering te geven van de hemodynamiek tijdens orthostatische stress bij patiënten gediagnosticeerd met ME/CVS.

Abstract (English)

Background: Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a clinically defined syndrome that can be severely debilitating. Although the etiology of ME/CFS remains unknown, orthostatic intolerance is a well-recognized pathophysiological mechanism. Previous studies showed that abnormalities in

hemodynamics related to orthostatic intolerance could be treated effectively, and that lower body compression application in particular is effective in this respect. In healthy subjects compression stockings showed to improve venous flow effectively. To date however, the effect of below-knee compression stockings on hemodynamics has not been studied in patients with ME/CFS.

Purpose: To determine the effect of graduated below-knee compression stockings (18-24 mmHg) on hemodynamics during orthostatic stress in patients with ME/CFS.

Methods: A retrospective study design was used. Clinical data from medical files were obtained. Medical files of patients diagnosed with ME/CFS (Fukuda 1994 criteria) where data of hemodynamics from a double tilt-table test (one with and one without below-knee compression application) were available were searched and screened for eligibility. Hemodynamic outcomes were blood pressure, heart rate, stroke volume index and cardiac index.

Results: 15 eligible cases were found and included. A consistent but non-significant increase in stroke volume index and cardiac index was found during tilt table tests with compression compared to without compression. A trend ($p < 0.10$) was found however during the tilt-table test with compression for the improvement of stroke volume index during supine position compared to no compression. No significant results were found for blood pressure and heart rate.

Conclusions: Graduated below-knee compression stockings of 18-24 mmHg do not seem to improve hemodynamics during orthostatic stress in patients diagnosed with ME/CFS.

Key words: ME/CFS, POTS, cerebral flow, compression garments

INTRODUCTION

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a clinically defined syndrome characterized by severe and disabling fatigue, which is not alleviated by rest or sleep, and may be worsened by physical or mental exertion, and is not due to ongoing exertion or other medical conditions.(1) Due to the different definitions of ME/CFS that are used in scientific studies, estimations of prevalence of ME/CFS consequently differ substantially. A recent meta-analysis estimated the prevalence of ME/CFS on 0.73% (95% confidence interval [CI] = 0.42-1.41). The study included populations from England, Korea, Nigeria, Brazil and the USA.(2) The prevalence of ME/CFS is estimated to be twice as high in women compared with men.(3)

Clinical presentation and severity of ME/CFS varies greatly, but can encompass post-exertional malaise,(4,5) unrefreshing or disturbed sleep,(5,6)widespread or migratory myofascial or joint pain,(6,7) neurocognitive symptoms (e.g. impaired memory, sensitivity to bright lights or noise),(5,7,8) autonomic dysfunction (e.g. neurally mediated hypotension, postural orthostatic tachycardia), neuroendocrine manifestations (e.g. feverishness, subnormal body temperature), and immune manifestations (flu-like symptoms, fevers, sweats).(9) Symptom manifestation is characterized by remission and relapse.(10) ME/CFS is considered to be as disabling as e.g. multiple sclerosis and rheumatoid arthritis.(10)

Although the etiology of ME/CFS is unknown, several pathophysiological mechanisms are recognized. Autonomic dysfunction, and orthostatic intolerance (OI) in particular, is a well-recognized pathophysiological mechanism of ME/CFS.(11-22) However, studies indicate a highly variable prevalence of OI.(15-17,19,23) OI usually manifests as neurally mediated hypotension or postural orthostatic tachycardia syndrome.(24) OI is related to a reduced quality of life, sleep problems, and excessive daytime sleeping.(25) Excessive gravitational venous pooling, hypovolemia or autonomic dysfunction are suggested to be the cause of symptoms occurring with OI.(19,26) The symptoms produced by orthostatic stress (e.g. fatigue, dizziness, lightheadedness) have a marked overlap with the symptoms of ME/CFS. It is

hypothesized that these symptoms are the result of deficient cerebral perfusion, thereby providing a possible explanation of the experienced neurocognitive impairments. To date however, empirical evidence supporting this hypothesis is conflicting.(14,18,21,27-34)

In a previous study, OI related symptoms in patients with ME/CFS immediately alleviated or completely ameliorated after pharmaceutical treatment aimed at treating hypotension.(15) In addition, in an intervention study where rigorous lower body compression was applied (with Military Anti-Shock Treatment [45 mmHg]) to assess the effect of compression on hemodynamic abnormalities during orthostatic stress in patients with ME/CFS, the compression immediately alleviated symptoms convincingly.(19) Although the empirical evidence that is provided by this study underlines the mechanism of venous pooling or hypovolemia, such intervention is not a feasible clinical treatment modality. The efficacy of simple below knee stockings on venous flow improvement, however, has been well established in healthy subjects; an increase of 124-138% of venous flow has been reported.(35,36) In accordance with the aforementioned evidence, the *International association for chronic fatigue syndrome/myalgic encephalomyelitis* prescribes compression garments to be included in the clinical management of OI.(37) Although evidence supporting that lower body venous pooling, autonomic dysfunction or hypovolemia is involved in the pathophysiological mechanism is convincing, to date the efficacy of simple below knee stockings in treating OI has never been investigated in patients with ME/CFS. Stockings provide an easy to use and inexpensive treatment modality that can potentially alleviate or completely ameliorate symptoms in patients with ME/CFS. Accurate insight in the workings of compression stockings, and in particular in relation to OI in patients with ME/CFS, is needed for proper clinical use.

Therefore, the research question for this study is:

"What is the effect of below-knee compression stockings on the hemodynamic responses during orthostatic stress in adult patients diagnosed with ME/CFS?"

OI has a very restrictive effect on activities in daily life and mobility. Successful treatment of OI therefore means that patients might be able to increase their activity

and participation levels, and that exercise might be possible to increase fitness levels. It is hypothesized that the effect of below-knee compression during orthostatic stress varies from partial reduction of hemodynamic abnormalities to full recovery of symptoms in patients with ME/CFS. To the authors' knowledge, this is the first study that examines the effect of commercially available below-knee compression stockings on the hemodynamics during orthostatic stress in patients diagnosed with ME/CFS.

PATIENTS AND METHODS

Patients

Medical files with clinical data that were obtained during standard care in the Parkstad Kliniek (PK) (Amsterdam, the Netherlands) from November 2012 until April 2013 were searched and screened for eligibility. All data were de-identified by FV before they were collected. To be eligible, medical files had to fulfill the following criteria: 1) the patient had to be an adult and diagnosed with ME/CFS according to the Fukuda 1994 criteria, and 2) two tilt-table tests had to be performed with hemodynamic measurements (blood pressure [BP], heart rate [HR] and stroke volume [SV]), one tilt-table test (TTT) with and one TTT without below-knee compression stockings. Patients that were using medication that could interfere with hemodynamics (e.g. beta blockers) during the examinations were excluded. The medical research committee of the University Medical Center Utrecht provided ethical approval for the study protocol.

Study design

A retrospective study design was used to study the effect of compression stockings on hemodynamic responses during orthostatic stress. Available data from medical files from the PK were obtained. The PK is a clinic in Amsterdam where diagnostic and therapeutic cardiology care specialized in the treatment of patients with ME/CFS is provided. Patients are referred to the clinic for diagnostic analyses in respect to the cardiovascular system.

Clinical procedures

Tilt-table procedures were performed according the 'Guideline for the diagnosis and management of syncope'.(38) Thus, the TTT started with a five-minute baseline

measurement in supine position, and continued with a ten-minute 70° tilt (or until termination upon request of the patient). Systolic blood pressure (SBP), diastolic blood pressure (DBP), HR and SV were measured with the *Nexfin HD monitor* (BMEYE B.V., Amsterdam, the Netherlands). The *Nexfin HD monitor* provides continuous and noninvasive beat-by-beat measures of SBP, DBP, HR and SV with excellent reliability and validity.(39-41) To account for body size, the SV was used to calculate the SV index (SVI). The SVI was calculated by dividing the SV by the body surface area. The body surface area was calculated with the Du Bois formula ($0.007184*\text{weight}^{0.425}*\text{height}^{0.725}$). To determine to volume of blood being pumped by the heart per minute, accounting for body size, the cardiac index (CI) was calculated by dividing the cardiac output (SV * HR) by the body surface area. Outcome values for these variables were determined by calculating the average of data from one minute at five and ten minutes post-tilt. The below-knee compression was applied by CEP® (CEP, Himmelkron, Germany) sport compression stockings, that apply so-called 'gradual compression'. These stockings provide 18-24 mmHg (class CCL I) of pressure around the ankle, with gradual decreasing pressure upwards to 18 mmHg at the most proximal point just below the knee joint. The size of the stocking was determined by the calf circumference, according to the sizing chart provided by the manufacturer. Determining the sock size by calf circumference has the advantage of a decreased risk of inappropriate compression application due to 'shoe size:calf circumference' ratio variability. The sequence of performing the TTT with and without compression stockings was done selectively, i.e. non-randomly. Duration between the two tests depended mostly on practical reasons issued by the patients.

Statistical analysis

All pre- and post-tilt means of hemodynamic variables (BP, HR, SVI and CI) with and without compression stockings were examined for normality. Normality was examined by visual inspection with a Q-Q plot and a histogram, and subsequently tested with a Shapiro-Wilk test for which a p-value level less then 0.05 was considered significant. If the assumption of normality was not violated, a two-sided pairwise t-test was performed. If the assumption for normality was violated, a Wilcoxon signed-ranks test was carried out to perform a non-parametric pairwise

analysis. For both pairwise tests a p-value of less then 0.05 was considered significant, and the null-hypothesis would be rejected accordingly.

RESULTS

Of the double tilt-table tests performed in the period between November 2012 and April 2013 in the PK, 15 cases were found eligible and were included in this study. 13 of the 15 cases were female. The average age was 42.1 years old (95% CI = 17.3-66.9), and the average body mass index was 23.9 (95% CI = 14.3 – 33.5). The characteristics of these cases can be found in table 1.

Table 1 – Patient characteristics.

Characteristic (n=15)	**Mean (95% CI)**
Age (years)	42.1 (35.8-48.4)
Female (n)	13 (86.7%)
Height (cm)	173 (169.5-176.5)
Weight (kg)	72.1 (64.1-80.1)
BMI (kg/m^2)	23.9 (21.5-26.3)

CI: confidence interval

The results of the double tilt-table test are provided in table 2. Two patients, both female, experienced presyncopal symptoms during tilting. In one patient, presyncopal symptoms occurred during the first minutes of tilting during the protocol without compression stockings. In the same patient, presyncopal symptoms occurred after 5 minutes of tilting during the tilt test with compression. In both occasions, the tilt test in this patient was terminated directly after the onset of the presyncopal symptoms. In the other patient, tilting was tolerated despite the experience of presyncopal symptoms. Therefore, only 14 patients were included for the analyses of the 5 and 10 minutes post tilt. The changes in the SVI and CI, pre and post tilt, were consistently higher with compression in comparison without compression. In the HR and blood pressure, no clear pattern could be discerned from the results. However, for none of the hemodynamic variables, pre- as well as post-tilt, significant differences were found. During pre tilt however, a trend for increase of the SVI was observed ($p<0.10$).

Table 2 – Hemodynamics with and without compression at baseline and during tilt

Hemodynamic variable	Protocol without compression	Protocol with compression	Mean difference$_{wc-c}$	P value
	Mean (95% CI)			
Supine position (n=15)				
Heart rate (bpm)	*74.5 (70.0-78.9)*	*74.0 (70.2-77.9)*	*0,47 (-1.58 – 2.52)*	*0,633*
Stroke volume index (ml/beat/m^2)	*47.8 (43.0-52.6)*	*50.1 (46.3-53.9)*	*-2,27 (-4.94 – 0.41)*	*0,091+*
Cardiac index (l/min/m^2)	*3.53 (3.17-3.90)*	*3.69 (3.39-3.99)*	*-0,16 (-0.41 – 0.09)*	*0,202*
Systolic blood pressure (mmHg)	*129.7 (117.7-141.7)*	*130.6 (122.9-138.3)*	*-0,93 (-8.65 – 6.78)*	*0,799*
Diastolic blood pressure (mmHg)	*76.3 (71.8-80.9)*	*76.1 (72.8-79.3)*	*0,27 (-3.67 – 4.21)*	*0,887*
Mean arterial pressure (mmHg)	*98.1 (90.7-105.4)*	*98.5 (94.3-102.8)*	*-0,47 (-6.31 – 5.37)*	*0,866*
5 minutes post tilt (n=14)				
Heart rate (bpm)	*86.9 (81.1-92.6)*	*86.4 (80.9-91.8)*	*0,50 (-2.77 – 3.77)*	*0,747*
Stroke volume index (ml/beat/m^2)	*38.0 (34.8-41.2)*	*38.5 (35.6-41.4)*	*-0,50 (-2.22 – 1.22)*	*0,541*
Cardiac index (l/min/m^2)	*3.29 (2.97-3.60)*	*3.32 (3.04-3.57)*	*-0,02 (-0.15 – 0.12)*	*0,801*
Systolic blood pressure (mmHg)	*136.6 (124.9-148.3)*	*135.2 (126.4-147.8)*	*-0,50 (-10.03 – 9.03)*	*0,912*
Diastolic blood pressure (mmHg)	*84.4 (79.0-89.7)*	*84.3 (79.8-88.5)*	*0,21 (-4.78 – 5.21)*	*0,928*
Mean arterial pressure (mmHg)	*104.7 (96.8-112.6)*	*104.0 (98.1-111.1)*	*0,14 (-6.25 – 6.53)*	*0,962*
10 minutes post tilt (n=14)				
Heart rate (bpm)	*87.2 (80.6-93.9)*	*87.6 (81.0-94.3)*	*-0,43 (-5.13 – 4.28)*	*0,847*
Stroke volume index (ml/beat/m^2)	*36.6 (33.0-40.2)*	*38.1 (35.1-41.1)*	*-1,50 (-4.30 – 1.30)*	*0,268*
Cardiac index (l/min/m^2)	*3.27 (2.90-3.64)*	*3.28 (3.03-3.53)*	*-0,01 (-0.25 – 0.22)*	*0,899*
Systolic blood pressure (mmHg)	*134.6 (122.3-147.0)*	*133.1 (122.9-143.4)*	*1,50 (-8.76 – 11.76)*	*0,757*
Diastolic blood pressure (mmHg)	*84.3 (79.1-89.5)*	*82.4 (77.9-87.0)*	*1,86 (-3.87 – 7.59)*	*0,496*
Mean arterial pressure (mmHg)	*105.0 (96.7-113.3)*	*101.9 (95.5-108.2)*	*3,14 (-5.17 – 11.45)*	*0,429*

Wc: without compression; c: with compression; CI: confidence interval; +: significant at a level of p<0.10

DISCUSSION

To the authors' knowledge, this is the first study that examined the effects of graduated below-knee compression stockings on hemodynamics during tilt table testing in patients with ME/CFS. Consistent but non-significant increases in SVI and CI were found pre and post tilt testing with compression stockings compared to the test protocols without compression. No clear pattern in the change of HR and blood pressure was shown as a result of the compression. However, all results were not significant at a 5% confidence level, although a trend ($p<0.10$) was found for the SVI improvement during baseline with compression. Since the supposed effect of the below-knee compression is to improve the venous return, and thereby to increase the SVI and CI, the direction of the effects of the SVI and CI that were observed were thus as expected. Markedly, the trend for SV improvement was seen only during supine position. Furthermore, the SBP remained relatively stable during tilt, and the DBP showed a small increase. These changes can be considered normal.(42) SVI and CI values during baseline, and the decrease of SVI and CI during tilt, 36.6-47.8 ml/m^2/beat and 3.27-3.53 l/min/m^2 respectively, are within the normal range as well.(42,43) Worth noticing is that the patient that dropped out during the protocol

without compression had the lowest pumping capacity (SVI=31 ml/m^2/beat and CI=2.21 l/min/m^2) at baseline with a pulse pressure of 17 mmHg. During the protocol with compression, hemodynamic values normalized (pulse pressure of 27 mmHg) during baseline and the CI increased accordingly. However, during the first five minutes of tilt, a heart rate increase of 92 bpm occurred (a clear case of postural orthostatic tachycardia syndrome), after which tilt was terminated due to occurrence orthostatic hypotension complaints.

Only one study examined the effect of compression application during orthostatic stress in patients diagnosed with ME/CFS before. In this study performed by Van Streeten et al (2000),(19) 11 out of 15 of the patients that were included were labeled as 'orthostatic intolerant'. Hemodynamics and subjective experiences were measured during recumbent position and during standing, and the applied compression during standing normalized hemodynamic abnormalities and mitigated subjective complaints convincingly. The 11 out of 15 'prevalence' (73%) of OI that was found by Van Streeten et al., is in contrast with the 2 out of 15 (13%) in this study. Furthermore, the compression applied by the gradual compression stockings (18-24 mmHg) in this study did not show to have any effect on hemodynamics. However, the lack of effect of the compression stockings on hemodynamics can possibly be explained by the lack of measured hemodynamic abnormalities during tilt. Therefore, compression stockings have not been tested on their capability to attenuate hemodynamic abnormalities effectively. An important difference between this study and the study by Van Streeten et al. is that in the study performed by Van Streeten et al. a 60-minute standing protocol was used in comparison with a passive tilt of 10 minutes in this study. Although a passive tilt reduces or eliminates muscle pump function, and effects of orthostatic stress can thus be expected to be more pronounced, Freeman et al (2011)(44) mentioned that orthostatic hypotension may occur at a lesser degree during passive tilt. If passive tilt or standing causes more orthostatic stress is therefore not clear. Another important discrepancy is the compression application method that was used. The compression in the study by Van Streeten et al. was applied with military antishock trousers, which applied 45 mmHg of compression (in contrast to 18-24 mmHg in this study), and the compression was applied over the complete lower body. Logically, the greater amount of pressure and the greater area of application can be expected to have a stronger effect on hemodynamics. The latter

has also been shown in a study where the effect of different modes of compression application on hemodynamics was examined in orthostatic hypotension patients, and where compression on the total lower body area including the abdomen region had superior effects over single location (calfs/thighs/abdomen) compression.(45) In a study where the effect of below-knee compression stockings was examined in healthy subjects during head-up tilt,(46) no effect of the stockings on hemodynamics was found as well. However, again, since no hemodynamic abnormalities were found, this might explain the lack of hemodynamic change due to compression stockings.

The results of this study have to be interpreted with the following strengths and limitations considered. An important strength is that the patients served as their own control and that the two tests were performed under highly comparable situations. The results therefore most likely reflect the true effect of the stockings since this was the only major difference in the two tests. Furthermore, besides blood pressure and HR, as mechanisms of controlling blood pumping volume, the actual stroke volume was measured, which provides important insight in the blood pumping capacity during supine and orthostatic positions. An obvious limitation is the retrospective design, and as a consequence the inability to obtain more important characteristics of the patients such as activity status, physical fitness, disease severity, et cetera. These characteristics are known to have an important influence on orthostatic tolerance.(44) The lacking of these characteristics limits interpretation and generalization of the found results. Furthermore, hemodynamics during baseline and responses during tilt were within normal limits. This questions the generalizability of the results to patients with ME/CFS that do show hemodynamic abnormalities.

On the basis of the results provided in this study, recommendation of below-knee compression stockings in patients diagnosed with ME/CFS should not be considered to improve hemodynamics. Since the difference in effect on hemodynamics of lower body compression during passive tilt and during daily life activities are not known, future studies should examine the possible merits of below-knee compression stockings during daily life activities. Furthermore, due to the absence of hemodynamic abnormalities during tilting, future studies should examine the effect of below-knee compression stockings as a feasible treatment modality in patients diagnosed with ME/CFS that do show hemodynamic abnormalities.

CONCLUSION

Graduated below-knee compression stockings of 18-24 mmHg do not seem to improve hemodynamics during orthostatic stress in patients diagnosed with ME/CFS.

REFERENCES

(1) Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. Ann Intern Med 1994 Dec 15;121(12):953-959.

(2) Johnston S, Brenu EW, Staines D, Marshall-Gradisnik S. The prevalence of chronic fatigue syndrome/ myalgic encephalomyelitis: a meta-analysis. Clin Epidemiol 2013;5:105-110.

(3) Turnbull N, Shaw EJ, Baker R, Dunsdon S, Costin N, Britton G, et al. Chronic fatigue syndrome/myalgic encephalomyelitis (or encephalopathy): diagnosis and management of chronic fatigue syndrome/myalgic encephalomyelitis (or encephalopathy) in adults and children. 2007.

(4) Jason LA, Taylor RR. Applying cluster analysis to define a typology of chronic fatigue syndrome in a medically-evaluated, random community sample. 2002;17:323-337.

(5) Jason LA, Taylor RR, Kennedy CL, Jordan K, Huang CF, Torres-Harding S, et al. A factor analysis of chronic fatigue symptoms in a community-based sample. Soc Psychiatry Psychiatr Epidemiol 2002 Apr;37(4):183-189.

(6) Nisenbaum R, Reyes M, Mawle AC, Reeves WC. Factor analysis of unexplained severe fatigue and interrelated symptoms: overlap with criteria for chronic fatigue syndrome. Am J Epidemiol 1998 Jul 1;148(1):72-77.

(7) Rowe KS, Rowe KJ. Symptom Patterns of Children and Adolescents with Chronic Fatigue Syndrome. International Perspectives on Child and Adolescent Mental Health Oxford: Elsevier Science Ltd.; 2002. p. 395-421.

(8) Ray C, Weir WRC, Cullen S, Philiph S. Development of a measure of symptoms in chronic fatigue syndrome: the Profile of Fatigue-Related Symptoms (PFRS). 1992(7):27-43.

(9) Jason LA, Evans M, Porter N, Brown M, Brown A, Hunnell J, et al. **The Development of a Revised Canadian Myalgic Encephalomyelitis Chronic Fatigue Syndrome Case Definition**. 2010;6(2):120-135.

(10) Centers for Disease Control and Prevention. Chronic Fatigue Syndrome. 2012; Available at: http://www.cdc.gov/cfs/symptoms/index.html. Accessed November 11, 2012.

(11) De Lorenzo F, Hargreaves J, Kakkar VV. Possible relationship between chronic fatigue and postural tachycardia syndromes. Clin Auton Res 1996 Oct;6(5):263-264.

(12) Freeman R, Komaroff AL. Does the chronic fatigue syndrome involve the autonomic nervous system? Am J Med 1997 Apr;102(4):357-364.

(13) Jacob G, Biaggioni I. Idiopathic orthostatic intolerance and postural tachycardia syndromes. Am J Med Sci 1999 Feb;317(2):88-101.

(14) Ocon AJ, Messer ZR, Medow MS, Stewart JM. Increasing orthostatic stress impairs neurocognitive functioning in chronic fatigue syndrome with postural tachycardia syndrome. Clin Sci (Lond) 2012 Mar;122(5):227-238.

(15) Rowe PC, Bou-Holaigah I, Kan JS, Calkins H. Is neurally mediated hypotension an unrecognised cause of chronic fatigue? Lancet 1995 Mar 11;345(8950):623-624.

(16) Schondorf R, Freeman R. The importance of orthostatic intolerance in the chronic fatigue syndrome. Am J Med Sci 1999 Feb;317(2):117-123.

(17) Stewart JM. Autonomic nervous system dysfunction in adolescents with postural orthostatic tachycardia syndrome and chronic fatigue syndrome is characterized by attenuated vagal baroreflex and potentiated sympathetic vasomotion. Pediatr Res 2000 Aug;48(2):218-226.

(18) Stewart JM, Medow MS, Messer ZR, Baugham IL, Terilli C, Ocon AJ. Postural neurocognitive and neuronal activated cerebral blood flow deficits in young chronic fatigue syndrome patients with postural tachycardia syndrome. Am J Physiol Heart Circ Physiol 2012 Mar 1;302(5):H1185-94.
(19) Streeten DH, Thomas D, Bell DS. The roles of orthostatic hypotension, orthostatic tachycardia, and subnormal erythrocyte volume in the pathogenesis of the chronic fatigue syndrome. Am J Med Sci 2000 Jul;320(1):1-8.
(20) Sulheim D, Hurum H, Helland IB, Thaulow E, Wyller VB. Adolescent chronic fatigue syndrome; a follow-up study displays concurrent improvement of circulatory abnormalities and clinical symptoms. Biopsychosoc Med 2012 Mar 21;6:10-0759-6-10.
(21) Tanaka H, Matsushima R, Tamai H, Kajimoto Y. Impaired postural cerebral hemodynamics in young patients with chronic fatigue with and without orthostatic intolerance. J Pediatr 2002 Apr;140(4):412-417.
(22) Wyller VB, Saul JP, Walloe L, Thaulow E. Sympathetic cardiovascular control during orthostatic stress and isometric exercise in adolescent chronic fatigue syndrome. Eur J Appl Physiol 2008 Apr;102(6):623-632.
(23) Bou-Holaigah I, Rowe PC, Kan J, Calkins H. The relationship between neurally mediated hypotension and the chronic fatigue syndrome. JAMA 1995 Sep 27;274(12):961-967.
(24) Okamoto LE, Raj SR, Biaggioni I. Chronic Fatigue Syndrome and the Autonomic Nervous System. *David Robertson, Italo Biaggioni, Geoffrey Burnstock, Phillip A. Low and Julian F.R. Paton*. In: Robertson D, Biaggioni I, Burnstock G, Low PA, Paton JFR, editors. Primer on the Autonomic nervous system. 3rd ed.: Elsevier Inc.; 2012. p. 531-534.
(25) Bagai K, Song Y, Ling JF, Malow B, Black BK, Biaggioni I, et al. Sleep disturbances and diminished quality of life in postural tachycardia syndrome. J Clin Sleep Med 2011 Apr 15;7(2):204-210.
(26) Hurwitz BE, Coryell VT, Parker M, Martin P, Laperriere A, Klimas NG, et al. Chronic fatigue syndrome: illness severity, sedentary lifestyle, blood volume and evidence of diminished cardiac function. Clin Sci (Lond) 2009 Oct 19;118(2):125-135.
(27) Costa F, Sulur P, Angel M, Cavalcante J, Haile V, Christman B, et al. Intravascular source of adenosine during forearm ischemia in humans: implications for reactive hyperemia. Hypertension 1999 Jun;33(6):1453-1457.
(28) Ichise M, Salit IE, Abbey SE, Chung DG, Gray B, Kirsh JC, et al. Assessment of regional cerebral perfusion by 99Tcm-HMPAO SPECT in chronic fatigue syndrome. Nucl Med Commun 1992 Oct;13(10):767-772.
(29) Schwartz RB, Komaroff AL, Garada BM, Gleit M, Doolittle TH, Bates DW, et al. SPECT imaging of the brain: comparison of findings in patients with chronic fatigue syndrome, AIDS dementia complex, and major unipolar depression. AJR Am J Roentgenol 1994 Apr;162(4):943-951.
(30) Yoshiuchi K, Farkas J, Natelson BH. Patients with chronic fatigue syndrome have reduced absolute cortical blood flow. Clin Physiol Funct Imaging 2006 Mar;26(2):83-86.
(31) Biswal B, Kunwar P, Natelson BH. Cerebral blood flow is reduced in chronic fatigue syndrome as assessed by arterial spin labeling. J Neurol Sci 2011 Feb 15;301(1-2):9-11.
(32) Fischler B, D'Haenen H, Cluydts R, Michiels V, Demets K, Bossuyt A, et al. Comparison of 99m Tc HMPAO SPECT scan between chronic fatigue syndrome,

major depression and healthy controls: an exploratory study of clinical correlates of regional cerebral blood flow. Neuropsychobiology 1996;34(4):175-183.
(33) MacHale SM, Lawrie SM, Cavanagh JT, Glabus MF, Murray CL, Goodwin GM, et al. Cerebral perfusion in chronic fatigue syndrome and depression. Br J Psychiatry 2000 Jun;176:550-556.
(34) Razumovsky AY, DeBusk K, Calkins H, Snader S, Lucas KE, Vyas P, et al. Cerebral and systemic hemodynamics changes during upright tilt in chronic fatigue syndrome. J Neuroimaging 2003 Jan;13(1):57-67.
(35) Charles T, Mackintosh D, Healy B, Perrin K, Weatherall M, Beasley R. Merino wool graduated compression stocking increases lower limb venous blood flow: a randomized controlled trial. Adv Ther 2011 Mar;28(3):227-237.
(36) Autar R. A review of the evidence for the efficacy of Anti-Embolism Stockings (AES) in Venous Thromboembolism (VTE) prevention. 2009;13:41-49.
(37) Friedberg F, Bateman L, Bested A, Davenport T, Friedman K, Gurwitt A, et al. Chronic Fatigue Syndrome. Myalgic Encephalomyelitis. A Primer for Clinical Practitioners. 2012.
(38) Task Force for the Diagnosis and Management of Syncope, European Society of Cardiology (ESC), European Heart Rhythm Association (EHRA), Heart Failure Association (HFA), Heart Rhythm Society (HRS), Moya A, et al. Guidelines for the diagnosis and management of syncope (version 2009). Eur Heart J 2009 Nov;30(21):2631-2671.
(39) Eeftinck Schattenkerk DW, van Lieshout JJ, van den Meiracker AH, Wesseling KR, Blanc S, Wieling W, et al. Nexfin noninvasive continuous blood pressure validated against Riva-Rocci/Korotkoff. Am J Hypertens 2009 Apr;22(4):378-383.
(40) Martina JR, Westerhof BE, van Goudoever J, de Beaumont EM, Truijen J, Kim YS, et al. Noninvasive continuous arterial blood pressure monitoring with Nexfin(R). Anesthesiology 2012 May;116(5):1092-1103.
(41) Truijen J, van Lieshout JJ, Wesselink WA, Westerhof BE. Noninvasive continuous hemodynamic monitoring. J Clin Monit Comput 2012 Aug;26(4):267-278.
(42) Tahvanainen A, Leskinen M, Koskela J, Ilveskoski E, Nordhausen K, Oja H, et al. Ageing and cardiovascular responses to head-up tilt in healthy subjects. Atherosclerosis 2009 Dec;207(2):445-451.
(43) Normal Hemodynamic Parameters and Laboratory Values. 2011; Available at: http://ht.edwards.com/scin/edwards/sitecollectionimages/edwards/products/presep/ar05688_parameters.pdf. Accessed July 1, 2013.
(44) Freeman R, Wieling W, Axelrod FB, Benditt DG, Benarroch E, Biaggioni I, et al. Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. Clin Auton Res 2011 Apr;21(2):69-72.
(45) Denq JC, Opfer-Gehrking TL, Giuliani M, Felten J, Convertino VA, Low PA. Efficacy of compression of different capacitance beds in the amelioration of orthostatic hypotension. Clin Auton Res 1997 Dec;7(6):321-326.
(46) Protheroe CL, Dikareva A, Menon C, Claydon VE. Are compression stockings an effective treatment for orthostatic presyncope? PLoS One 2011;6(12):e28193.