Technology and Health Care 29 (2021) 629–642
DOI 10.3233/THC-202669
IOS Press

Comparison of the finger plethysmography derived stroke volumes by Nexfin CO Trek and suprasternal aortic Doppler derived stroke volume measurements in adults with myalgic encephalomyelitis/chronic fatigue syndrome and in healthy controls

C. (Linda) M.C. van Campen[a], Freek W.A. Verheugt[b], Peter C. Rowe[c] and Frans C. Visser[a]
[a]*Stichting CardioZorg, Hoofddorp, The Netherlands*
[b]*Radboud UMC, Nijmegen, The Netherlands*
[c]*Department of Paediatrics, Johns Hopkins University School of Medicine, Baltimore, MD, USA*

Received 21 October 2020
Accepted 1 November 2020

Abstract.
BACKGROUND: Finger plethysmography derived stroke volumes are frequently measured during tilt table testing. There are two algorithms to determine stroke volumes: Modelflow and Nexfin CO Trek. Most tilt studies used Modelflow, while there are differences between the two algorithms.
OBJECTIVE: To compare stroke volume indices by Nexfin CO Trek ($SVI_{NexfinCOTrek}$) with suprasternal Doppler derived SVI ($SVI_{Doppler}$) in healthy controls (HC) and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) patients during tilt testing. These patients may have a large SVI decrease during the tilt enabling a large range of SVI to be studied.
METHODS: One hundred and fifty-four patients and 39 HC with a normal tilt test were included. Supine and end-tilt $SVI_{Doppler}$ and $SVI_{NexfinCOTrek}$ were compared using the Bland-Altman analysis. Also, the effect of calibrating supine $SVI_{NexfinCOTrek}$ to $SVI_{Doppler}$ was studied.
RESULTS: Supine and end-tilt $SVI_{NexfinCOTrek}$ were significantly higher than $SVI_{Doppler}$: both $P < 0.005$. Bias, limits of agreement, and percent error (PE) were high with PE's between 37 and 43%. The calibration procedure resulted in an acceptable variance with a PE of 29%.
CONCLUSIONS: $SVI_{NexfinCOTrek}$ overestimates stroke volumes compared to $SVI_{Doppler}$, leading to high PE's. Calibration reduced variance to an acceptable level, allowing $SVI_{NexfinCOTrek}$ to be used for assessment of SVI changes during tilt testing.

Keywords: Stroke volume index, aortic VTI Doppler imaging, finger plethysmography, tilt table testing, chronic fatigue syndrome, myalgic encephalomyelitis

*Corresponding author: Frans C. Visser, Stichting CardioZorg, Planetenweg 5, 2132 HN Hoofddorp, The Netherlands. Tel.: +31 653475995; Fax: +31 205241235; E-mail: fransvisser@stichtingcardiozorg.nl.

1. Introduction

Finger plethysmography is a non-invasive technique to measure blood pressures and to estimate both stroke volumes and cardiac output. A large number of studies have focussed on its use in the perioperative and intensive care environments as hemodynamic monitoring may be crucial in these settings. Thermodilution has been used as the main method of validating cardiac output/cardiac index by finger plethysmography Two recent reviews showed that disagreement between the reference method (thermodilution) and finger plethysmography (expressed as percent error) was unacceptably high, and that a high inter-study heterogeneity was present [1,2]. This lack of agreement and heterogeneity limits the interchangeability of thermodilution and finger plethysmography in the perioperative and intensive care settings.

Another application of finger plethysmography is its use during head-up tilt table testing. Tilt table testing is used as a diagnostic tool for unexplained syncope [3–5] as well as for quantification of hemodynamic changes during orthostatic stress [6–8]. The use of the continuous heart rate and blood pressure measurements during tilt testing has been reported in previous studies [9–15].

Also, the use of finger plethysmography to assess stroke volume and cardiac output changes during tilt testing has been reported [2,16–25]. However, two studies of healthy controls demonstrated that stroke volume changes derived from finger plethysmography underestimated changes as compared to suprasternal Doppler derived stroke volume changes during tilt testing [26,27]

There are two algorithms available to estimate stroke volumes from finger plethysmography: Modelflow and Nexfin CO Trek, using the same underlying model of the three element Windkessel model [28,29]. One study demonstrated that Nexfin CO Trek derived cardiac output correlated well with thermodilution measurements in post-operative patients while Modelflow derived cardiac output differed significantly from thermodilution [30]. All of the above mentioned tilt table studies used Modelflow to estimate SV changes [16–27]. There is little information on stroke volume/cardiac output changes during tilt testing using Nexfin CO Trek.

Therefore, the primary aim of this study was to compare stroke volume indices as measured by Nexfin CO Trek with suprasternal Doppler derived stroke volume indices during tilt testing. For this purpose, a Bland-Altman analysis was performed, incorporating bias and precision statistics [31]. We examined both healthy controls as well as patients with ME/CFS, both groups having a normal tilt test. We previously demonstrated that in ME/CFS patients with a normal head-up tilt test, a larger decrease in cardiac output was found as compared to healthy controls [32]. Therefore, a large range in stroke volumes/cardiac output responses to tilt testing in these patients and healthy controls could be expected.

We also investigated the effects of calibration of the finger plethysmography, as some studies have recommended calibration of the baseline finger plethysmography derived SVI to other techniques [25,28, 30]. Finally, we explored factors that could negatively affect the relation between Doppler and Nexfin CO Trek derived SVI.

2. Material and methods

2.1. Patient selection

Participants with ME/CFS were eligible for this study if they had been referred to the Stichting CardioZorg, a cardiology clinic with a specialist focus on ME/CFS, between November 2012 and December 2016, and if an assessment of orthostatic intolerance was judged to be necessary. Healthy

controls were recruited through advertisements in publications and web sites of ME/CFS societies and patient groups, and through posters in the clinic (which were viewed by healthy employees in the building as well as by healthy family members of those with ME/CFS).

All participants underwent tilt testing using finger plethysmography recording for heart rate (HR), blood pressure (BP), and SVI determination, and also suprasternal aortic Doppler measurements for SVI ($SVI_{Doppler}$) quantification (see below). For the calculation of $SVI_{Doppler}$, a transthoracic echocardiogram was performed to measure aortic valve diameter.

The study was carried out in accordance with Declaration of Helsinki and was approved by the MEC of the Slotervaart Hospital (METC number P1411) Amsterdam, The Netherlands.

2.2. Headup tilt table test

ME/CFS patients and healthy controls received no oral or intravenous fluids or food in the two hours before the tilt test [33–35]. They were instructed to drink enough fluids in the preceding day, to avoid confounding effects of relative dehydration. No patients or volunteers used medications expected to affect intravascular volume (e.g., diuretics) or heart rate and blood pressure lowering drugs (beta-adrenergic antagonists, calcium-channel blockers, angiotensin converting enzyme inhibitors, angiotensin II antagonists, or ivabradine). The test started with a supine rest period of at least 15 minutes during which the supine Doppler echocardiographic measurements were performed. The Nexfin device was connected at the start of this resting period. At the end of 15 minutes supine, participants were brought to a 70-degree upright position over approximately 30 sec. While in the head-up position, the ME/CFS patients and healthy controls were instructed to avoid movement of the lower leg musculature in order to minimize venous return by the skeletal muscle pump. In the absence of important discomfort and patient requests to terminate the study, due to increased symptoms, the test was terminated between the 25^{th} and 30^{th} minutes of upright posture. The changes in heart rate and blood pressures during the tilt test were classified according to the consensus statement: normal heart rate and blood pressure response, classic orthostatic hypotension, delayed orthostatic hypotension, postural orthostatic tachycardia syndrome (POTS), and syncope or near-syncope [36]. In this study we studied only patients and healthy controls who had a normal HR and BP response.

2.3. Finger plethysmography measurements

For this study we used the Nexfin [13]. We placed an appropriate-sized finger cuff around the mid-phalanx of the middle finger of the left hand. We positioned the left arm and hand alongside the body to facilitate stable measurements. We used a level correction, adjusted for the hydrostatic difference between the finger and the heart [13]. During the entire protocol, HR, BP and SVI/CI were continuously recorded. SVI was automatically computed using the Nexfin CO Trek algorithm ($SVI_{NexfinCOTrek}$). Data were stored digitally and transferred to an Excel file.

2.4. Doppler echocardiographic measurements

The velocity-time integral (VTI) was obtained by one operator (FCV) using a continuous wave Doppler pencil probe (2.0 MHz) connected to a Vivid I machine (GE, Hoevelaken, The Netherlands) with the transducer positioned in the suprasternal notch. We have previously validated this technique in ME/CFS patients [37]. A maximal Doppler signal was assumed to be the optimal flow alignment. At least 2 frames of 6 seconds were obtained to measure $SVI_{Doppler}$. VTI frames were obtained in the resting supine

position, halfway through the upright position of the tilt test, and at the end of the upright period. The times of the start of the finger plethysmography recording and the moment of the start of tilting were noted from an independent radio controlled clock, and the Vivid-I times were corrected for the times of the radio clock. The start of tilting was set at 0 minutes.

Using nasal prongs end-tidal CO_2 was measured with a Lifesense (Nonin, Finland) device.

2.5. Data analysis

The VTI was measured by manual tracing of at least 6 cardiac cycles by one operator (CMCvC), using the GE EchoPac post-processing software. $SVI_{Doppler}$, expressed in ml/m^2/beat were calculated from the VTI's of the aortic valve times the corrected aortic valve area [38,39], and divided by the body surface area (BSA; Mosteller formula). CI, expressed in l/min/m^2, was calculated by multiplying SVI with the heart rate. $SVI_{Doppler}$ measurements of the separate cycles were averaged.

For comparison of the $SVI_{Doppler}$ data with $SVI_{NexfinCOTrek}$ data, the start and end of the Doppler echo recordings were noted and in this time interval data of heart rate, blood pressure, $SVI_{NexfinCOTrek}$ were averaged. Data of patients with 2 and 3 Doppler recordings were combined by defining the last available recording as end-tilt recording. From the mean arterial pressure (MAP) and the Doppler derived CI ($CI_{Doppler}$) the total peripheral resistance ($TPR_{Doppler}$) was calculated: $TPR_{Doppler} = MAP/CI_{Doppler}$.

As both in the supine position and at end-tilt $SVI_{Doppler}$ differed significantly from $SVI_{NexfinCOTrek}$ (see Table 2 and Fig. 1), we performed two different normalization procedures, in an attempt to reduce the difference between $SVI_{Doppler}$ and $SVI_{NexfinCOTrek}$. First, supine $SVI_{NexfinCOTrek}$ data were normalized to the supine $SVI_{Doppler}$ values of an individual patient: calibration factor = $SVI_{Doppler}/SVI_{NexfinCOTrek}$. This calibration factor was applied to the end-tilt $SVI_{NexfinCOTrek}$ data. Second, end-tilt SVI were calculated as the percent change from supine: %decrease in SVI = (1-end-tilt SVI/supine SVI)*100.

3. Statistical analysis

Data were analysed using SPSS version 21 (IBM Statistics, Armonk, NY, USA). Baseline characteristics and hemodynamic data of the patients and healthy controls were analysed using a t test for unpaired data. A Bland-Altman analysis (comparing $SVI_{Doppler}$ vs $SVI_{NexfinCOTrek}$) was performed on the baseline and end-tilt data before and after the calibration procedure. For this purpose, the mean of $SVI_{Doppler}$ and $SVI_{NexfinCOTrek}$ was calculated, the difference between the two, the upper and lower limits of agreement and the percent error (1.96*SD of the difference $SVI_{Doppler}$ minus $SVI_{NexfinCOTrek}$/mean $SVI_{Doppler}$ and $SVI_{NexfinCOTrek}$.

To explore the differences between the supine $SVI_{Doppler}$ and the $SVI_{NexfinCOTrek}$, a multiple regression analysis was performed as outlined by Leard Statistics [40]. The calibration factor: $SVI_{Doppler}/SVI_{NexfinCOTrek}$ was used as the dependent variable and plotted against the independent variables: gender, age, patient or healthy control classification, systolic and diastolic supine blood pressures, supine total peripheral resistance, supine heart rate, length, weight, supine end-tidal CO_2 and tilt duration. To explore the differences between the %decrease $SVI_{Doppler}$ and $SVI_{NexfinCOTrek}$ during the tilt a multiple regression was performed, in which the ratio %decrease $SVI_{Doppler}$/%decrease $SVI_{NexfinCOTrek}$ was used as the dependent variable and plotted against gender, age, patient or healthy control classification, the changes in systolic (SBP) and diastolic (DBP) blood pressures, the increase in TPR, the increase in HR, length, weight, change in end-tidal CO_2, and tilt duration.

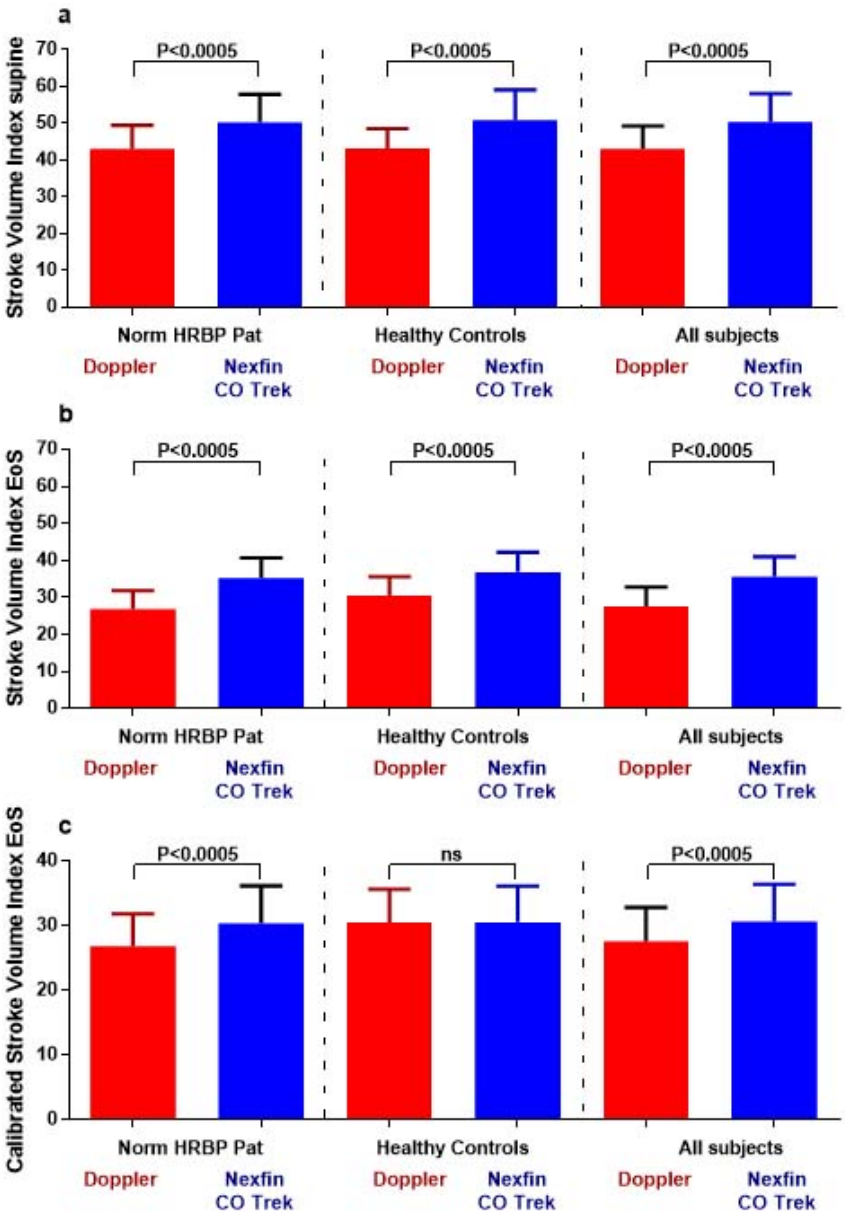

Fig. 1. Comparison between SVI as measured by Doppler and by Nexfin CO Trek in patients and healthy controls. Comparison between SVI as measured by Doppler and by Nexfin CO Trek in patients and healthy controls. Panel a: comparison of supine data, Panel b: comparison of end-tilt data. Panel c: comparison of end-tilt data after calibration of the supine $SVI_{NexfinCOTrek}$ to the supine $SVI_{Doppler}$. EoS: end of study; HC: healthy controls; Norm HRBP: patients with a normal heart rate and blood pressure response.

Graphs and regression lines were constructed and compared using Graphpad Prism version 6.00 for Windows (Graphpad software, La Jolla, CA, USA).

For measurement of intra- and inter-observer variation, we considered 60 aortic Doppler images. The operator (CMCvC) measured the VTI's at least 3 months apart, being blinded for the first analysis. A

Table 1
Baseline characteristics of ME/CFS patients and healthy controls

	ME/CFS pat with NormHRBP $N = 154$	HC with NormHRBP $N = 39$	P value
Age (years)	40 (11)	36 (15)	ns
Female/Male	131/23	33/6	ns
Duration ME/CFS (years)	13 (8)	–	
Length (cm)	171 (8)	172 (7)	ns
Weight (kg)	73 (15)	72 (14)	ns
BSA (m^2; Mosteller formula)	1.85 (0.21)	1.85 (0.19)	ns
BMI	25 (5)	24 (4)	ns

BMI: body mass index; BSA: body surface area; HC: healthy controls; NormHRBP: subjects with a normal heart rate and blood pressure response during tilt.

second operator (FCV) measured the same VTI's being blinded for the name of the patients on the PC screen. This analysis was performed at least 6 months after the tilt study. The intra-class correlation coefficient (ICC) for intra and inter-observer reliability was calculated with SPSS. Because of the multiple comparisons, we elected a more conservative P value of < 0.01 to be considered statistically significant.

4. Results

4.1. Participants

From November 2012 to December 2016, we studied 286 ME/CFS patients and 48 healthy controls. In 5 ME/CFS patients, the finger plethysmography recordings were of insufficient quality, and in 10 the Doppler studies were also of insufficient quality, leading to exclusion. The following hemodynamic changes were observed: 154 patients showed a normal heart rate and blood pressure response, 3 patients had a classic orthostatic hypotension, 60 patients POTS, 44 a delayed orthostatic hypotension and in 9 a neurally mediated (near) syncope was observed. For comparison with the healthy controls with a normal heart rate and blood pressure response, only patients with a normal heart rate and blood pressure response were studied here ($n = 154$). Three healthy controls were excluded because of an insufficient Doppler image quality, 4 with a delayed orthostatic hypotension and 2 with vasovagal syncope, leaving 39 studied healthy controls.

Baseline characteristics of ME/CFS patients with a normal heart rate and blood pressure response and healthy controls are presented in Table 1. The baseline characteristics were not different between patients and healthy controls.

4.2. Hemodynamic measurements

Doppler recordings were made at a mean of 2.0 (0.8) min before the start of the tilt and 15.6 (3.1) min (mid-tilt) and 26.5 (3.3) min after the start of the tilt (end-tilt). Imaging recording lasted a mean of 0.8 ± 0.9 min. In 64 ME/CFS patients, a third VTI was not available: in 6 because of insufficient quality of the recording, in 3 because recordings were not available, in 26 because of prematurely termination at the request of the patient, and in 29 because of premature termination because of severe OI symptoms. For the VTI measurements, the ICC of intra-observer variation was 0.98 and the ICC of inter-observer variation was 0.99.

Table 2
Tilt table test results of ME/CFS patients and healthy controls

	ME/CFS patients with NormHRBP $n = 154$	HC with NormHRBP $n = 39$	All with NormHRBP $n = 193$	P value patients vs HC
HR supine	69 (9)	62 (9)	68 (10)	< 0.0005
HR EOS	86 (12)	80 (16)	85 (13)	
SBP supine	135 (18)	131 (12)	134 (17)	
SBP EOS	131 (16)	125 (13)	130 (15)	
DBP supine	78 (8)	78 (6)	78 (8)	
DBP EOS	85 (9)	80 (8)	84 (9)	< 0.01
MAP supine	101 (11)	98 (8)	100 (11)	
MAP EOS	103 (12)	97 (10)	102 (11)	< 0.01
$SVI_{Doppler}$ supine	43 (6)	43 (5)	43 (6)	
$SVI_{Doppler}$ EOS	27 (5)	31 (5)	28 (5)	< 0.0005
$SVI_{NexfinCOTrek}$ supine	50 (8)	51 (8)	50 (7)	
$SVI_{NexfinCOTrek}$ EOS	35 (5)	37 (5)	36 (5)	
$CI_{Doppler}$ supine	2.97 (0.51)	2.69 (0.46)	2.92 (0.51)	< 0.005
$CI_{Doppler}$ EOS	2.29 (0.44)	2.40 (0.37)	2.31 (0.43)	
$TPR_{Doppler}$ supine	34.8 (6.8)	37.4 (6.4)	35.3 (6.8)	
$TPR_{Doppler}$ EOS	46.3 (9.3)	41.5 (7.9)	45.3 (9.2)	< 0.005
$P_{et}CO_2$ supine	36 (4)	37 (3)	37 (3)	
$P_{et}CO_2$ EOS	32 (5)	36 (3)	33 (5)	< 0.0005

$CI_{Doppler}$: cardiac index as derived from Doppler in l/min/m^2; DBP: diastolic blood pressure in mmHg; EOS: end of study, HC: healthy controls; HR: heart rate in bpm; n: number; MAP: mean arterial pressure; NormHRBP: subjects with a normal heart rate and blood pressure response during tilt; $PetCO_2$: end-tidal CO_2; SBP: systolic blood pressure in mmHg; $SVI_{Doppler}$: stroke volume index in ml/m^2/beat as obtained by Doppler; $SVI_{NexfinCOTrek}$: stroke volume index in ml/m^2/beat as obtained by Nexfin CO Trek algorithm; TPR: total peripheral resistance calculated from $MAP/CI_{Doppler}$.

Table 2 shows the hemodynamic data of ME/CFS patients and healthy controls. Supine heart rates were significantly higher in ME/CFS patients than in healthy controls ($P < 0.0005$). Supine $SVI_{Doppler}$ was not different between the two groups. As a consequence of the higher supine heart rate, $CI_{Doppler}$ was significantly higher in patients compared to healthy controls ($P < 0.005$). At end-tilt $SVI_{Doppler}$ of patients was significantly lower than that of healthy controls ($P < 0.0005$). $SVI_{NexfinCOTrek}$ supine and at end-tilt were not significantly different between the two groups. $CI_{Doppler}$ at end-tilt was not significantly different between the two groups. Supine $TPR_{Doppler}$ was not significantly different between patients and healthy controls. End-tilt $TPR_{Doppler}$ was significantly higher in patients ($P < 0.005$) due to the higher MAP at end-tilt in patients ($P < 0.01$). End-tidal CO_2 at end-tilt was significantly lower in patients than in healthy controls ($P < 0.0005$).

Figure 1a and b show the graphical representation of the comparison between $SVI_{Doppler}$ and $SVI_{NexfinCOTrek}$ in the supine position (Panel a) and at end-tilt (Panel b). All $SVI_{NexfinCOTrek}$ data were significantly higher than the $SVI_{Doppler}$ data (all $P < 0.0005$).

Figure 2a–d show the linear regression analysis of $SVI_{Doppler}$ vs $SVI_{NexfinCOTrek}$. The slope of the relation between supine $SVI_{Doppler}$ vs supine $SVI_{NexfinCOTrek}$ was not significantly different from zero. The slopes of the other three relations were significantly different from zero, but R^2 values of the end-tilt data, and of the %decrease data were low.

Table 3 and Fig. 3a and b show the Bland-Altman analyses of the patients and healthy controls for the supine and end-tilt data. The upper and lower limits of agreement of the difference $SVI_{Doppler}$ minus $SVI_{NexfinCOTrek}$ were widespread and a high percent error was found, ranging between 37 and 40% for

Table 3
Bland-Altman analysis of the $SVI_{Doppler}$ versus the $SVI_{NexfinCOTrek}$

	ME/CFS NormHRBP $n = 154$	HC NormHRBP $n = 39$	All subjects $N = 193$
Mean SVI supine (Doppler + NexfinCOTrek/2)	47	47	47
Bias SVI supine (Doppler-NexfinCOTrek)	−7	−8	−7
Upper Limit Agreement SVI supine	12	10	11
Lower Limit Agreement SVI supine	−26	−25	−26
Percent Error SVI supine	40%	37%	40%
Mean SVI EoS (Doppler+NexfinCOTrek/2)	31	34	32
Bias SVI EoS (Doppler-NexfinCOTrek)	−8	−6	−8
Upper Limit Agreement SVI EoS	5	7	5
Lower Limit Agreement SVI EoS	−22	−20	−21
Percent Error SVI EoS	43%	39%	42%
After calibration of supine $SVI_{NexfinCOTrek}$ to supine $SVI_{Doppler}$			
Mean SVI EoS (Doppler+NexfinCOTrek/2)	29	31	29
Bias SVI EoS (Doppler-NexfinCOTrek)	−4	−1	−4
Upper Limit Agreement SVI EoS	5	7	5
Lower Limit Agreement SVI EoS	−12	−9	−12
Percent Error SVI EoS	29%	25%	29%
Mean %decrease SVI (Doppler+NexfinCOTrek/2)	34	28	32
Bias %decrease SVI (Doppler-NexfinCOTrek)	8	2	7
Upper Limit Agreement %decrease SVI	27	19	26
Lower Limit Agreement %decrease SVI	−11	−14	−12
Percent Error %decrease SVI EoS	57%	61%	59%

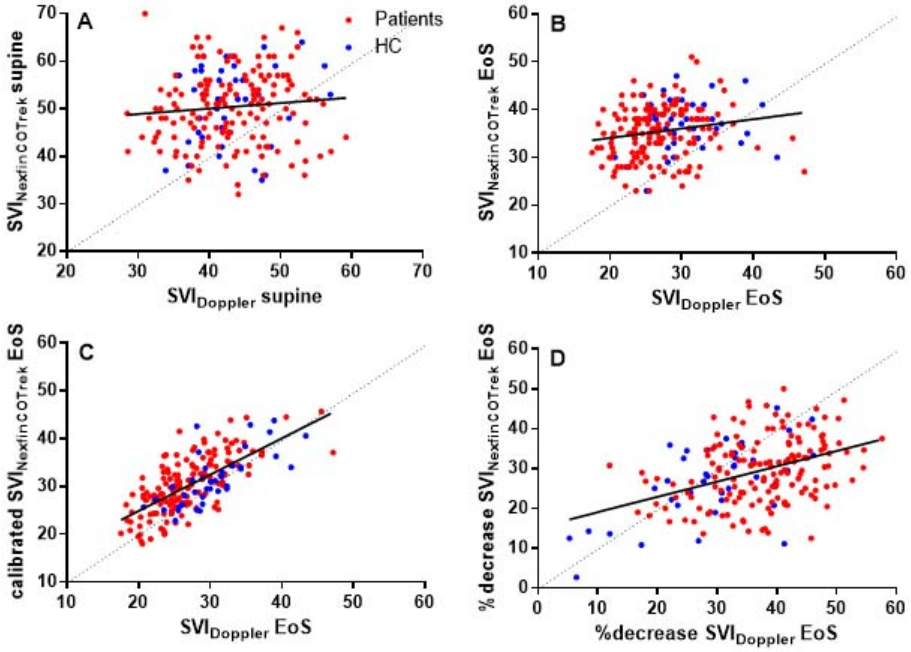

Fig. 2. Linear regression analysis of $SVI_{Doppler}$ versus $SVI_{NexfinCOTrek}$. Linear regression analysis of $SVI_{Doppler}$ versus $SVI_{NexfinCOTrek}$. Panel a: supine SVI, panel b: end-study SVI, panel c: end-study SVI after calibration of the supine $SVI_{NexfinCOTrek}$ to the supine $SVI_{Doppler}$, panel d: %decrease SVI at end-tilt. HC: healthy controls, solid line: regression line of all subjects.

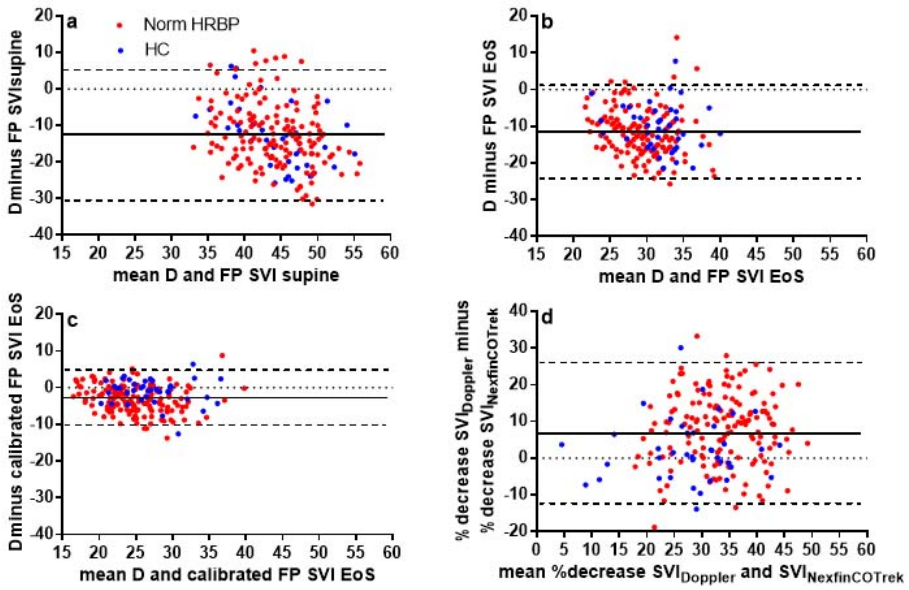

Fig. 3. Bland-Altman plots of $SVI_{Doppler}$ versus $SVI_{NexfinCOTrek}$. Bland-Altman plots of $SVI_{Doppler}$ versus $SVI_{NexfinCOTrek}$. Panel a: supine SVI, panel b: end-study SVI, panel c: end-study SVI after calibration of the supine $SVI_{NexfinCOTrek}$ to the supine $SVI_{Doppler}$. Panel d: %decrease SVI at end-tilt. HC: healthy controls; solid line: bias for all subjects, dashed lines: upper and lower limits of agreement for all subjects.

the supine data (mean for all subjects: 40%) and between 39 and 43% for the end-tilt data (mean for all subjects: 42%). Figure 1c shows the effect of the calibration procedure on $SVI_{NexfinCOTrek}$. Figure 3c shows that the limits of agreement after calibration were smaller and the percent error at end-tilt ranged between 25 and 29% (mean for all subjects 29%). The slope of the regression line after calibration was significantly lower than the line of identity (0.7597 vs 1; $P < 0.0005$).

Table 3 and Fig. 3d also show the normalization procedure using the %decrease of $SVI_{Doppler}$ vs the %decrease of $SVI_{NexfinCOTrek}$. The upper and lower limits of agreement were high and the percent error ranged between 57 and 61% (mean for al subject 59%).

4.3. Multiple regression analysis

The calibration factor showed a significant correlation with age, supine DBP, supine TPR and supine HR (all $P < 0.0005$): calibration factor = 0.974 + 0.009*age + 0.016*supine diastolic blood pressure (DBP) – 0.011*supine HR – 0.026*supine TPR, adjusted $R^2 = 0.758$. The ratio %decrease $SVI_{Doppler}$/%decrease $SVI_{NexfinCOTrek}$ was significantly correlated with %increase TPR, %increase HR and %increase DBP: %decrease $SVI_{Doppler}$/%decrease $SVI_{NexfinCOTrek}$ = 2.131 + 2.085*%increase TPR – 3.989*%increase DBP + 0.636*%increase HR, with P values of < 0.0005 for all parameters, with the exception of %increase HR: $P < 0.005$. The adjusted $R^2 = 0.427$.

5. Discussion

The main findings of this study can be summarized as follows: in ME/CFS patients and in healthy controls, $SVI_{NexfinCOTrek}$ measurements were, both in the supine position as well as during the tilt,

systematically higher than the $SVI_{Doppler}$ data (Fig. 1). In the recent meta-analysis of Saugel et al. of intensive care patients, the differences between cardiac output (CO) or $CI_{NexfinCOTrek}$ and the reference method (thermodilution) was large between studies [2], with highly variable 95% confidence intervals of the differences. Assuming that HR measurements were equal between the $CO/CI_{NexfinCOTrek}$ and thermodilution derived CO and CI, it indicates that variation between thermodilution derived stroke volumes (SV or SVI) and $SVI_{NexfinCOTrek}$ is unacceptably high. Also, a study using MRI as reference showed too large a variation between CO by MRI and Nexfin CO Trek in stable cardiac patients. In the present study we confirmed this high variation in healthy controls and ME/CFS patients during tilt table testing. The Bland-Altman and percent error analysis of the comparison between $SVI_{Doppler}$ and $SVI_{NexfinCOTrek}$ shows that limits of agreement and percent errors of supine and end-tilt data were unacceptably high: percent error of all subjects was 40% in the supine position and 42% at end-tilt. Critchley and Critchley showed in their meta-analysis of cardiac output measurements by different techniques that, when both techniques have a similar errors in measurement of around 20%, the resulting percent error in the Bland-Altman analysis is 30% [31]. A detailed analysis of the errors in cardiac output measurements are described by Truijen et al. [41].

The calibration procedure (supine $SVI_{Doppler}$/supine $SVI_{NexfinCOTrek}$) reduced the difference between $SVI_{NexfinCOTrek}$ and $SVI_{Doppler}$ (Fig. 3) considerably with a mean percent error at end-tilt of 29%. This value is within the acceptable limits of percent error of less than 30% [31]. This indicates that calibrated finger plethysmography using the Nexfin CO trek algorithm results in similar SVI data as SVI data derived from suprasternal Doppler imaging. The major advantage is that finger plethysmography is a continuous beat-to-beat technique and therefore dynamic changes can be better observed than a relatively static technique like aortic VTI imaging. Nevertheless, even after calibration, the $SVI_{NexfinCOTrek}$ decrease during the tilt test was less than of $SVI_{Doppler}$. The underestimation of $SVI_{NexfinCOTrek}$ changes is in line with a previous study with heart failure patients undergoing resynchronization therapy and with two studies during tilt table testing, although the latter two studies used Modelflow for SVI determination [26,27,42].

The reasons for the underestimation of finger plethysmography changes are unclear. Suggested mechanisms in other patient groups (in the setting of an intensive care unit and anaesthesia) are peripheral vasoconstriction and oedema of the finger [43,44]. In ME/CFS patients, the presence of central hypovolemia can also lead to peripheral vasoconstriction [45,46]. Extreme vasodilatation can contribute to abnormal SVI finger plethysmography results as was previously demonstrated [47]. In an attempt to explain the differences between supine $SVI_{Doppler}$ and $SVI_{NexfinCOTrek}$ the calibration factor: $SVI_{Doppler}/SVI_{NexfinCOTrek}$ was plotted against a variety of clinical factors and hemodynamic parameters in a multiple linear regression analysis. In the present study, the retrospective analysis of factors contributing to a difference between the supine $SVI_{NexfinCOTrek}$ values versus the supine $SVI_{Doppler}$ values identified four significant factors: younger age, a lower supine DBP, higher supine HR, and a higher supine TPR resulted in a larger difference between supine $SVI_{Doppler}$ and $SVI_{NexfinCOTrek}$. The combination of age, supine DBP, supine HR, and supine TPR explained 76% of the variation. In a similar manner, a higher increase in TPR, a higher increase in HR and a lower change in DBP from supine to end-tilt resulted in a larger difference between %decrease $SVI_{Doppler}$ vs %decrease $SVI_{NexfinCOTrek}$, explaining 43% of the variation of changes of $SVI_{Doppler}$ vs $SVI_{NexfinCOTrek}$. The exact algorithm of Nexfin CO Trek is not known, but one study using Modelflow, also found that $CO_{Modelflow}$ underestimated acute changes of peripheral resistance compared to suprasternal Doppler imaging [27]. The influence of age on $CO_{Modelflow}$ was also studied and the authors found a limited contribution of age to the measurement errors [28]. Future studies are needed to determine whether discrepancies between a reference CO/SV assessment (like thermodilution or Doppler imaging) and $CO/SV_{NexfinCOTrek}$ data can be reduced. Furthermore, one study demonstrated significant

differences between $CO_{NexfinCOTrek}$ and $CO_{Modelflow}$ when both were compared to CO measurements by thermodilution. Thus, although underestimation of SVI changes of Modelflow and Nexfin CO Trek are present, and the effect of peripheral resistance are similar, there may be differences between Nexfin CO Trek and Modelflow. This also needs to be further explored in the future.

In the present study SVI determination by suprasternal continuous wave Doppler was used. Most studies, using a variety of echocardiographic techniques have focussed on intensive care and perioperative patients and compared the cardiac output by echocardiography with thermodilution. In a recent meta-analysis the authors concluded that, although the difference in cardiac output between echocardiography by different types or sites and thermodilution was not entirely consistent, the overall effect showed no significant differences between ultrasound and thermodilution [48]. A limited number of studies have used suprasternal Doppler ultrasound to measure cardiac output during tilt table testing [26,27,32,49,50]. We recently validated this technique by comparison with a transthoracic echocardiogram [37] in patients with a normal tilt test, with POTS, and with delayed orthostatic hypotension. In all three groups, there were no significant differences of the regression line between the suprasternal SVI and transthoracic echo derived SVI, with high R values ranging between 0.91 and 0.94. Based on the meta-analysis of Zhang et al. and our own comparison, we can be reasonably certain that the $SVI_{Doppler}$ can be used as a reference technique [37,48].

In the present study two different groups were studied: HC and ME/CFS patients. Both groups had a normal tilt table test, defined as a normal heart rate and blood pressure response. Supine $SVI_{Doppler}$ values were not significantly different between the two groups, but end-tilt $SVI_{Doppler}$ in patients was lower than in HC, in line with previous studies [20,32]. In contrast, end-tilt $SVI_{NexfinCOTrek}$ were not significantly different between patients and HC. Despite hemodynamic differences between patients and HC, bias and limits of agreement of the Bland-Altman analysis of $SVI_{Doppler}$ vs $SVI_{NexfinCOTrek}$ were similar between patients and HC. It implies that the underperformance of the Nexfin CO Trek is not related to a specific pathophysiology in patients but is algorithm related.

5.1. Limitations

Single beat comparison between $SVI_{Doppler}$ and $SVI_{NexfinCOTrek}$ was not performed in this study: $SVI_{NexfinCOTrek}$ data were compared to $SVI_{Doppler}$ data in the time duration of Doppler acquisition. This might have led to a larger discrepancy between $SVI_{Doppler}$ and $SVI_{NexfinCOTrek}$, but would not be expected to alter the relation between the two In the present study we analysed 6 heartbeats. Other studies have analysed SV over an acquisition period of 10 respiratory cycles in ventilated subjects [51]. While it is possible that our SVI assessments may deviate from the true values, we think this is unlikely due to the lack of variability and the large number of patients studied. This was a single centre study and needs to be replicated by others. The limitations of Doppler SVI determination are that acquisition is more time consuming, and is dependent on investigator and patient echo windows. An inadequate echo window leads to a low image quality: in the present study in thirteen patients and HC a poor image quality of the standing VTI recording led to exclusion, whereas only 5 patients with an inadequate finger plethysmography recording were excluded. Production of Nexfin monitors has been discontinued, however the algorithm has been incorporated in the ClearSight systems (Edwards Lifesiences, Irvine, CA, USA). The presented results are therefore relevant to the Nexfin CO Trek technology.

6. Conclusion

During head-up tilt testing in ME/CFS patients and healthy controls $SVI_{NexfinCOTrek}$ overestimates stroke volumes at rest and during the head-up position compared to $SVI_{Doppler}$. This resulted in high bias, limits

of agreement and percent errors (supine percent error 40%, end-tilt 42%). After calibration of the resting $SVI_{NexfinCOTrek}$ to the resting $SVI_{Doppler}$, bias, limits of agreement and percent errors were significantly reduced with an acceptable percent error of 29%. The use of calibrated $SVI_{NexfinCOTrek}$ measurements allows assessment of the hemodynamic changes during tilt testing. In contrast, the calculation of percent $SVI_{NexfinCOTrek}$ changes during the tilt, does not result in acceptable bias, limits of agreement and percent errors compared to percent $SVI_{Doppler}$ changes during the tilt. Finally, the multiple regression analysis of factors influencing the calibration factor showed that TPR and DBP are major determinants of the differences between $SVI_{Doppler}$ and $SVI_{NexfinCOTrek}$.

Acknowledgments

We would like to acknowledge all healthy controls and patients who, by participation, made this study possible. Furthermore, we would like to thank Berend E. Westerhof of TU Twente, the Netherlands, for his critical review of the manuscript.

Conflict of interest

None to report.

References

[1] Joosten A, Desebbe O, Suehiro K, Murphy LS, Essiet M, Alexander B, Fischer MO, Barvais L, Van Obbergh L, Maucort-Boulch D, Cannesson M. Accuracy and precision of non-invasive cardiac output monitoring devices in perioperative medicine: a systematic review and meta-analysisdagger. Br J Anaesth. 2017; 118(3): 298-310. doi: 10.1093/bja/aew461.

[2] Saugel B, Hoppe P, Nicklas JY, Kouz K, Korner A, Hempel JC, Vos JJ, Schon G, Scheeren TWL. Continuous noninvasive pulse wave analysis using finger cuff technologies for arterial blood pressure and cardiac output monitoring in perioperative and intensive care medicine: a systematic review and meta-analysis. Br J Anaesth. 2020; 125(1): 25-37. doi: 10.1016/j.bja.2020.03.013.

[3] Strickberger SA, Benson DW, Biaggioni I, Callans DJ, Cohen MI, Ellenbogen KA, Epstein AE, Friedman P, Goldberger J, Heidenreich PA, Klein GJ, Knight BP, Morillo CA, Myerburg RJ, Sila CA, American Heart Association Councils on Clinical Cardiology CNCDitY, Stroke, Quality of C, Outcomes Research Interdisciplinary Working G, American College of Cardiology F, Heart Rhythm S, American Autonomic S. AHA/ACCF Scientific Statement on the evaluation of syncope: from the American Heart Association Councils on Clinical Cardiology, Cardiovascular Nursing, Cardiovascular Disease in the Young, and Stroke, and the Quality of Care and Outcomes Research Interdisciplinary Working Group; and the American College of Cardiology Foundation: in collaboration with the Heart Rhythm Society: endorsed by the American Autonomic Society. Circulation. 2006; 113(2): 316-327. doi: 10.1161/CIRCULATIONAHA.105.170274.

[4] Sutton R. The Value of Tilt Testing and Autonomic Nervous System Assessment. Cardiol Clin. 2015; 33(3): 357-360. doi: 10.1016/j.ccl.2015.04.003.

[5] Brignole M, Moya A, de Lange FJ, Deharo JC, Elliott PM, Fanciulli A, Fedorowski A, Furlan R, Kenny RA, Martin A, Probst V, Reed MJ, Rice CP, Sutton R, Ungar A, van Dijk JG, Group ESCSD. 2018 ESC Guidelines for the diagnosis and management of syncope. Eur Heart J. 2018; 39(21): 1883-1948. doi: 10.1093/eurheartj/ehy037.

[6] Mellingsaeter MR, Wyller TB, Ranhoff AH, Bogdanovic N, Wyller VB. Reduced sympathetic response to head-up tilt in subjects with mild cognitive impairment or mild Alzheimer's dementia. Dement Geriatr Cogn Dis Extra. 2015; 5(1): 107-115. doi: 10.1159/000375297.

[7] Lim E, Chan GS, Dokos S, Ng SC, Latif LA, Vandenberghe S, Karunanithi M, Lovell NH. A cardiovascular mathematical model of graded head-up tilt. PLoS One. 2013; 8(10): e77357. doi: 10.1371/journal.pone.0077357.

[8] Tahvanainen A, Leskinen M, Koskela J, Ilveskoski E, Nordhausen K, Oja H, Kahonen M, Koobi T, Mustonen J, Porsti I. Ageing and cardiovascular responses to head-up tilt in healthy subjects. Atherosclerosis. 2009; 207(2): 445-451. doi: 10.1016/j.atherosclerosis.2009.06.001.

[9] Heusdens JF, Lof S, Pennekamp CW, Specken-Welleweerd JC, de Borst GJ, van Klei WA, van Wolfswinkel L, Immink RV. Validation of non-invasive arterial pressure monitoring during carotid endarterectomy. Br J Anaesth. 2016; 117(3): 316-323. doi: 10.1093/bja/aew268.
[10] Balzer F, Habicher M, Sander M, Sterr J, Scholz S, Feldheiser A, Muller M, Perka C, Treskatsch S. Comparison of the non-invasive Nexfin(R) monitor with conventional methods for the measurement of arterial blood pressure in moderate risk orthopaedic surgery patients. J Int Med Res. 2016; 44(4): 832-843. doi: 10.1177/0300060516635383.
[11] Weiss E, Gayat E, Dumans-Nizard V, Le Guen M, Fischler M. Use of the Nexfin device to detect acute arterial pressure variations during anaesthesia induction. Br J Anaesth. 2014; 113(1): 52-60. doi: 10.1093/bja/aeu055.
[12] Garnier RP, van der Spoel AG, Sibarani-Ponsen R, Markhorst DG, Boer C. Level of agreement between Nexfin non-invasive arterial pressure with invasive arterial pressure measurements in children. Br J Anaesth. 2012; 109(4): 609-615. doi: 10.1093/bja/aes295.
[13] Martina JR, Westerhof BE, van Goudoever J, de Beaumont EM, Truijen J, Kim YS, Immink RV, Jobsis DA, Hollmann MW, Lahpor JR, de Mol BA, van Lieshout JJ. Noninvasive continuous arterial blood pressure monitoring with Nexfin(R). Anesthesiology. 2012; 116(5): 1092-1103. doi: 10.1097/ALN.0b013e31824f94ed.
[14] Eeftinck Schattenkerk DW, van Lieshout JJ, van den Meiracker AH, Wesseling KR, Blanc S, Wieling W, van Montfrans GA, Settels JJ, Wesseling KH, Westerhof BE. Nexfin noninvasive continuous blood pressure validated against Riva-Rocci/Korotkoff. Am J Hypertens. 2009; 22(4): 378-383. doi: 10.1038/ajh.2008.368.
[15] Akkermans J, Diepeveen M, Ganzevoort W, van Montfrans GA, Westerhof BE, Wolf H. Continuous non-invasive blood pressure monitoring, a validation study of Nexfin in a pregnant population. Hypertens Pregnancy. 2009; 28(2): 230-242. doi: 10.1080/10641950802601260.
[16] Murrell CJ, Cotter JD, George K, Shave R, Wilson L, Thomas K, Williams MJ, Ainslie PN. Cardiorespiratory and cerebrovascular responses to head-up tilt I: influence of age and training status. Exp Gerontol. 2011; 46(1): 9-17. doi: 10.1016/j.exger.2010.06.005.
[17] van den Bogaard B, Westerhof BE, Best H, Davis SC, Secher NH, van den Born BJ, van Lieshout JJ. Arterial wave reflection decreases gradually from supine to upright. Blood Press. 2011; 20(6): 370-375. doi: 10.3109/08037051.2011.588484.
[18] Freitas J, Santos R, Azevedo E, Carvalho M, Boomsma F, Meiracker A, Falcao de Freitas A, Abreu-Lima C. Hemodynamic, autonomic and neurohormonal behaviour of familial amyloidotic polyneuropathy and neurally mediated syncope patients during supine and orthostatic stress. Int J Cardiol. 2007; 116(2): 242-248. doi: 10.1016/j.ijcard.2006.03.052.
[19] Youde J, Panerai R, Gillies C, Potter J. Reproducibility of circulatory changes to head-up tilt in healthy elderly subjects. Age Ageing. 2003; 32(4): 375-381.
[20] Timmers HJ, Wieling W, Soetekouw PM, Bleijenberg G, Van Der Meer JW, Lenders JW. Hemodynamic and neurohumoral responses to head-up tilt in patients with chronic fatigue syndrome. Clin Auton Res. 2002; 12(4): 273-280. doi: 10.1007/s10286-002-0014-1.
[21] Chandler MP, Mathias CJ. Haemodynamic responses during head-up tilt and tilt reversal in two groups with chronic autonomic failure: pure autonomic failure and multiple system atrophy. J Neurol. 2002; 249(5): 542-548. doi: 10.1007/s004150200062.
[22] Houtman S, Colier WN, Oeseburg B, Hopman MT. Systemic circulation and cerebral oxygenation during head-up tilt in spinal cord injured individuals. Spinal Cord. 2000; 38(3): 158-163.
[23] Wieling W, Van Lieshout JJ, Ten Harkel AD. Dynamics of circulatory adjustments to head-up tilt and tilt-back in healthy and sympathetically denervated subjects. Clin Sci (Lond). 1998; 94(4): 347-352.
[24] Fujimura J, Camilleri M, Low PA, Novak V, Novak P, Opfer-Gehrking TL. Effect of perturbations and a meal on superior mesenteric artery flow in patients with orthostatic hypotension. J Auton Nerv Syst. 1997; 67(1-2): 15-23.
[25] Stewart JM, Pianosi P, Shaban MA, Terilli C, Svistunova M, Visintainer P, Medow MS. Postural Hyperventilation as a Cause of Postural Tachycardia Syndrome: Increased Systemic Vascular Resistance and Decreased Cardiac Output When Upright in All Postural Tachycardia Syndrome Variants. J Am Heart Assoc. 2018; 7(13): doi: 10.1161/JAHA.118.008854.
[26] Lieshout van JJ, Toska K, Van Lieshout EJ, Eriksen M, Walloe L, Wesseling KH. Beat-to-beat noninvasive stroke volume from arterial pressure and Doppler ultrasound. EurJApplPhysiol. 2003; 90(1-2): 131-137.
[27] Dyson KS, Shoemaker JK, Arbeille P, Hughson RL. Modelflow estimates of cardiac output compared with Doppler ultrasound during acute changes in vascular resistance in women. Exp Physiol. 2010; 95(4): 561-568. doi: 10.1113/expphysiol.2009.050815.
[28] Wesseling KH, Jansen JR, Settels JJ, Schreuder JJ. Computation of aortic flow from pressure in humans using a nonlinear, three-element model. JApplPhysiol. 1993; 74(5): 2566-2573.
[29] Truijen J, van Lieshout JJ, Wesselink WA, Westerhof BE. Noninvasive continuous hemodynamic monitoring. J Clin Monit Comput. 2012; 26(4): 267-278. doi: 10.1007/s10877-012-9375-8.
[30] Bogert LW, Wesseling KH, Schraa O, Van Lieshout EJ, de Mol BA, van Goudoever J, Westerhof BE, van Lieshout JJ. Pulse contour cardiac output derived from non-invasive arterial pressure in cardiovascular disease. Anaesthesia. 2010; 65(11): 1119-1125. doi: 10.1111/j.1365-2044.2010.06511.x.
[31] Critchley LAH, Critchley JAJH. A meta-analysis of studies using bias and precision statistics to compare cardiac output

measurements techniques. J Clin Monit. 1999; (15): 85-91.
[32] van Campen CMC, Visser FC. 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. J Thrombo Circ. 2018; 2018(2): 1-8. doi: 10.29011/.JTC-107.000007.
[33] Voice RA, Lurie KG, Sakaguchi S, Rector TS, Benditt DG. Comparison of tilt angles and provocative agents (edrophonium and isoproterenol) to improve head-upright tilt-table testing. Am J Cardiol. 1998; 81(3): 346-351.
[34] Benditt DG, Ferguson DW, Grubb BP, Kapoor WN, Kugler J, Lerman BB, Maloney JD, Raviele A, Ross B, Sutton R, Wolk MJ, Wood DL. Tilt table testing for assessing syncope. American College of Cardiology. J Am Coll Cardiol. 1996; 28(1): 263-275.
[35] Forleo C, Guida P, Iacoviello M, Resta M, Monitillo F, Sorrentino S, Favale S. Head-up tilt testing for diagnosing vasovagal syncope: a meta-analysis. Int J Cardiol. 2013; 168(1): 27-35. doi: 10.1016/j.ijcard.2012.09.023.
[36] Freeman R, Wieling W, Axelrod FB, Benditt DG, Benarroch E, Biaggioni I, Cheshire WP, Chelimsky T, Cortelli P, Gibbons CH, Goldstein DS, Hainsworth R, Hilz MJ, Jacob G, Kaufmann H, Jordan J, Lipsitz LA, Levine BD, Low PA, Mathias C, Raj SR, Robertson D, Sandroni P, Schatz IJ, Schondorf R, Stewart JM, van Dijk JG. Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. AutonNeurosci. 2011; 161(1-2): 46-48. doi: S1566-0702(11)00035-X.
[37] van Campen CMC, Visser FC. Validation of Stroke Volume Measured with Suprasternal Aortic Doppler Imaging: Comparison to Transthoracic Stroke Volume Measurements. J Thrombo Circ JTC. 2018; 106(2): 1-5. doi: 10.29011/JTC-106.000006.
[38] van Campen CM, Visser FC, de Cock CC, Vos HS, Kamp O, Visser CA. Comparison of the haemodynamics of different pacing sites in patients undergoing resynchronisation treatment: need for individualisation of lead localisation. Heart. 2006; 92(12): 1795-1800. doi: 10.1136/hrt.2004.050435.
[39] Kusumoto F, Venet T, Schiller NB, Sebastian A, Foster E. Measurement of aortic blood flow by Doppler echocardiography: temporal, technician, and reader variability in normal subjects and the application of generalizability theory in clinical research. J Am Soc Echocardiogr. 1995; 8(5 Pt1): 647-653.
[40] Leard Statistics. Multiple regression using SPSS Statistics, Statistical tutorials and software guides, 2015.
[41] Truijen J, Westerhof BE, Kim YS, Stok WJ, de Mol BA, Preckel B, Hollmann MW, van Lieshout JJ. The effect of haemodynamic and peripheral vascular variability on cardiac output monitoring: thermodilution and non-invasive pulse contour cardiac output during cardiothoracic surgery. Anaesthesia. 2018; 73(12): 1489-1499. doi: 10.1111/anae.14380.
[42] van Geldorp IE, Delhaas T, Hermans B, Vernooy K, Broers B, Klimusina J, Regoli F, Faletra FF, Moccetti T, Gerritse B, Cornelussen R, Settels JJ, Crijns HJ, Auricchio A, Prinzen FW. Comparison of a non-invasive arterial pulse contour technique and echo Doppler aorta velocity-time integral on stroke volume changes in optimization of cardiac resynchronization therapy. Europace. 2011; 13(1): 87-95. doi: 10.1093/europace/euq348.
[43] Taton O, Fagnoul D, De Backer D, Vincent JL. Evaluation of cardiac output in intensive care using a non-invasive arterial pulse contour technique (Nexfin((R))) compared with echocardiography. Anaesthesia. 2013; 68(9): 917-923. doi: 10.1111/anae.12341.
[44] Maass SW, Roekaerts PM, Lance MD. Cardiac output measurement by bioimpedance and noninvasive pulse contour analysis compared with the continuous pulmonary artery thermodilution technique. J Cardiothorac Vasc Anesth. 2014; 28(3): 534-539. doi: 10.1053/j.jvca.2014.01.007.
[45] Hurwitz BE, Coryell VT, Parker M, Martin P, Laperriere A, Klimas NG, Sfakianakis GN, Bilsker MS. Chronic fatigue syndrome: illness severity, sedentary lifestyle, blood volume and evidence of diminished cardiac function. Clin Sci (Lond). 2010; 118(2): 125-135.
[46] van Campen CMC, Rowe PC, Visser FC. Blood Volume Status in ME/CFS Correlates With the Presence or Absence of Orthostatic Symptoms: Preliminary Results. Front Pediatr. 2018; 6: 352. doi: 10.3389/fped.2018.00352.
[47] Siebenmann C, Rasmussen P, Sorensen H, Zaar M, Hvidtfeldt M, Pichon A, Secher NH, Lundby C. Cardiac output during exercise: a comparison of four methods. Scand J Med Sci Sports. 2015; 25(1): e20-27. doi: 10.1111/sms.12201.
[48] Zhang Y, Wang Y, Shi J, Hua Z, Xu J. Cardiac output measurements via echocardiography versus thermodilution: A systematic review and meta-analysis. PLoS One. 2019; 14(10): e0222105. doi: 10.1371/journal.pone.0222105.
[49] Zhang J, Critchley LA, Lee DC, Khaw KS, Lee SW. The effect of head up tilting on bioreactance cardiac output and stroke volume readings using suprasternal transcutaneous Doppler as a control in healthy young adults. J Clin Monit Comput. 2016; 30(5): 519-526. doi: 10.1007/s10877-016-9835-7.
[50] Arbeille P. Doppler sensors and harnesses for cardiac and peripheral arterial flow monitoring. Ultrasound Med Biol. 1997; 23(3): 415-423. doi: 10.1016/s0301-5629(96)00225-6.
[51] Elstad M, Walloe L. Heart rate variability and stroke volume variability to detect central hypovolemia during spontaneous breathing and supported ventilation in young, healthy volunteers. Physiol Meas. 2015; 36(4): 671-681. doi: 10.1088/0967-3334/36/4/671.