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Comparative lower limb hemodynamics using neuromuscular electrical stimulation (NMES) versus intermittent pneumatic compression (IPC)

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Abstract

Deep Vein Thrombosis (DVT) is a life threatening condition and a serious concern among hospitalised patients, with death occurring in approximately 6% of cases. Intermittent pneumatic compression (IPC) is commonly used for DVT prevention, however suffers from low compliance and issues of usability and portability. Neuromuscular electrical stimulation (NMES) has been shown to improve lower limb hemodynamics but direct comparison with IPC in terms of hemodynamics is rare but very important to determine the potential effectiveness of NMES in DVT prevention.

Lower limb IPC was compared to calf NMES, in 30 healthy volunteers (18–23 years). Each intervention was carried out on each leg, on the popliteal vein measured using Doppler ultrasound. All interventions produced significantly greater haemodynamic responses compared to baseline. Calf-IPC and NMES produced significant increases in venous blood velocity (cm/s) and volume of blood ejected per cycle (1 cycle of NMES expels 23.22 ml compared to the baseline ejected volume of 2.52 ml, measured over 1 s ($p < 0.001$ versues baseline).

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Improving lower limb hemodynamics is vital in preventing DVT. NMES resulted in larger ejected volumes compared to IPC (x3 greater than foot-IPC and x1.7 greater than calf-IPC) more effectively emptying the veins and soleal sinuses. This is an important finding as DVT occurs predominantly in the soleal sinuses. NMES is silent and portable and thus does not suffer many of the issues associated with IPC. This work supports the potential widespread application of NMES in hospital and home settings where the risk of DVT formation is high.

Keywords: electrical stimulation, hemodynamics, muscles, thrombosis, veins

(Some figures may appear in colour only in the online journal)

1. Introduction

Prevention of Deep Vein Thrombosis (DVT) in postoperative and other medical settings primarily involves the use of anticoagulants, Graduated Compression Stockings (GCS) and/or Intermittent Pneumatic Compression (IPC) (MacLellan and Fletcher 2007). Each of these methods has associated issues with contraindications to use and poor levels of compliance by the patient population while in use in the clinic and laterally at home. The ideal prophylaxis should promote good hemodynamics, be portable, have good usability characteristics and thus sustain high levels of compliance. An intervention that will combine all of these factors will ultimately reduce DVT incidence. Neuromuscular Electrical Stimulation (NMES) is a potential alternative method that may compete favorably with existing methods hemodynamically, in user-friendliness and ultimately in patient compliance (Broderick *et al* 2010, Czyrny *et al* 2010, Broderick *et al* 2011). NMES like IPC is a technological intervention that results in the movement of blood out of the lower limb during the active cycle of the device. Current standard therapy employs IPC which involves the use of a cycle of compression and relaxation of pumped air in an inflatable chamber placed around the limb. Its main objective is to mechanically squeeze blood from the underlying veins. The blood is displaced proximally, assuming competent venous valve function. IPC is an effective method used as part of surgical practice to assist blood flow following surgery and prevent or reduce complications such as DVT (Vanek 1998, Tamir *et al* 1999, Fujisawa *et al* 2003, Morris and Woodcock 2004). IPC has also been used in the prevention of DVT in non-surgical patients, such as those with stroke or cancer, as well as in the treatment of edema, lymphedema and chronic arterial disease (Morris 2008, Vanscheidt *et al* 2009, Chang and Cormier 2013, Collaboration 2013). However despite its widespread use there are significant patient compliance issues with IPC and thus its full effectiveness is often not achieved, as patients do not adhere to recommended use for the required amount of time despite the increased risk of DVT (Geerts *et al* 2004, MacLellan and Fletcher 2007, Bockheim *et al* 2009). Patients report cuffs are difficult to put on, uncomfortable to wear, the device is not portable and it is noisy to the point that patients stop the therapy. This is particularly true in an orthopedic ward setting where often multiple devices are in use at once.

The hemodynamic properties of IPC, such as peak venous velocity, volume of blood expelled and blood flow duration during each compression cycle, are easily measured using Doppler ultrasound. Both the site of blood flow measurement and the part of the limb compressed are important in assessing the effectiveness of any intervention. Blood flow velocity depends on vein diameter and it is clear that the venous compartment of the foot holds a smaller volume of blood than that of the calf or thigh. Consequently, foot compression has been shown to produce more modest results when compared to calf and thigh compression (Ricci *et al* 1997, Delis *et al* 2000, Whitelaw *et al* 2001). IPC devices can have single or multiple chambers, which can compress sequentially and in a proximal direction starting from the ankle. These chambers can encompass the whole limb or different parts of the limb separately or in combination (Morris and Woodcock 2010). Duration of compression/relaxation cycle, applied pressures and overall cycle times vary with device manufacturer and is further modified by personal choice of the attending physician. However in all cases the goal of compression is to give a significant increase in venous blood flow which subsequently returns to baseline between pulses (Faghri *et al* 1997). However as IPC does not activate the skeletal muscle pump in the calf, it has been suggested that blood is pushed past the soleal sinuses, leaving the blood in the soleal sinuses stagnant (Laverick *et al* 1990, Faghri *et al* 1997). As a result, compression may not be adequate to induce complete emptying of blood from the lower limb venous system. Thus while IPC when used correctly reduces DVT risk there is room for improvement in its haemodynamic performance aside from the well documented compliance issues. Complications with IPC are rare but serious and include compartment syndrome, common peroneal nerve palsy due to nerve damage caused by the intermittent compression, and skin ulceration (Werbel and Shybut 1986, Pittman 1989, Strup *et al* 1993). Thus there is a gap in the post-surgical arsenal available to prevent DVT and reduce swelling. For any intervention to fill this gap the most important element will be that it performs at least as well as IPC in terms of haemodynamic performance. Following establishing its bona fides at this fundamental physiological level, issues of easy of use, portability and compliance will come into focus. Surface neuromuscular electrical stimulation (NMES) is emerging as an alternative method of assisting venous blood flow following surgery. NMES is used to generate a physiological contraction of muscles by delivering a series of controlled electrical pulses via skin surface electrodes placed over the motor points of the targeted muscle. For example, NMES applied to the calf muscle artificially activates the calf muscle pump and results in ejection of blood from the venous compartment (Lyons *et al* 2002). This calf muscle activation produces venous flow similar to that of a voluntary muscle contraction, with relaxation of the muscle allowing the vessels to refill. NMES has been shown to improve venous return (Clarke Moloney *et al* 2006, Broderick *et al* 2010, Broderick *et al* 2013). Research into stimulation waveform configurations and shapes, advanced skin surface electrodes and electrode placement has improved the performance of NMES whilst maintaining patient comfort (Lyons *et al* 2004, Breen *et al* 2009, Broderick *et al* 2011). NMES is delivered through a portable, noiseless device that does not require clinical expertise to operate, making it an attractive method to be used in the home. Furthermore, removal of electrodes is not necessary for patient ambulation as stimulation can be paused during use. As this device has the potential to be worn while a patient is either immobile, standing or walking, it would be suitable for use both during the early stage of immobilisation following surgery and throughout the recovery/rehabilitation period in the home, therefore bridging the gap between the hospital and home settings. In this paper, we directly compare the haemodynamic performance of NMES-induced contractions of the calf muscle pump with IPC of the foot and calf separately on a pulse by pulse basis. This paper is the first direct comparison of NMES versus a clinic standard IPC device in terms of haemodynamic performance and an important step in establishing the potential of NMES as a DVT prophylaxis.

2. Methods

2.1. Subjects

Thirty healthy subjects (21 male and 9 female) mean age of 21 ± 1.08, weight (kg) 75.26 ± 13.88, height (m) 1.78 ± 0.10, BMI (kg/m^2) 23.54 ± 3.04 and with no history of

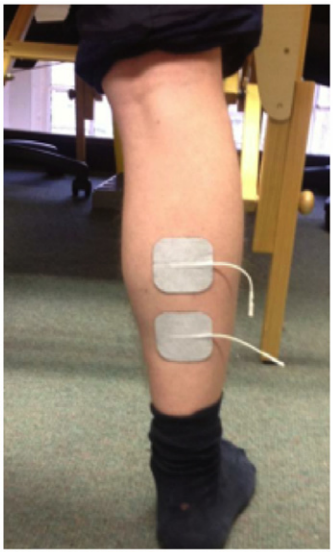

Figure 1. Position of the self-adhesive 5 cm × 5 cm PALS skin surface electrodes placed over the motor points of the soleus muscle.

cardiovascular problems were recruited for this study. Ethical approval was obtained from the Research Ethics Committee, NUI Galway and all subjects provided written, informed consent.

2.2. Study protocol

Lower limb haemodynamic performance was the primary outcome of this study. Four interventions of five-minute duration were applied to each subject: Baseline (rest), foot-IPC, calf-IPC and calf-NMES. The order of each intervention and the leg on which it began was randomised before the study began. To ensure that baseline equilibrium venous flow was reached, a rest period of three minutes was allowed between each intervention and at the beginning of the study. Each intervention was carried out for five minutes, no measurements were taking in the first minute. No order effect was observed in the data collected.

2.3. IPC protocol

Intermittent pneumatic compression (IPC) was applied using the Novamedix AV Impulse System Model 6000 (Covidien, Mansfield, MA, USA). This device is designed to allow for compression to be applied to the foot or calf separately. Inflation pads were placed on the subject's foot and calf separately and connected to the IPC device. Once the pads were positioned correctly the device was programmed to deliver compression pulses (one pulse is defined as 130 mmHg for 1 s) every 20 s, over a period of 5 min. Compression of the foot and calf was performed separately.

2.4. NMES protocol

A custom-built, two-channel muscle stimulator (Duo-STIM, Bioelectronics Research Cluster, NUI Galway) was used to deliver NMES to the calf muscles (Breen *et al* 2009). Two self-adhesive 5 cm × 5 cm PALS surface electrodes (Ultrastim, Axelgaard Manufacturing Co. Ltd. CA, USA) were placed over the motor points of the soleus muscles of both legs (figure 1). To

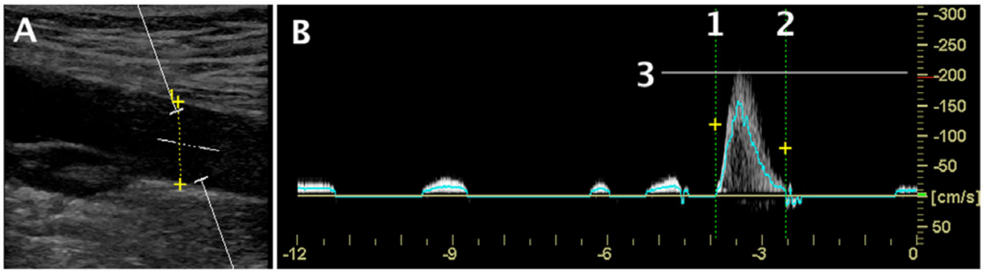

Figure 2. Representative Doppler ultrasound capture window used for blood flow analysis. (*a*) Representative screen shot from Duplex Doppler ultrasound measuring Popliteal vein diameter. (*b*) Representative screen shot from Duplex Doppler ultrasound showing blood flow waveform in response to NMES stimulation. For haemodynamic analysis each waveform produced in response to the intervention is analysed by positioning calipers appropriately. Peak venous velocity (cm/s, line 3), time averaged mean velocity (TAMEAN (cm/s), mean flow between lines 1 and 2) and volume flow (mL/min, volume flow between lines 1 and 2). The *x*-axis reflects time in seconds.

ensure correct electrode placement and to ensure that the subject was comfortable with the sensation of the electrical stimulation, a series of test pulses were applied initially at a very low intensity. The stimulus intensity was gradually increased until a contraction of the calf muscle was observed. Correct electrode placement was confirmed by either a visible tightening of the soleus muscle or a slight plantar flexion. Once the subject reached the maximum comfortable stimulation intensity this intensity was set and used for the remainder of the NMES protocol. The stimulation intensity voltage across all participants had a median and interquartile range of 32 V (25.6; 38.4).

The Duo-STIM was set to a total cycle time of 22 s (one pulse is defined by an active contraction time of 1 s) with an OFF time of 20 s, repeated over 5 min. This time profile was selected to match the timing of the Novamedix AV Impulse System Model 6000. The stimulator was programmed to provide a pulse frequency of 36 Hz and a balanced biphasic waveform with a pulse width of 350 μs. A comfortable calf muscle contraction was produced using a Ramp-Up Time of 0.5 s, a contraction time of 1 s and a Ramp-Down Time of 0.5 s. The stimulation parameters were selected to provide an effective contraction while maximising subject comfort and were chosen based on previous work using NMES (Breen *et al* 2012). The electrical stimulation was applied to one leg at a time in accordance with the randomisation of the interventions.

2.5. Hemodynamic measurement

Subjects' were positioned in a semi recumbent position and lower limb hemodynamics assessed with a Duplex Doppler ultrasound using a 4–8 MHz linear transducer (LOGIQ e; GE Medical Systems). To ensure the validity and precision of the Doppler ultrasound operator, a reliability analysis was performed using Cronbach's alpha which was found to be 0.952.

All blood flow measurements were taken at the popliteal vein to reflect venous outflow from the deep veins of the lower leg. No measurement was taken during the first minute of the 5 min intervention. Blood flow was sampled 3 times for rigor over the remaining 4 min and the mean of the three measurements used for analysis. Popliteal vein diameter (cm, figure 2(*a*)) was measured from the Doppler image. Peak venous velocity (cm/s, figure 2(*b*), line 3) measured from the Doppler waveform. The blood flow response to the intervention (NMES, Calf-IPC,

Table 1. Median and (interquartile range) of ejected volume (EV), peak venous velocity (PV) and time averaged mean (TAMEAN) in subgroups of features. *P* value using Bonferroni correction.

Feature	EV (ml)	P	PV (cm/s)	P	TAMEAN (cm/s)	P
GENDER						
Male	9.9(4; 17)		73.3(19; 115)		15.7(6; 22)	
Female	7.0(2; 12)	P = 0.065	88.0(23; 130)	P = 0.003	17.5(6; 25)	P = 0.042
INTERVENTION						
Control	2.1(2; 3)		10.8(9; 13)		3.6(3; 5)	
Foot-IPC	7.2(5; 10)	P < 0.001*	50.5(35; 67)	P < 0.001*	11.5(8; 15)	P < 0.001*
Calf-IPC	12.3(9; 15)	P < 0.001*	125.6(110;146)	P < 0.001*	21.8(19; 27)	P < 0.001*
NMES	19.8(15; 31)	P < 0.001*	108.8(87; 131)	P < 0.001*	22.2(17; 28)	P < 0.001*

*P < 0.01 vs. Control

Foot-IPC) is clearly identifiable. The blood flow waveform response to intervention is selected for analysis on the Doppler instrument as indicated by vertical calipers positioned at the start and end of the waveform indicated by lines 1 and 2 in figure 2(*b*). The Doppler unit's in-built software calculates time averaged mean velocity (TAMEAN) (cm/s) and volume flow (mL/min) between the vertical calipers. Volume flow is calculated as the product of the TAMEAN (cm/s) **X** the measured cross-sectional area of the popliteal vein (cm^2).

Ejected volume measures the volume of blood displaced through the popliteal vein during a single pulse of the intervention and was calculated offline using equation (1):

$$\begin{aligned}\text{Ejected Volume(mL)} = {} & \text{Volume Flow}(\text{mL min}^{-1}) \\ & \times \text{Duration of single Intervention pulse(min)}\end{aligned} \tag{1}$$

The duration of a single intervention pulse, represents the time for one pulse of the intervention (NMES or IPC, stimulation or compression respectively) as defined under IPC and NMES Protocols above. For the baseline the Duration of Intervention pulse was taken as 1 s.

2.6. Statistical analysis

As this study followed a repeated measures design, the data were fitted to a multivariate repeated measures model. A multivariate repeated measures analysis was used to identify any differences between each intervention in terms of blood flow. The Greenhouse-Geisser correction was used to correct any violations to the assumption of sphericity. All statistical analyses were carried out using SPSS (SPSS for Windows, version 22, IBM Corporation).

3. Results

Measurements of peak venous velocity, TAMEAN and ejected volume are summarised in table 1. Peak venous velocity, TAMEAN and ejected volume improved significantly with all interventions ($p < 0.001$ versus baseline). There is evidence of an overall intervention effect and gender effect on lower limb hemodynamics ($p < 0.001$ for both factors). Gender was found to have a significant effect on peak venous velocity ($p = 0.003$) and TAMEAN ($p = 0.042$), with females having a greater peak venous velocities and TAMEAN. The interaction between intervention and gender was found to have a significant effect on TAMEAN ($p = 0.023$).Both calf-IPC and calf-NMES resulted in a significantly greater peak venous velocity (figure 3) and TAMEAN (figure 4) when compared to foot-IPC ($p < 0.001$). There was no

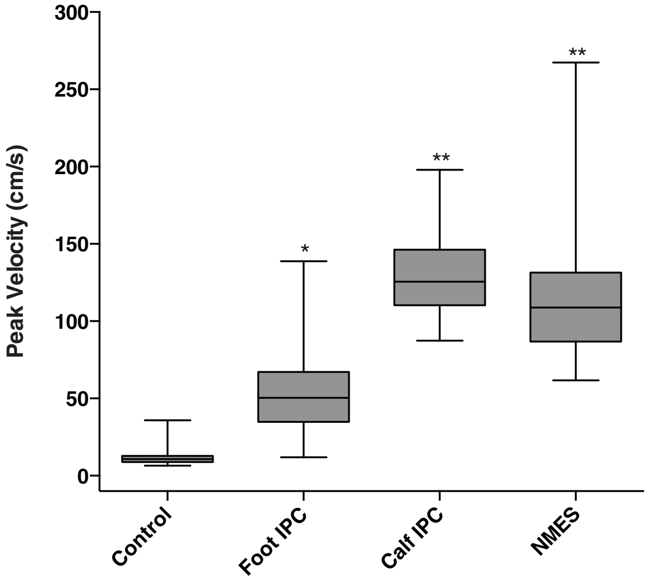

Figure 3. Effect of intervention on the peak venous velocity (cm/s). Both NMES and calf-IPC produced similar increases in peak venous velocity, which were significantly greater than both foot-IPC and *baseline*. **p < 0.001 versus. baseline, **p < 0.001 versus. foot-IPC.*

significant difference observed between calf-IPC and NMES for either peak venous velocity or TAMEAN ($p = 0.283$ and $p = 1.000$ respectively).Significantly, NMES produced the largest increase in ejected volume 19.81 ml (15.4–30.81), which was 1.7 times that of calf-IPC (figure 5).

4. Discussion

In this paper, for the first time, we have demonstrated enhanced lower limb hemodynamics using NMES compared to IPC. In matched device active/silent protocols NMES was as effective as IPC in terms of peak velocity and TAMEAN and out-performed both foot-IPC and calf-IPC in terms of ejected volume. In the clinical arena this is a very significant finding as the greater the ejected volume, the less blood is left in stasis in the veins and soleal sinuses and therefore it is less likely for a DVT to form. This data is supported by a number of other studies which have found ejected volumes due to NMES to be significantly higher than baseline (Broderick *et al* 2010, Breen *et al* 2012, Corley *et al* 2012).

The main technologic intervention in common use for DVT prevention is IPC, but IPC suffers from low compliance and thus there is a need for viable alternatives. IPC compresses the limb externally, leading eventually to the compression of the underlying muscles, the superficial veins and finally the deep veins. This action does not mimic a normal physiological process. Unlike IPC, NMES produces a physiological muscle contraction similar to that observed during normal walking, resulting in the large increase in ejected volume that was observed. Additionally, at the end of the NMES-elicited contraction, we were able to observe in some case that the Doppler recording of blood flow fell to zero, whereas following the IPC cycle, Doppler blood flow returned to the non-zero baseline level. This suggests that NMES

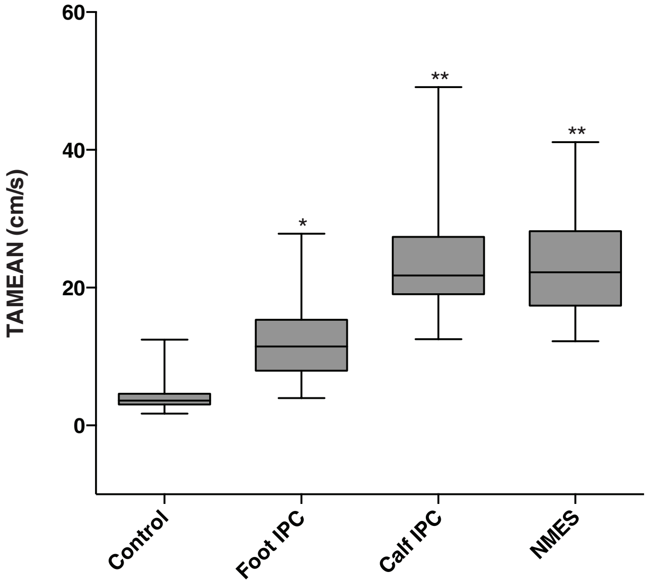

Figure 4. Effect of intervention on TAMEAN (cm/s). Both NMES and calf-IPC produced similar increases in TAMEAN, which were significantly greater than both foot-IPC and *baseline*. *$*p < 0.001$ versus. baseline, $**p < 0.001$ versus. foot-IPC.*

more completely empties the venous compartments than IPC, which is a critical element in DVT prevention. More data and further study is required to support this observation. However this observation was also made by Faghri *et al* (1997) and Laverick *et al* (1990) as being a feature of NMES-elicited enhanced venous blood flow.

The aim of both IPC and NMES in the prevention of DVT is to prevent venous stasis. Peak venous velocity is a measurement commonly used to assess the effectiveness of DVT prophylaxis methods in preventing venous stasis. In this study, all interventions were found to significantly increase peak venous velocity from baseline resting values. These results are in contrast to Izumi *et al* (2010) and Czyryn *et al* (2010) who found NMES produced greater peak venous velocities than IPC. However, these differences may be accounted for by differences in muscles stimulated and different stimulation parameters used in these studies. Izumi *et al* stimulated the tibialis anterior muscle as opposed to the soleus muscle used a square wave pulse 500 μs in duration at a rate of 50 Hz, whereas in this study we employed a balanced biphasic waveform with a pulse width of 350 μs and a rate of 36 Hz. These parameters were chosen as our previous work found them to optimise both muscle contraction and patient comfort (Lyons *et al* 2004). Izumi *et al* also used a compression of 40 mmHg on the calf as opposed to the 130 mmHg used in our study (Izumi *et al* 2010). These parameters may account for the differences observed in peak venous velocities. Czyryn *et al* applied NMES to the foot using a biphasic symmetrical square wave 300 ms in duration and at a rate of 50 Hz and they applied IPC to the foot at a pressure of 130 mmHg for a 3 s duration (Czyrny *et al* 2010). The different stimulation parameters used in this study, coupled with both the stimulation and compression being applied to the foot as opposed to the calf, may account for the differences observed. Although foot-IPC does improve lower limb hemodynamics, it does so to a lesser degree than calf-IPC or NMES applied to the calf. While it is important to increase venous velocity in reducing venous stasis, it is important to do so to a safe level. An excessive increase

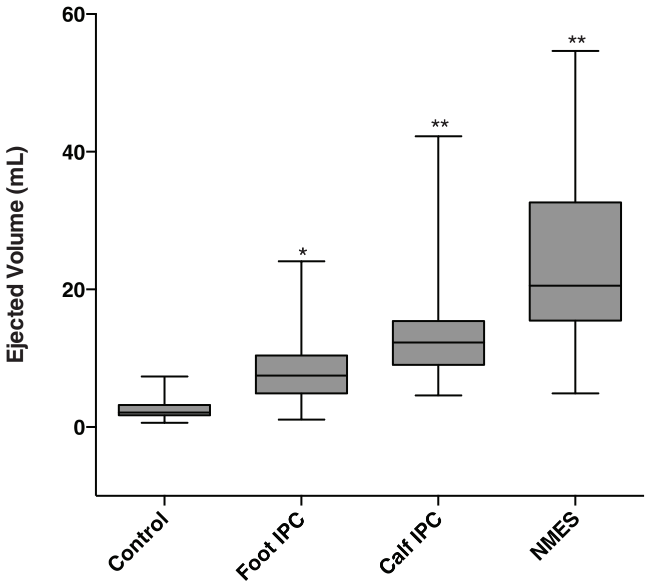

Figure 5. Effect of intervention on the ejected volume (ml). NMES produced the greatest ejected volume compared to all other interventions. $*p < 0.001$ *versus. baseline*, $**p < 0.001$ *versus.* foot-IPC, $***p < 0.001$ *versus.* calf-IPC.

in venous velocity could possibly damage the blood vessel endothelium and lead to thrombus formation or potentially dislodge a clot already present in the deep veins or soleal sinuses. Consequently, other factors, such as the ejected volume, need to be considered when assessing the effectiveness of DVT prophylaxis methods.

The current study was carried out in young (18–23 years), healthy participants. There was a gender difference in the responses measured with females having a lower ejected volume and higher TAMEAN, which is likely to result from anatomical size difference in the gender groups with males generally having a larger calf musculature. However, the population most at risk for DVT development would be an older age group, many with pre-existing health problems. As DVT is most likely to occur following surgery, especially orthopedic surgery (Hull *et al* 1993, Eriksson *et al* 1994, Bergqvist 1997, Francis *et al* 1997, Robinson *et al* 1998, Schindler and Dalziel 2005), where prolonged bed rest and immobilisation are common, a follow-on study should be carried out in this patient population. Further study is required to establish the longer-term effects of NMES and to evaluate the use of NMES over the a full recovery/rehabilitation period until the patient is mobile as there is still a high risk of DVT development up to 5 weeks post-surgery (Huber *et al* 1992, Johnson *et al* 1977). Furthermore to strengthen the data presented here studies should examine an older population cohort and assess effects of NMES on enhancing fibrinolytic activity. However significantly in this study we have shown that NMES is equal to IPC in terms of peak velocity and TAMEAN and outperforms IPC in terms of ejected venous volume. Our results suggest that NMES is a superior method of improving lower limb hemodynamics and supports the viable use of NMES as a DVT prophylaxis method. This significant validation of the haemodynamic performance of NMES make it a viable alternative to IPC in the clinical and home setting. Furthermore NMES does not suffer the negative aspects of IPC use, NMES is silent, portable and has very favorable usability characteristics which would support a high rate of compliance.

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Disclosures

None.

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