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Intermittent calf compression reverses lower limb pooling and improves cardiovascular control during passive orthostasis

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ABSTRACT

When upright, venous pooling and capillary filtration reduce the effective circulating volume and are key contributors to susceptibility to syncope (fainting). Recurrent syncope has a devastating impact on quality of life. Static calf compression garments are frequently prescribed for patients with syncope, but have questionable efficacy. Intermittent calf compression, which mimics the skeletal muscle pump to minimize pooling and filtration, is a potential alternative that holds promise for the management of syncope. We aimed to evaluate use of intermittent calf compression compared to commonly prescribed compression stockings, and determine the optimal intermittent calf compression paradigm, for improvement of orthostatic fluid shifts and cardiovascular control.

We evaluated heart rate, blood pressure, stroke volume, cardiac output and peripheral resistance (finger plethysmography with Modelflow™) and calf pooling and filtration (calf circumference; strain gauge plethysmography) during a series of 10-min head-upright tilts. We first compared (protocol one) low (ICLF; 4 s on, 11 s off) and high (ICHF; 4 s on, 6 s off) frequency 0–100 mm Hg intermittent calf compression with static elastic and inelastic compression stockings and a placebo condition (n = 19, 5 males, aged 23.5 ± 0.1 years). We then compared (protocol two) ICLF applied at 0–40 mm Hg, 0–60 mm Hg, 0–80 mm Hg and 0–100 mm Hg as well as a placebo condition (n = 15, 5 males, aged 22.7 ± 0.5 years). The intervention order was randomized.

In protocol one, all compression conditions significantly reduced calf circumference ($p < 0.001$) compared to placebo after 10-min upright; however, this reduction was greater in ICLF (−0.88 ± 0.18%) and ICHF (−1.14 ± 0.21%) conditions than both elastic (+0.49 ± 0.17%) and inelastic (−0.01 ± 0.19%) compression ($p < 0.001$). ICLF and ICHF, but not elastic or inelastic compression, were associated with improved stroke volume ($p \leq 0.001$), allowing cardiac output to be maintained at a reduced heart rate ($p < 0.001$) without increases in vascular resistance responses, increasing hemodynamic reserve. ICHF showed no significant benefit over ICLF, evidenced by the lack of significant difference between ICLF and ICHF in any parameter measured. In protocol two, 0–60 mm Hg ICLF was considered the optimal intermittent compression because it was the lowest pressure that abolished the increase in calf circumference during orthostasis, while improving SV ($p = 0.002$), and reducing HR ($p < 0.001$) throughout tilt.

Intermittent calf compression from 0 to 60 mm Hg ICLF is the optimal intermittent compression paradigm to ameliorate orthostatic fluid shifts and improve hemodynamic control. Commonly prescribed static calf compression garments do not improve orthostatic cardiovascular responses.

1. Introduction

Syncope, or fainting, is defined as a loss of consciousness and postural tone due to transient cerebral hypoperfusion, with rapid onset, short duration and spontaneous recovery (Stewart, 2013). Typically triggered by an upright posture, syncope is a heterogeneous condition, caused by a reduction in peripheral resistance, cardiac output, or a combination of the two, resulting in global cerebral hypoperfusion (Task Force for the Diagnosis and Management of Syncope, D. in collaboration et al., 2009).

Prevalence rates for syncope vary widely in the literature (17%–39%) (Colman et al., 2004). In a survey of 2011 young adults,

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598 (30%) had experienced at least one episode of syncope in their lifetime, with 182 (31%) of those individuals experiencing recurrent episodes (Lamb et al., 1960). The distribution of syncope is bimodal, with a high prevalence in young children and older adults, accounting for 1–3% of emergency room visits and up to 6% of hospitalizations, creating a significant healthcare burden (Grossman et al., 2014). Recurrent syncope has a devastating impact on quality of life; resulting falls cause injury, and recurrent episodes lead to decreased school attendance or community engagement, job loss, and loss of independence (Rose et al., 2000).

The management of recurrent syncope is challenging. Patient counselling and lifestyle advice are recommended as a first line approach, including patient education, avoidance of known triggers, increased fluid intake (often with salt supplementation) and physical countermaneuvers (Shen et al., 2017). While these recommendations certainly improve outcomes in syncope management, they are not usually sufficient for management of frequent episodes in more severely affected patients (Romme et al., 2010). Furthermore, although physical countermaneuvers are effective for the maintenance of orthostatic blood pressure, (Wieling et al., 2015) some individuals with orthostatic disorders have difficulty performing them safely (e.g. frail older adults or those with gait/balance disorders) and they are not applicable to those with lower limb paralysis (e.g. individuals with spinal cord injuries) who are particularly prone to orthostatic hypotension. Cardiac pacing for syncope with cardioinhibition, and pharmacologic therapies aimed at increasing peripheral vasoconstriction (Midodrine) and expanding plasma volume (Fludrocortisone) are additional approaches used to manage frequent episodes, however the utility and efficacy of these has been questioned (Maggi and Brignole, 2007; Salim and Di Sessa, 2005; El-Bedawi et al., 1994; Connolly et al., 2003).

Orthostatic fluid shifts are a key factor contributing to susceptibility to syncope. Upon assuming an upright posture, there is an immediate gravitational shift of blood towards the legs, which accumulates in the compliant capacitance veins of the legs and splanchnic circulation (Stewart, 2013; White and Tsikouris, 2000). This venous pooling causes a rapid drop in the effective circulating blood volume, thus reducing venous return, blood pressure and cerebral blood flow (White and Tsikouris, 2000; Ricci et al., 2015). In turn, venous pooling promotes enhanced capillary filtration that exacerbates the fluid accumulation over time (Brown and Hainsworth, 1999). In the legs, this pooling and filtration is substantial, with 500 mL of blood accumulating in just 10-min of 60° head-up tilting (Brown and Hainsworth, 1999). Accordingly, preventing or reducing orthostatic fluid shifts represents a therapeutic target for improving the management of orthostatic intolerance.

In an effort to reduce orthostatic fluid shifts with an external counter-pressure, static compression garments are often prescribed to patients with recurrent syncope and, according to current guidelines, are a class IIa recommendation for the management of orthostatic syncope (Shen et al., 2017). Because orthostatic fluid shifts redistribute hydrostatic pressures throughout the body, with highest pressures at the ankles, graduated compression garments that apply greater counter-pressures at the extremities are thought to be more effective (Hainsworth and Claydon, 2010).

Compression garments that apply counter-pressure to the whole leg and/or abdominal region have been shown to be efficacious at improving cardiovascular control during short term orthostasis (Stenger et al., 2010; Stenger et al., 2013; Platts et al., 2009; Podoleanu et al., 2006; Smit et al., 2004; Denq et al., 1997), with the caveat that compression of the thighs may actually promote venous pooling while sitting, due to a reversal of the pressure gradient (Walker and Lamont, 2008). Despite the promise offered by these garments, the reported discomfort and difficulty applying and removing them represent significant barriers to their therapeutic use, and as such they are associated with poor patient compliance (Benkö et al., 2001; Raju et al., 2007). Although patient adherence to compression interventions is greater with below knee calf compression stockings (Wade et al., 2017), their efficacy in mitigating orthostatic intolerance has been questioned (Protheroe et al., 2011).

Intermittent calf compression, which more accurately mimics the actions of the skeletal muscle pump to minimize venous pooling and capillary filtration, is a potential alternative that holds promise for the management of syncope (Killewich et al., 1995; Delis et al., 2000a). When delivered at high enough pressures and with rapid inflation rates, intermittent compression can close the deep venous vasculature and pump blood up past one-way valves, increasing venous return (Delis et al., 2000a; Groothuis et al., 2008). Further, prior studies have shown that intermittent calf compression can reduce lower limb pooling and increase venous return while supine (Labropoulos et al., 2000). We sought to evaluate use of intermittent compression paradigms for the prevention of orthostatic venous pooling and capillary filtration compared to commonly prescribed static inelastic and elastic compression stockings, while also assessing the cardiovascular impact during orthostasis.

This study encompassed two experimental protocols. In protocol one, we aimed to evaluate the effect of intermittent calf compression compared to standard, commonly prescribed static elastic and inelastic compression stockings, as well as a placebo condition, on venous pooling and cardiovascular control during a 10-min orthostatic challenge. We hypothesized that intermittent calf compression would reduce orthostatic fluid shifts more effectively than static compression stockings and placebo conditions, and thus would improve cardiovascular responses during orthostatic stress.

In an effort to optimize the intermittent compression paradigm, in protocol two of this study we aimed to determine the optimal calf intermittent compression pressure for the improvement of orthostatic fluid shifts and hemodynamic control during orthostasis.

2. Methods

2.1. Ethics statement

Ethical approval was obtained from the Simon Fraser University Research Ethics Board and experiments were conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent.

2.2. Study design

Nineteen healthy young adults (5 males; aged 23.7 ± 0.8 years; height 171 ± 2 cm; weight 69.3 ± 2.2 kg; skinfold thickness 13.1 ± 0.9 mm; calf circumference 37.9 ± 0.5 cm; muscle cross sectional area (MCSA) 85.3 ± 3.3 cm^2) participated in the first phase of this study (protocol one), and 15 healthy young adults (5 males; aged 22.7 ± 0.5 years; height 172 ± 2 cm; weight 73.3 ± 2.8 kg; skinfold thickness 19.5 ± 1.8 mm; calf circumference 40.1 ± 0.6 cm; MCSA 83.1 ± 4.1 cm^2) participated in the second phase (protocol two). Prior to testing, all participants completed a brief medical history; all were free of cardiovascular and neurological disease. None of the participants were taking medications, with the exception of six females who were using oral contraceptives. Tests were typically conducted in the morning (n = 19) but for scheduling reasons some started late morning (n = 4) and some were conducted later in the day (n = 10). Participants were instructed to eat only a light breakfast on the morning of testing and were asked to refrain from vigorous exercise, alcohol and caffeine consumption for the 12-h preceding testing. We did not control for phase of the menstrual cycle in females because comparisons were made between conditions on each test day and not across test days (and therefore the within-subject phase of the menstrual cycle was controlled). Furthermore, although sex hormones do undoubtedly impact the cardiovascular system, at least in healthy women, there is no net effect of phase of the menstrual cycle on orthostatic tolerance or cardiovascular responses to orthostasis (Claydon et al., 2006). Both

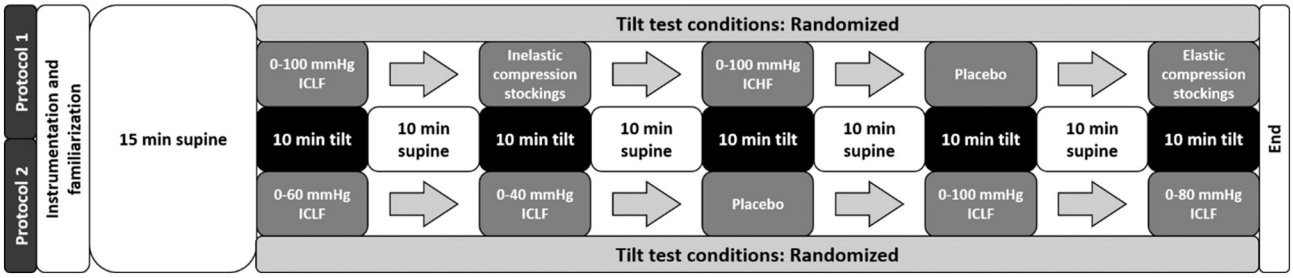

Fig. 1. Methodology employed for the two test protocols. On each test day participants were familiarized with the experimental approach, provided written informed consent, and were instrumented with cardiovascular and plethysmographic monitoring. After a 15-min supine rest period they underwent a series of five 10-min 60° head-upright tilt tests, each with a different compression paradigm applied. A 10-min supine rest period was incorporated between each tilted phase. In protocol one, high and low frequency intermittent compression was compared to elastic and inelastic compression, and a placebo condition with no compression. In protocol two, four different levels of low frequency intermittent compression and a placebo condition were compared. Abbreviations: ICLF, low frequency intermittent compression; ICHF, high frequency intermittent compression.

experiments were conducted in a randomized, placebo-controlled and double-blind fashion.

Prior to testing, anthropometric measures were taken at the calf using a standard tape measure and skinfold calipers (Slim Guide™, Creative Health Products, Plymouth, USA). The maximum calf circumference was determined and marked to fit the participant for strain gauges and to guide the placement of the intermittent compression cuffs. Skinfold measures were similarly taken at the widest level of the calf. MCSA was calculated as (calf circumference [cm]^2/4π)-(calf circumference[cm] × skinfold thickness[cm]/2)-6 (Protheroe et al., 2011; Fuller et al., 1999).

2.3. Experimental protocol

Apart from the calf compression interventions applied, the experimental protocol, as shown in Fig. 1, was identical in both study protocols. Protocols one and two were performed on different days and included different participant pools. While supine on a manual tilt table with a footboard support, participants were instrumented with cardiovascular monitoring equipment and familiarized with the test procedure. Participants rested for 15-min in the supine position to allow any pooled fluid to be reabsorbed and to assess supine cardiovascular parameters. To test the effects of the five compression interventions for each protocol during orthostatic stress the participant then underwent a series of five 60° head-up tilts (~90% of a full vertical displacement (Protheroe et al., 2013)) for 10-min each, while wearing each of the five compression interventions, in a randomized fashion. A 10-min supine "washout" period was introduced between each tilt to allow the calf intervention to be changed, orthostatic fluid shifts to resolve, and for cardiovascular parameters to return to baseline values.

In protocol one, high (six 4 s pulses/min with 6 s between pulses; ICHF) and low (four 4 s pulses/min with 11 s between pulses; ICLF) frequency intermittent calf compression paradigms using a 100 mm Hg "on" pressure (chosen because it was in excess of the orthostatic venous pressure at the ankle (Groothuis et al., 2008)) and 0 mm Hg "off" pressure (chosen to permit venous filling between pulses and prime the venous pump prior to each compression) (0–100 mm Hg), were evaluated in comparison to standard of care approaches including static inelastic compression stockings (27 mm Hg – matched to the mean pressure of the ICLF condition), class II lower leg elastic compression stockings (Knee-high Graded Support Therapy Socks, Sigvaris Inc., Peachtree City, USA; reported to apply 20 mm Hg at the ankle graduated to 15 mm Hg at the knee [www.sigvarisusa.com]) and a placebo condition in which ankle socks were worn that terminated at the malleolus and did not compress the calf. For intermittent compression conditions we chose compression frequencies in excess of 3–4 pulses per minute, because these are shown to increase venous velocity. (Killewich et al., 1995; Delis et al., 2000b) Short duration pulses and low "off" pressures are necessary to prevent distal edema. (Lurie et al., 2003; Rucinkski et al., 1991)

In protocol 2, the optimal paradigm based on the results from protocol one, the ICLF condition, was used. This paradigm was chosen because intermittent compression was superior to static elastic and inelastic compression, and ICHF showed no significant benefit over ICLF. As 0–100 mm Hg ICLF reduced calf circumference below supine values, we chose to evaluate whether lower compression pressures would be sufficient to prevent increases in calf circumference (and therefore pooling and filtration). A range of lower inflation ICLF pressures, 0–40 mm Hg, 0–60 mm Hg, 0–80 mm Hg, were compared to 0–100 mm Hg ICLF as well as a placebo condition in which the compression cuffs were worn, but no compression was applied.

In both protocols, the compression garments were applied out of sight of the primary investigator, and an opaque chamber was placed over the participant's legs so that compression garments could not be seen. Although participants were aware of the different look and feel of the garments in the two protocols, they were not told which garment they were wearing, or whether it was expected to improve, worsen have no effect on their responses to the test.

2.4. Cardiovascular monitoring

Throughout testing cardiovascular parameters were monitored continuously and non-invasively using the Finometer Pro™ device (Finometer, Finapres Medical Systems, Amsterdam, The Netherlands). This device monitors beat-to-beat systolic (SAP), diastolic (DAP) and mean (MAP) arterial pressure using photoplethysmography to reconstruct the brachial arterial pressure waveform from the digital arteries in the middle finger. This device also uses the Modelflow™ technique to enable beat-to-beat estimation of stroke volume (SV) (Wesseling et al., 1993; Harms et al., 1999; Jellema et al., 1996). Heart rate (HR) and rhythm were monitored using a lead II electrocardiogram (ECG; Finapres ECG Module, Finapres Medical Systems, Amsterdam, The Netherlands). Cardiac output (CO) was calculated by multiplying HR and SV, while total peripheral resistance (TPR) was calculated using the ratio of MAP and CO. For parameters determined by Modelflow, absolute measurements when reported on an individual basis can be subject to inaccuracy, although changes in these variables in response to intervention have reasonable agreement with gold standard measures. (Pitt et al., 2004; Manen et al., 2015) Accordingly, we report these responses as both averages across conditions, and relative changes. In addition, brachial blood flow velocity was measured continuously and non-invasively using an 8 MHz ultrasound probe, held in place with an adjustable clamp so that the angle of insonation remained constant, with the arm supported at heart level (Doppler Box, Compumedics Germany GmbH, The DWL Doppler Company, Singen, Germany). (Protheroe et al., 2013) Using this technique blood velocity is

proportional to flow, assuming the diameter of the brachial artery is constant and alterations in vascular tone occur in downstream arterioles (Claydon and Hainsworth, 2005; Tschakovsky et al., 1995). Forearm vascular resistance (FVR) was calculated as the ratio of MAP and brachial blood flow velocity. All cardiovascular recordings were sampled at 1 KHz using an analog-to-digital converter (Powerlab 16/30, AD Instruments, Colorado Springs, CO, United States) and stored for offline analysis.

2.5. Lower limb plethysmography

Estimations of limb volume changes (expressed as percentage changes from the supine volume) due to venous pooling and capillary filtration combined were performed using strain-gauge plethysmography. Strain gauges were calibrated prior to each protocol, and their size selected according to the participants' leg circumference. Two strain gauges were placed on each leg, one at the level of maximum calf circumference (approximately at the center of the location of the compression intervention when applied), while the second was placed at the gaiter (mid-point between the medial malleolus and the level of maximum calf circumference). This second strain gauge was used as an indirect means to monitor for edema distal to the site of compression. In preliminary experiments we confirmed that the compression approaches employed did not interfere with the strain gauge accuracy. For intermittent compression, we analysed strain gauge data during the "off" phases.

2.6. Compression system

A custom-made compression system (Fig. 2) with rapid inflation and deflation rates (< 1 s) was used to deliver intermittent compression at the aforementioned compression pressures. For protocol two, a pressure transducer (Reusable BP Transducer MLT0380/D, ADInstruments, Colorado Springs, CO, United States) monitored compression pressures within the inflatable cuffs during testing and confirmed successful application of our target pressures (placebo: 0 ± 0 mm Hg; 0–40 mm Hg: 42.3 ± 0.8 mm Hg; 0–60 mm Hg: 61.5 ± 0.9 mm Hg; 0–80 mm Hg: 82.4 ± 0.8 mm Hg; 0–100 mm Hg: 97.3 ± 1.2 mm Hg).

2.7. Data and statistical analyses

All analyses were conducted blinded to the test condition. Cardiovascular data are presented as the averages of the final 30-s of every 2-min period for the duration of each 10-min tilt. Calf circumference data derived from strain gauges are presented as 10-s averages, during the compression-free (off) phase during intermittent compression paradigms, or the equivalent time point during placebo and elastic or inelastic compression, every 2-min throughout each tilt and are reported as a percentage change from supine. Strain gauge data from each region were averaged for the right and left legs. Supine values (time point zero) for both cardiovascular and strain gauge data were calculated as an average over the final 30-s of the last minute of the supine period. FVR data are reported only as the change from baseline because the absolute values are influenced by the angle of insonation of the brachial ultrasound probe, which was not standardized between participants. Note, however, that the angle of insonation was held constant within participants, so examination of the changes in FVR throughout the protocol would be valid.

Statistical analyses and data visualisation were performed using SigmaPlot Version 14 (Systat Software Inc., San Jose, CA). Data were tested for normality using the Shapiro-Wilk test and are reported as means ± SEM. Differences were determined to be statistically significant where $p < 0.05$. Comparisons between tilt conditions and over time were conducted using two-way repeated measures ANOVA with a Holm-Sidak post-hoc test. Correlations between changes in venous pooling and filtration during orthostasis with baseline calf circumference or MCSA were evaluated using the Spearman correlation coefficient.

Comparisons between each baseline period for each protocol were conducted for all parameters (one-way repeated measured ANOVA with a Holm-Sidak post-hoc test). There were no significant differences between baseline measures for any parameter (see online data supplement), so a combined average within-protocol baseline was calculated and used for representation in figures and tables to aid visualisation. Note that for statistical comparisons or determination of changes relative to baseline, the relevant baseline condition for *each* paradigm was used, not the combined average within-protocol baseline.

3. Results

3.1. Protocol one

Of the 19 participants tested, two experienced presyncope consistent with a vasovagal response during the protocol, warranting early termination of the test prior to the completion of all phases. Due to technical difficulties, strain gauge data were not obtained in one additional participant. Therefore, data from 17 individuals were included in cardiovascular analyses, and 16 individuals were included in strain gauge analyses.

3.1.1. Venous pooling and filtration

Changes in calf circumference over the course of the tilt and after 10-min upright are shown in Fig. 3. In the placebo condition, after 10-min of orthostatic stress, circumference increased by +1.57 ± 0.17%, relative to supine. All calf compression interventions reduced pooling and filtration (calf circumference) during tilt compared to placebo ($p < 0.001$). Relative to supine, with elastic compression, calf circumference increased by +0.49 ± 0.17% after 10-min upright, while

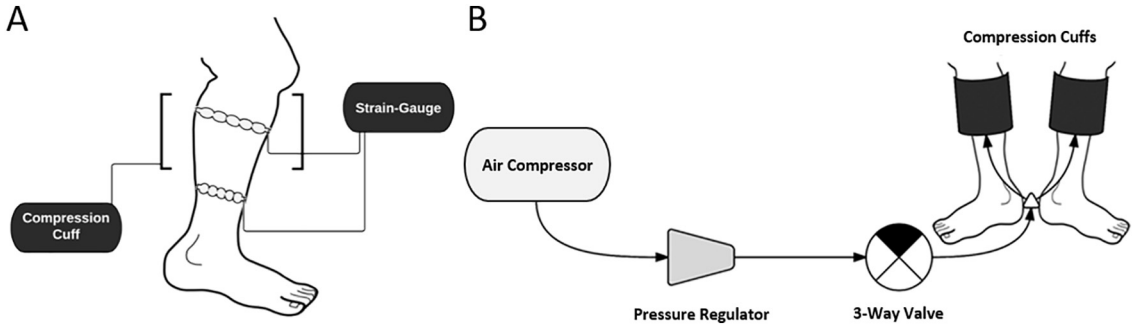

Fig. 2. Strain gauges and custom compression system. **A**. Participants were instrumented with two strain gauges on each leg, one at the site of maximum calf circumference, and one at the level of the gaiter above the ankle. **B**. The compression system incorporated an air compressor, a pressure regulator, a valve-switch unit and two compression cuffs, shown above from left to right.

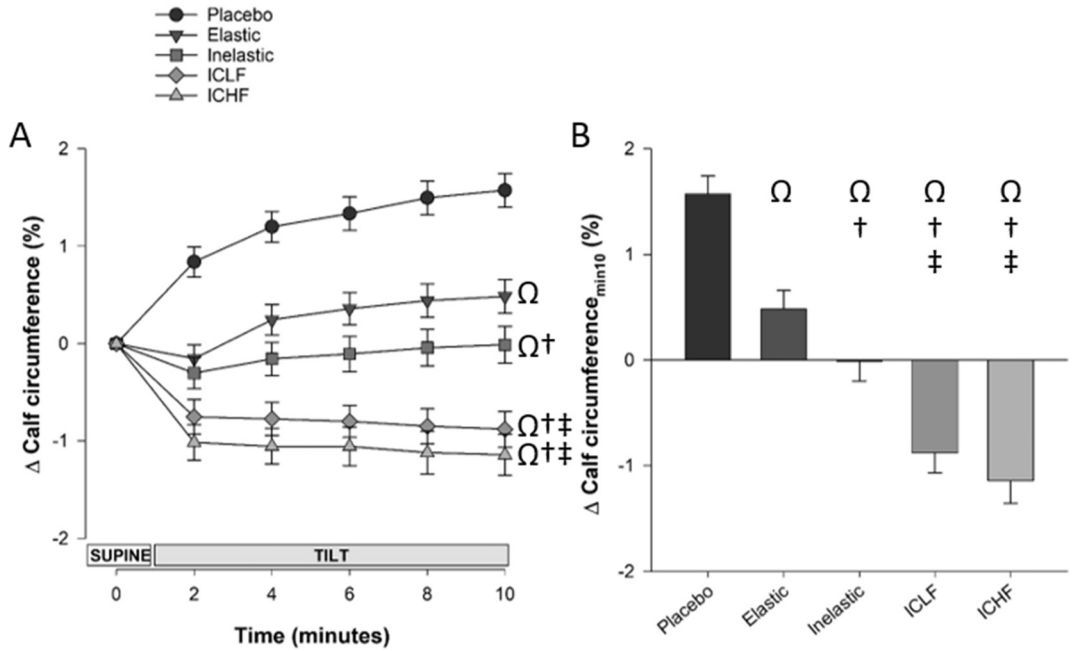

Fig. 3. Venous pooling and capillary filtration during protocol one. **A**. The time course of pooling and filtration in the calf. Symbols (mean ± SEM) reflect averaged data from the right and left calves combined, over the last 10-s of every two-minute interval and are reported as a percentage change from supine values. Main effects of condition throughout tilt are shown. **B**. Cumulative percentage volume change in the calf from supine after a 10-min tilt. Differences between conditions at the 10-min time point are shown. Symbols: **Ω** Significantly different from placebo; † Significantly different from elastic compression condition; ‡ Significantly different from inelastic compression condition. Abbreviations: ICLF, low frequency intermittent compression; ICHF, high frequency intermittent compression.

inelastic compression prevented calf pooling and filtration (−0.01 ± 0.19%). In contrast, both ICLF (−0.88 ± 0.18%) and ICHF (−1.14 ± 0.21%) not only prevented pooling and filtration, but actually reduced calf circumference relative to supine values. Overall, and at the 10-min time point, ICLF and ICHF paradigms were more effective at reducing orthostatic fluid shifts than both elastic and inelastic static compression stockings ($p < 0.001$). Comparisons of venous pooling (calf circumference) between ICLF and ICHF conditions were not significantly different, suggesting no additional benefit of ICHF compared to ICLF in reducing orthostatic fluid shifts. For all conditions, there were no significant correlations between measures of pooling and filtration (the change in calf circumference) and the supine calf circumference ($r = 0.018–0.486$; $p = 0.06–0.95$) or MCSA ($r = 0.007–0.400$; $p = 0.125–0.980$).

At the level of the gaiter, elastic compression and both intermittent compression paradigms reduced distal edema during tilt compared to placebo and inelastic compression ($p < 0.001$). Although inelastic compression prevented pooling at the level of the calf, it did not reduce distal edema compared to placebo ($p = 0.964$). Edema in the gaiter region was not significantly different between ICLF, ICHF and elastic compression ($p = 0.404–0.673$).

3.1.2. Cardiovascular responses

Supine cardiovascular parameters were similar between compression conditions (Table 1). After 10-min in the upright posture, SAP (Table 1) significantly decreased in the elastic compression ($p < 0.001$) and ICHF ($p = 0.002$) conditions, but did not decrease appreciably with placebo, inelastic compression or ICLF. Throughout tilt, SAP was similar between conditions, but after 10-min SAP was elevated in the ICLF condition compared to elastic compression ($p = 0.003$). After 10-min upright, DAP (Table 1) increased similarly in all conditions ($p < 0.001$), except ICHF ($p = 0.270$). When expressed as a change from supine, the DAP increase during tilting was blunted in the ICHF condition compared to placebo ($p = 0.050$). After 10-min upright, MAP (Table 1) remained similar to supine values across all conditions, and did not vary significantly between conditions.

HR (Fig. 4 and Table 1) increased during tilt across all conditions ($p < 0.001$). Throughout tilt ($p < 0.001$), and after 10-min upright ($p < 0.003$), HR remained significantly lower in both ICLF and ICHF conditions compared to placebo, and both elastic and inelastic compression. The magnitude of the HR increase during tilt was significantly reduced with ICHF, compared to placebo ($p < 0.001$) and inelastic compression ($p = 0.027$). With ICLF, the magnitude of the tilted HR increase tended to be reduced compared to placebo ($p = 0.090$), and after 10-min upright the blunting of the HR response achieved statistical significance ($p = 0.007$).

Across all conditions, SV (Fig. 4 and Table 1) decreased during tilt ($p < 0.001$). However, SV was higher in ICLF and ICHF conditions compared to placebo ($p \leq 0.001$), and elastic compression ($p \leq 0.009$) conditions. Furthermore, the magnitude of the orthostatic reduction in SV was decreased in ICLF and ICHF conditions compared to placebo ($p \leq 0.002$), elastic ($p \leq 0.023$) and inelastic ($p \leq 0.025$) compression stockings.

After 10-min upright, CO (Fig. 4 and Table 1) was reduced in the placebo, elastic and inelastic conditions ($p \leq 0.012$), but not with ICLF and ICHF. The magnitude of the orthostatic CO reduction was significantly reduced with ICLF compared to elastic compression ($p = 0.015$).

After 10-min upright, TPR (Table 1) was increased compared to supine in the placebo, elastic and inelastic compression conditions ($p < 0.001$) but not in ICLF or ICHF conditions.

After 10-min upright, there was a significant increase in FVR with elastic compression ($p = 0.032$), and the response almost achieved statistical significance in the placebo condition ($p = 0.051$) (Table 1). There were no significant differences in the magnitude of the FVR response between conditions.

3.2. Protocol two

Fifteen individuals participated in this experiment. Tilt was terminated prematurely for one individual due to presyncope during the 0–40 mm Hg condition, and one individual requested to stop the test

Table 1
Cardiovascular responses after 10-min of tilting during protocol one. Baseline data reflect the mean supine parameter for all conditions. Data during compression conditions after 10-min of tilt are presented as the mean ± SEM for each condition (10-min) with absolute changes from supine indicated in shaded columns (Δ). Symbols: * Significantly different from baseline; * Comparison to baseline is trending (p = 0.051); **Ω** Significantly different from placebo condition; Significantly different from elastic compression condition † Significantly different from elastic compression condition; ‡ Significantly different from inelastic compression condition. Abbreviations: SAP, systolic arterial pressure; DAP, diastolic arterial pressure; MAP, mean arterial pressure; HR, heart rate; SV, stroke volume; CO, cardiac output; TPR, total peripheral resistance; FVR, forearm vascular resistance; ICLF, low frequency intermittent compression; ICHF, high frequency intermittent compression.

Outcome measure	Baseline (average)	Compression condition (min_{10} values)									
		Placebo		Elastic		Inelastic		ICLF		ICHF	
		10-min	Δ	10-min	Δ	10-min	Δ	10-min	Δ	10-min	Δ
SAP (mmHg)	119.6±1.1	114.7±3.0	-3.7±2.5	111.6±2.9*	-7.4±2.3*	115.6±2.4	-4.4±2.1	118.1±2.5†	-2.0±1.9	112.3±2.2*	-7.0±2.4*
DAP (mmHg)	71.9±0.7	78.3±1.9*	+6.4±1.3*	76.0±2.0*	+5.1±1.4*	76.8±1.4*	+5.6±1.2*	77.6±1.6*	+5.2±1.0*	75.1±1.5	+2.0±1.1**Ω**
MAP (mmHg)	87.8±0.8	90.4±2.2	+3.0±1.6	87.9±2.1	+0.7±1.6	89.8±1.7	+2.2±1.4	91.1±1.8	+2.8±1.3	86.8±1.5	-0.9±1.5
HR (bpm)	65.7±0.8	88.5±2.1*	+22.7±1.6*	86.1±2.3*	+19.1±1.9*	86.1±2.1*	+20.0±1.4*	81.2±2.0***Ω†‡**	+17.0±2.0***Ω**	80.9±2.0***Ω†‡**	+15.3±1.9***Ω‡**
SV (mL)	82.7±1.7	55.7±3.2 *	-25.7±2.4*	56.4±4.3*	-25.5±2.9*	59.4±3.4*	-24.3±1.8*	64.0±3.4***Ω†**	-19.0±1.7***Ω†‡**	64.4±4.2***Ω†**	-19.3±2.7***Ω†‡**
CO ($L.min^{-1}$)	5.41±0.12	4.88±0.23*	-0.38±0.13*	4.82±0.28*	-0.67±0.18*	5.06±0.25*	-0.43±0.15*	5.18±0.24	-0.14±0.13†	5.14±0.32	-0.36±0.19*
TPR ($mmHg.min.L^{-1}$)	17.1±4.4	19.1±0.8*	+1.8±0.29*	18.9±0.9*	+1.9±0.9*	18.4±0.9*	+1.8±0.2*	18.2±0.7	+1.0±0.4	18.5±1.3	+1.0±0.5
FVR ($mmHg.sec.cm^{-1}$)	-	-	+3.8±1.5*	-	+4.1±2.2*	-	+1.3±1.5	-	+1.6±1.9	-	+3.0±2.1

due to postural discomfort (but not presyncope) during the 0–100 mm Hg condition. Otherwise, all tilt conditions were completed by all participants. Due to technical difficulties strain gauge data was not obtained in two participants. Therefore, data from 13 participants were included for strain gauge analyses.

Given that in protocol one intermittent compression was superior to static compression, and ICHF showed no significant benefit over ICLF (with no significant differences in any parameter between ICHF and ICLF) we chose to proceed with ICLF paradigms in protocol two.

3.2.1. Venous pooling and filtration

Changes in calf circumference over the course of the tilt and after 10-min upright are shown in Fig. 5. In the placebo condition, after 10-min of orthostatic stress, calf circumference increased by +1.22 ± 0.10%. All calf compression interventions reduced pooling and filtration (calf circumference) during tilt compared to placebo ($p < 0.001$) in a dose-dependent manner. There was no difference between the 0–80 and 0–100 mm Hg conditions ($p = 0.600$).

At the level of the gaiter, all ICLF conditions reduced distal edema during tilt compared to placebo ($p < 0.001$). With 0–40 mm Hg ICLF gaiter circumference was not different from supine after 10-min of tilt (+0.16 ± 0.10%; $p = 0.093$), while gaiter circumference was reduced compared to supine in the 0–60 mm Hg (−0.15 ± 0.09%; $p = 0.031$), 0–80 mm Hg (−0.41 ± 0.12%; $p \leq 0.001$) and 0–100 mm Hg (−0.47 ± 0.07%; $p \leq 0.001$) conditions in a dose-dependent manner. Both 0–80 mm Hg ($p = 0.040$) and 0–100 mm Hg ($p = 0.033$) ICLF reduced distal edema compared to the 0–60 mm Hg condition. There was no difference between the 0–80 and 0–100 mm Hg conditions ($p = 0.814$).

3.2.2. Cardiovascular responses

Supine cardiovascular parameters were similar between compression conditions (Table 2). After 10-min in the upright posture, SAP (Table 2) was reduced relative to supine in the placebo ($p = 0.005$) and 0–40 mm Hg ($p = 0.027$) ICLF conditions, but did not decrease appreciably in the higher pressure conditions. Throughout tilt ($p = 0.002$), and after 10-min ($p = 0.016$), SAP values were higher with 0–100 mm Hg ICLF condition compared to 0–40 mm Hg ICLF; however, when data were reported as changes from supine, there were no significant differences between conditions. After 10-min upright, DAP (Table 2) increased similarly relative to supine values in all conditions ($p \leq 0.004$). After 10-min upright, MAP (Table 2) was not different from supine across all conditions. Throughout tilt, MAP was higher in the 0–100 mm Hg ICLF condition compared to 0–40 mm Hg ICLF ($p = 0.012$); however, this was not significant at the 10-min time point. When data were reported as changes from supine, MAP was not different between conditions throughout tilt, or after 10-min upright.

HR (Fig. 6 and Table 2) increased during tilt compared to supine, across all conditions ($p < 0.001$). Throughout tilt ($p < 0.001$), and after 10-min upright ($p \leq 0.001$), HR remained lower in the 0–60 mm Hg, 0–80 mm Hg and 0–100 mm Hg ICLF conditions compared to both placebo and 0–40 mm Hg ICLF. The magnitude of the HR increase over the tilt duration ($p \leq 0.011$) and after 10-min ($p \leq 0.003$) was significantly reduced in the 0–60 mm Hg, 0–80 mm Hg and 0–100 mm Hg ICLF conditions, compared to both placebo and 0–40 mm Hg ICLF conditions. HR responses were not different between placebo and 0–40 mm Hg conditions, and were not blunted further by the 0–80 mm Hg and 0–100 mm Hg ICLF compared to 0–60 mm Hg ICLF.

Across all conditions, SV (Fig. 6 and Table 2) decreased during tilt ($p < 0.001$). However, SV was higher in the 0–60 mm Hg, 0–80 mm Hg, and 0–100 mm Hg ICLF conditions during tilt ($p \leq 0.011$) and after 10-min upright ($p < 0.010$), compared to both placebo and 0–40 mm Hg ICLF. During tilt ($p \leq 0.007$), and after 10-min ($p \leq 0.031$), the magnitude of the orthostatic SV reduction was significantly decreased in the 0–80 mm Hg and 0–100 mm Hg ICLF conditions compared to both placebo and 0–40 mm Hg ICLF. SV responses were not different between placebo and 0–40 mm Hg conditions, and were not increased in the 0–80 mm Hg and 0–100 mm Hg ICLF conditions relative to 0–60 mm Hg ICLF.

After 10-min upright, CO (Fig. 6 and Table 2) was reduced in the 0–60 mm Hg ICLF condition ($p = 0.016$), but did not fall significantly in the remaining conditions. CO responses were not different between conditions, both throughout tilt and after 10-min.

TPR responses did not change with tilting, and were not different between conditions (Table 2).

For all conditions, FVR increased significantly with tilting ($p < 0.05$) (Table 2). FVR responses were not different between

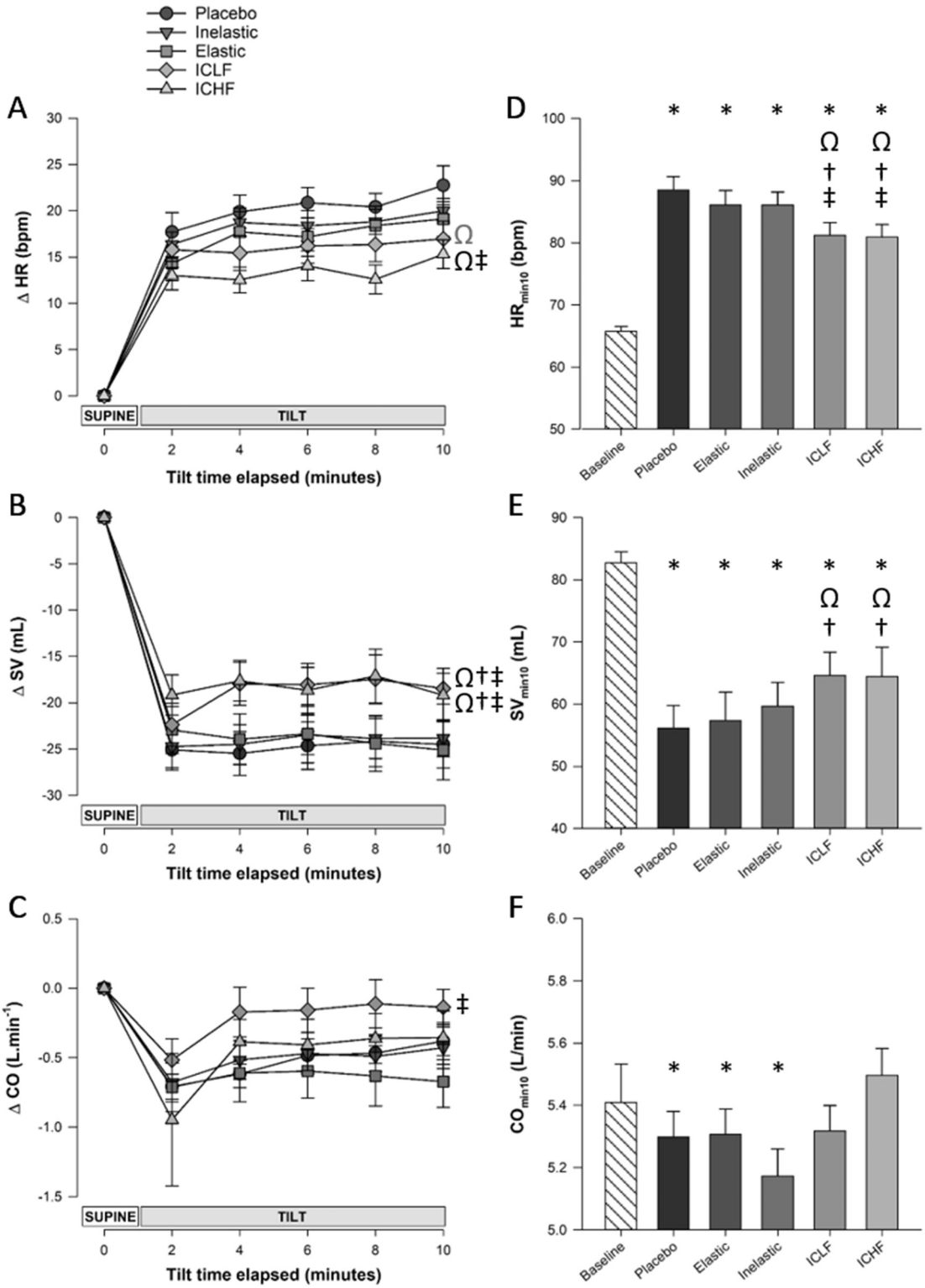

Fig. 4. Cardiovascular responses to tilt during protocol one. **A–C.** Time course of HR, SV and CO responses throughout tilt. Symbols (mean ± SEM) reflect averaged data over the last 30-s of every two-minute interval and are reported as absolute change from supine. Main effects of condition throughout tilt are indicated. **D–F.** HR, SV and CO values, while supine and after 10-min of tilting. Differences between conditions and from baseline at the 10-min time point are shown. Baseline data reflect the mean supine parameter averaged for all conditions. However, for comparisons between 10-min and baseline values, each condition has been compared to its own baseline. Symbols: Ω Comparison to placebo is trending ($p = 0.090$); **Ω** Significantly different from placebo; † Significantly different from elastic compression condition; ‡ Significantly different from inelastic compression condition; * Significantly different from baseline. Abbreviations: CO, cardiac output; ICLF, low frequency intermittent compression; ICHF, high frequency intermittent compression; HR, heart rate; SV, stroke volume.

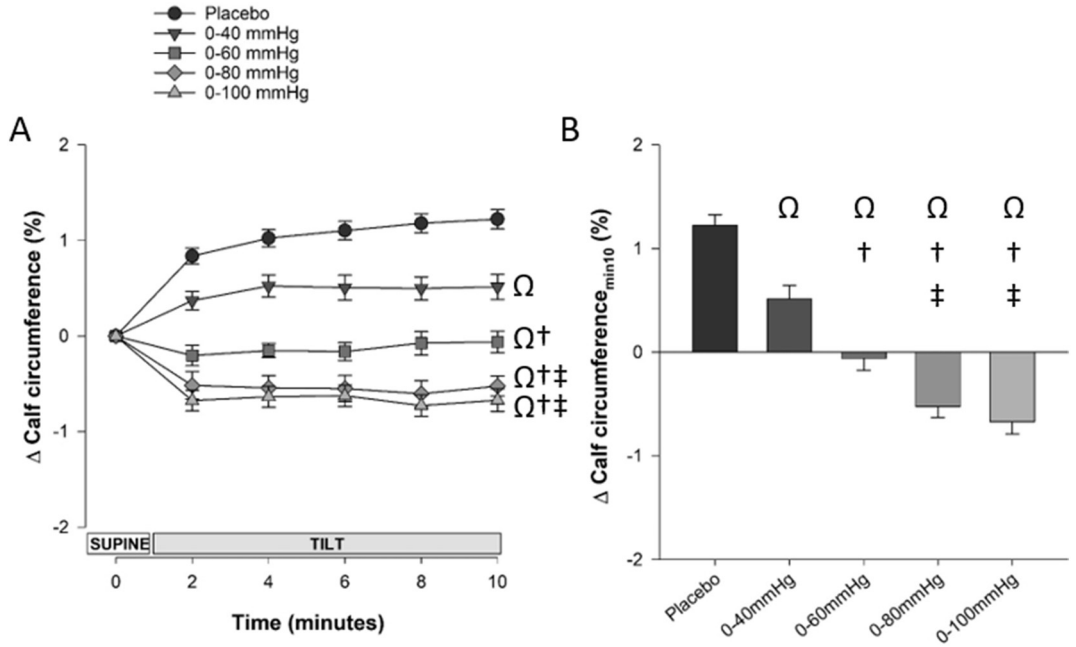

Fig. 5. Venous pooling responses during protocol two. **A**. The time course of pooling and filtration in the calf. Symbols (mean ± SEM) reflect averaged data from the right and left calves combined, over the last 10-s of every two-minute interval and are reported as the percentage change from supine values. Main effects of condition throughout tilt are shown. **B**. Cumulative percentage volume change in the calf from supine after a 10-min tilt. Differences between conditions at the 10-min time point are shown. Symbols: **Ω** Significantly different from placebo; † Significantly different from 0 to 40 mm Hg condition; ‡ Significantly different from 0 to 60 mm Hg condition.

conditions.

4. Discussion

In this study we firstly demonstrate that 0–100 mm Hg intermittent calf compression is superior to placebo, and static elastic and inelastic compression stockings commonly recommended for individuals with orthostatic intolerance. During passive orthostasis, this effect was noted both in the ability to prevent, or even reverse, venous pooling and capillary filtration, as well as in key hemodynamic parameters, with improved orthostatic SV allowing CO to be maintained with a reduced HR response. In these healthy controls, use of the intermittent compression paradigm was associated with smaller vascular resistance responses. This might reflect that either the baroreflex-mediated stimulus to vasoconstrict was smaller in the face of reduced orthostatic fluid shifts and improved blood pressure control, or that the protection of cardiac output with intermittent compression will inherently reduce resistance, according to Ohm's law, even if blood pressure does not change. This is important because a key feature in patients with syncope is a failure to constrict (Brown and Hainsworth, 2000; Bush et al., 2000) - particularly in young women - intermittent compression may be particularly useful in these individuals. Another feature of some disorders of orthostatic

Table 2
Cardiovascular responses after 10-min of tilting during protocol two. Baseline data reflect the mean supine parameter for all conditions. Data during compression conditions after 10-min of tilt are presented as the mean ± SEM for each condition (10-min) with absolute changes from supine indicated in shaded columns (Δ). Symbols: * Significantly different from baseline; **Ω** Significantly different from placebo condition; † Significantly different from 0 to 40 mm Hg ICLF condition. Abbreviations: SAP, systolic arterial pressure; DAP, diastolic arterial pressure; MAP, mean arterial pressure; HR, heart rate; SV, stroke volume; CO, cardiac output; TPR, total peripheral resistance; FVR, forearm vascular resistance.

Outcome measure	Baseline (average)	Compression condition (min_{10} values)									
		Placebo		0-40mmHg		0-60mmHg		0-80mmHg		0-100mmHg	
		10-min	Δ	10-min	Δ	10-min	Δ	10-min	Δ	10-min	Δ
SAP (mmHg)	119.3±3.0	113.0±3.0*	-7.8±3.0*	111.8±3.0*	-6. 2±3.7*	115.2±1.8	-3.8±1.6	115.5±2.1	-3.4±2.7	118.0±3.2 †	-1.8±3.6
DAP (mmHg)	67.5±2.0	73.2±1.7*	+4.4±1.7*	72.2±2.4*	+5.1±1.7*	71.8±1.6*	+4.6±1.3*	72.4±1.4*	+5.7±1.4*	74.2±1.7*	+5.0±1.9*
MAP (mmHg)	84.8±2.2	86.4±2.0	+0.3±2.0	85.3±2.5	+1.3±2.3	86.2±1.6	+1.8±1.3	86.7±1.5	+2.7±1.8	88.8±2.1	+2.7±2.5
HR (bpm)	63.7±1.6	86.6±2.0*	+22.9±2.4*	85.5±2.5*	+23.6±2.8*	79.5±1.7***Ω†**	+15.7±1.5 ***Ω†**	79. 2±1.3***Ω†**	+14.7±1.5 ***Ω†**	80.4±2.0***Ω†**	+15.9±1.3 ***Ω†**
SV (mL)	88.1±3.2	61.5±3.1*	-26.4±3.2*	60.9±3.0*	-26.0±2.4*	67.4±3.0***Ω†**	-22.2±2.4*	67.1±2.8***Ω†**	-20.0±2.4 ***Ω†**	68.5±3.5 ***Ω†**	-18.5±2.2 ***Ω†**
CO ($L.min^{-1}$)	5.60±0.23	5.30±0.279	-0.21±0.21	5.14±0.22	-0.25±0.21	5.31±0.22*	-0.39±0.21*	5.32±0.26	-0.31±0.14	5.47±0.27	-0.10±0.15
TPR ($mmHg.min.L^{-1}$)	15.8±0.3	17.1±0.7	+1.0±0.5	17.1±0.8	+0.9±0.4	16.8±0.8	+1.5±0.5*	17.0±0.9	+1.0±0.4	16.8±0.8	+0.9±0.3
FVR ($mmHg.sec.cm^{-1}$)	-	-	+4.2±2.4*	-	+5.0±2.0*	-	+5.9±1.7*	-	+6.0±2.6*	-	+6.3±1.8*

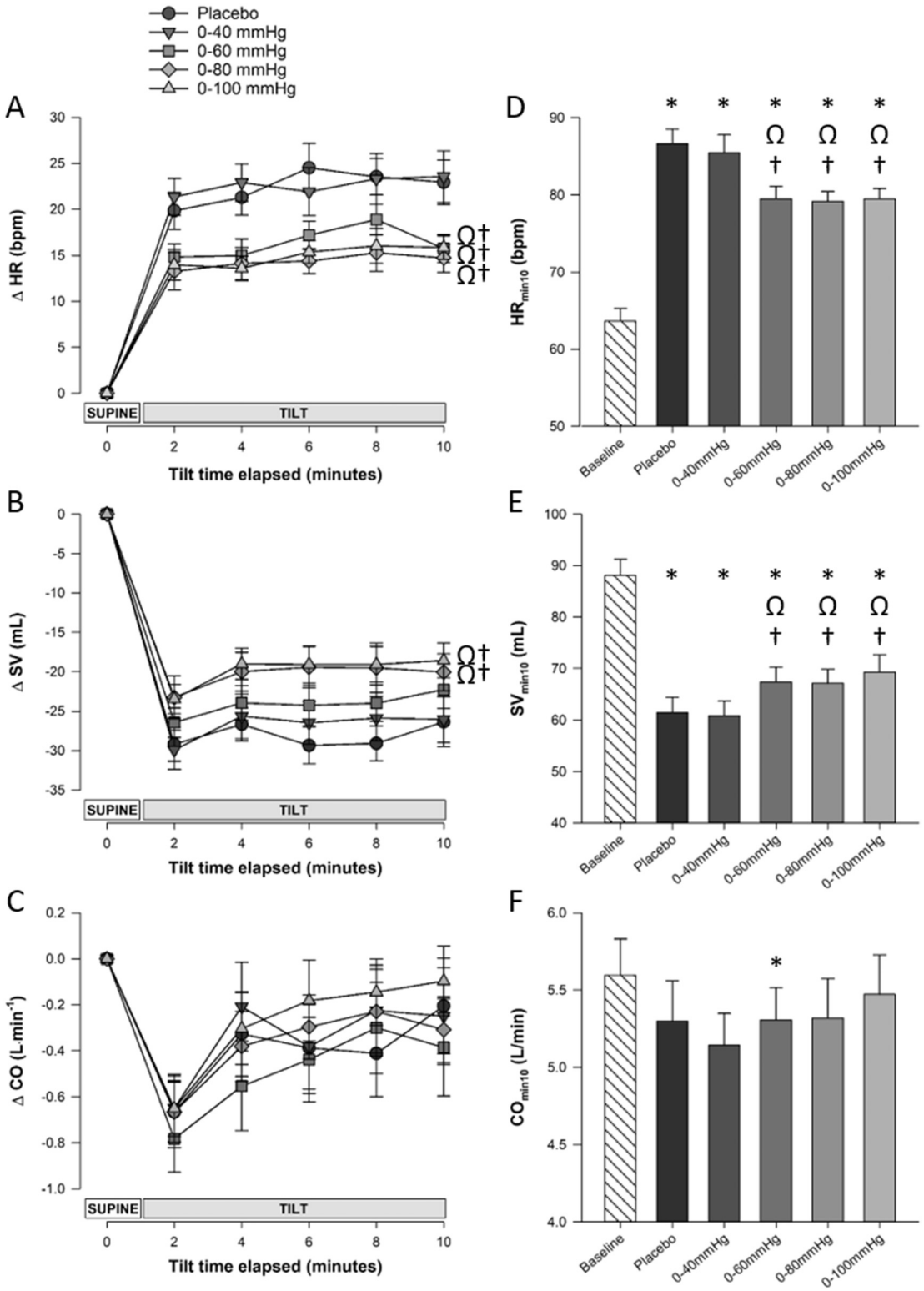

Fig. 6. Cardiovascular responses to tilt during protocol two. **A–C**. Time course of HR, SV and CO responses throughout tilt. Symbols (mean ± SEM) reflect averaged data over the last 30-s of every two-minute interval and are reported as absolute change from supine baseline. Main effects of condition throughout tilt are indicated. **D–F**. HR, SV and CO values at baseline, and after 10-min of tilting. Differences between conditions and from baseline at the 10-min time point are shown. Baseline data reflect the mean baseline supine parameter averaged for all conditions. However, for comparisons between 10-min and baseline values, each condition has been compared to its own baseline. Symbols: **Ω** Significantly different from placebo; † Significantly different from 0 to 40 mm Hg condition; * Significantly different from baseline. Abbreviations: CO, cardiac output; HR, heart rate; SV, stroke volume.

tolerance is excessive HR responses to orthostasis (Postural Orthostatic Tachycardia Syndrome), leading to palpitations and impaired quality of life. Given the blunting of HR in the intermittent compression conditions, secondary to reduced orthostatic fluid shifts and improved hemodynamics, use of this approach might also be of benefit to patients with excessive orthostatic HR responses.

The beneficial effects of intermittent compression were seen with both low and high frequency compression paradigms, with no additional benefit from high compression frequencies on any of the cardiovascular parameters tested, or the metrics of venous pooling and capillary filtration. Given the additional engineering requirements of the high frequency paradigm and potential impact on patient comfort, we advocate for low frequency compression. The lack of additive effect of high frequency compression may reflect that venous filling between compression pulses is necessary in order to prime the venous pump, maximizing the upwards mobilization of blood during the compression pulse (Mosti and Partsch, 2012). It is possible that with high compression frequencies there would be reduced refilling of the leg veins prior to the next pressure pulse, and so the impact of the pressure applied on venous return would be reduced.

The use of static elastic and inelastic compression stockings did convey some benefit compared to placebo – with modest, but significant reductions in venous pooling and capillary filtration. However, the magnitude of this effect was insufficient to convey a meaningful cardiovascular benefit, evidenced by the failure to blunt the orthostatic reductions in SV and CO, or the increase in HR during orthostasis. This is similar to previous studies (Protheroe et al., 2011; Moein et al., 2017), and suggests that, while static compression garments are beneficial for patients with limb edema (Jones et al., 1980; Mayberry et al., 1991; Mosti and Partsch, 2013; Ohgi et al., 1994; Partsch et al., 2004; Spence and Cahall, 1996), they are unlikely to provide significant benefit to patients with disorders of orthostatic tolerance. This is in keeping with prior literature showing that both elastic and inelastic compression stockings reduce or prevent edema, particularly during ambulation through enhancement of muscle pump function (Mosti and Partsch, 2012; Jones et al., 1980; Mayberry et al., 1991; Mosti and Partsch, 2013; Ohgi et al., 1994; Partsch et al., 2004; Spence and Cahall, 1996; Mosti and Partsch, 2011). However, they do not provide the same benefit during motionless standing, which is a key trigger for syncope (Protheroe et al., 2011).

In the second series of experiments, we observed that incrementing ICLF compression pressure produces a dose-dependent effect, both in terms of the impact on orthostatic fluid shifts, and cardiovascular control. We advocate 0–60 mm Hg as the optimal ICLF pressure paradigm, because this was the lowest pressure that both prevented orthostatic fluid shifts, while providing measurable benefits in orthostatic cardiovascular control. Based on our data (Fig. 7), ICLF of 0–57 mm Hg would result in no net change in calf volume, and hence prevention of venous pooling and capillary filtration. While higher ICLF pressures might convey some additional benefit by mobilizing fluid, perhaps with a contribution from enhanced lymphatic drainage (Kitayama et al., 2017; Tran and Argáez, 2017), rather than simply preventing venous pooling and capillary filtration, from an engineering and comfort perspective lower pressures would likely be preferable. Considering these practicalities and the non-linear relationship between the calf pressure applied and impact on calf pooling and stroke volume (Fig. 7), any additional benefit with the application of higher pressures is likely to be small.

We used a 0 mm Hg holding pressure because this allows for maximal filling of the veins between pulses, priming the venous pump and preventing edema distal to the compression device (Lurie et al., 2003; Rucinkski et al., 1991). In order to maximize peak flow velocities to optimally increase venous return, we used rapid inflation rates (< 1 s) (Morris et al., 2006).

We used calf circumference as a proxy for venous pooling and capillary filtration. This is a well-established approach (Rosfors et al., 2014; Halliwill et al., 1999; Whitney, 1953; Oeffinger et al., 2015; Gamble et al., 1993). A change in posture from supine to upright is known to produce predictable fluid shifts in the lower limbs, with a rapid (~2 min) pooling phase and slow (> 2 min) filtration phase (Brown and Hainsworth, 1999), and this established biphasic pattern of fluid loss was evident in our data in the placebo conditions. Based on

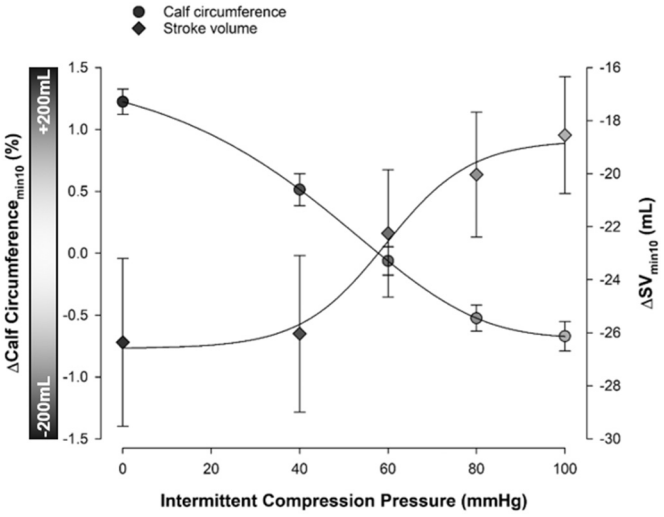

Fig. 7. The dose dependence of intermittent calf compression paradigms in protocol two. Mean changes in calf circumference and SV were dependent on the magnitude of the compression pulse pressure during intermittent calf compression. We estimate that a 1.5% increase in calf circumference reflects a total fluid loss of ~200 mL to the calves (Brown and Hainsworth, 1999). Abbreviations: SV, stroke volume.

known pooling values of ~100 mL per calf per 10-min of 60° head-up tilt, we expect that the ~1.5% change in calf volume during the placebo condition correlates to a fluid loss to the calves of approximately 200 mL (Brown and Hainsworth, 1999). This means that the intermittent compression paradigms, in addition to preventing fluid loss to the calves, also mobilized approximately 200 mL of fluid into the effective circulating volume. One additional consideration with calf compression is the possibility to create distal edema, with high upstream pressures preventing venous return. We measured changes in circumference at the level of the gaiter, distal to the compression site, and did not observe the formation of edema with intermittent compression. We postulate that use of the 0 mm Hg holding pressure is important in this respect.

Previous studies have shown that static compression garments better prevent orthostatic fluid shifts if they are applied while supine, prior to orthostasis (Thijs et al., 2010), reflecting that they are more effective at preventing fluid shifts than reversing them. For technical reasons, and because of the applicability to a device that would apply compression only during times of need, we introduced a long supine period between tilts to allow reabsorption and reversal of pooling, and only initiated intermittent compression at the onset of orthostasis. Despite this, we showed that intermittent calf compression paradigms are able to reverse fluid accumulation in the calf relative to supine values. We chose to evaluate the garments during tilting, rather than standing, because this standardizes the level of muscle activation across all conditions, permits measurements of strain gauge plethysmography (which might be subject to noise artefact during active standing), and is a stronger orthostatic stress than active standing (and so is more applicable to the extent of pooling and filtration that might be anticipated in patients with orthostatic intolerance). Future studies should evaluate their efficacy during motionless standing.

In this study, we tested young healthy controls with no known cardiovascular impairments. Accordingly, we saw little effect of intermittent compression paradigms on blood pressure control during tilt, presumably because healthy controls defend their blood pressure effectively during short bouts of orthostatic stress with or without compression garments. During intermittent compression paradigms they did, however, maintain their blood pressure with reduced sympathetically-mediated increases in HR and vascular resistance, likely reflecting increased hemodynamic reserve and a greater capacity to mount

baroreflex responses when necessary. Future studies will be necessary to confirm that these benefits also apply to individuals with impaired orthostatic cardiovascular control, the target population for the intervention. Evaluation of individual characteristics that might impact responses to intermittent compression (orthostatic tolerance, age, sex) would also be of interest.

We did not formally evaluate the comfort of our intermittent compression paradigms, but none of our participants reported discomfort related to the device. Others have formally evaluated the perceived comfort of active compression devices, with participants reporting good wearability and comfort during ambulatory use (Moein et al., 2017). A key bonus of intermittent calf compression is the high paradigm efficacy, without compression of large muscle beds in the thighs and abdomen, which is associated with patient discomfort. Intermittent compression of the calves is likely a more comfortable alternative to full leg and abdominal garments that would maximize patient compliance. As intermittent calf compression garments would be easier to put on and remove, elderly patients or those with neurological or hand function impairments would be able to put them on and remove them independently, thus improving quality of life.

While not a main focus of this study, we did consider the potential impact of baseline calf circumference and MCSA on pooling and filtration, and the efficacy of intermittent calf compression. There was no significant relationship between the efficacy of the intermittent compression paradigms and baseline calf circumference or MCSA over a wide range of calf sizes in this study. This suggests that these findings would extend to all individuals, regardless of their baseline anthropometric data.

In the future, we hope that this study will guide the engineering of a "smart" ambulatory device that rapidly applies (< 1 s) 0–60 mm Hg of pressure at a rate of 4 pulses per-minute (4 s on; 11 s off), incorporated into a comfortable and portable garment. This might be achieved using shape memory alloys(Moein et al., 2017; Moein and Menon, 2014) or dielectric elastomer actuators (Pourazadi et al., 2015). This device should be mobile and should contain accelerometers to activate intermittent compression during motionless standing, and deactivate during ambulation (when cardiovascular deficits are offset by skeletal muscle pumping activity) or during sitting/supine postures (when orthostatic stress is minimal). Previous research has shown that the efficacy of intermittent compression is reduced, and not necessary, during walking (Moein et al., 2017).

These data reiterate that standard static compression garments applied to the calf, while ameliorating edema, do not improve orthostatic cardiovascular control and should not be considered for patients who primary disorder is orthostatic intolerance. In those with orthostatic intolerance who also have edema, they may be of benefit.

4.1. Limitations

We conducted these experiments in a double-blind fashion, in that neither the participants nor the primary investigators were made aware of the study condition. However, we recognize that the blinding may have been imperfect, because participants would be aware of the sensation of the compression paradigm applied. In protocol one, the garments were visually distinct, but participants were not able to distinguish pressure levels, and were not told whether any given condition was theorized to improve, worsen or not change their results. In protocol two, the garments were visually similar, and although participants could feel the compression applied, they were not able to consistently identify the compression pressure, and were not told the expected effect of the intervention. In all cases, experiments and analyses were conducted by blinded investigators.

It is known that patients with reduced orthostatic tolerance experience increased venous pooling compared to controls (Brown and Hainsworth, 1999). As we tested young, healthy controls in the current study, it is possible that our observations underestimate the benefit intermittent calf compression would convey in patient populations. Nevertheless, some of our participants appeared to have poor orthostatic tolerance, and two experienced presyncope during testing, similar to that of patient populations. The efficacy of the intermittent compression in these individuals provides encouragement that a similar effect would be seen in patient populations.

We considered whether wrapping the intermittent compression device applied some level of compression to the limb, which might have influenced the placebo condition, or the holding pressure in the intermittent compression paradigms. In protocol two, we measured the internal cuff pressure throughout testing and confirmed that it was 0 mm Hg in the placebo condition. Furthermore, the baseline strain gauge data were not affected by application of the device. We do not think that application of the cuffs in the absence of compression could have influenced either the measures of pooling and filtration or the pressure applied. These measurements also confirmed that we successfully achieved the target pressures and timing for each intermittent compression paradigm.

While the cohort of participants was different in each study, there was a remarkable similarity between the responses in the two placebo and 0–100 mm Hg ICLF conditions that were common to both protocols. This suggests that these results are robust and the test is repeatable.

We did not measure orthostatic tolerance in this study and thus cannot comment on whether the intermittent compression paradigms employed would have be sufficient to prevent or delay syncope. In the future, changes in orthostatic tolerance should be measured between our optimal intermittent calf compression paradigm and a placebo condition to confirm that the reductions in lower limb fluid accumulation and improvements in orthostatic hemodynamic control are sufficient to reduce susceptibility to syncope.

5. Conclusions

We have demonstrated the efficacy of intermittent calf compression for the prevention of lower limb orthostatic fluid shifts and improvement of hemodynamic control during orthostatic stress. We also showed that current static elastic and inelastic compression garments, while efficacious for the prevention of lower limb edema, do not improve orthostatic hemodynamic control. We have identified optimal criteria for calf compression paradigms for the improvement of orthostatic fluid shifts and cardiovascular control. These data have important implications for the use of lower limb compression garments in patients with disorders of orthostatic tolerance.

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Competing interest statement

The authors declare no conflict of interest. This work received the 2016 Finapres Medical Systems/Penaz-Wesseling Research Award for trainee research excellence.

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