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Vascular Endothelial Function is improved after active mattress use.

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Keywords:

Active Mattress, Endothelial Function, Post Occlusive Reactive Hypemia, Cardio Vascular System, Hypertension.

Abstract

Background: Active mattresses are used to prevent, treat and relieve pressure ulcers by intermittent contact pressure/relief. However, no studies have directly assessed the vascular endothelial response to long-term active mattress use. This study investigated the hypothesis that 8 weeks use of an active mattress would lead to improvements in vascular endothelial function in healthy participants.

Methods: Physiological parameters of baseline skin temperature (BskT), resting blood flow (RBF) and endothelial function as measured using post-occlusive reactive hyperemia (PORH), were assessed at baseline (week 0); following 8 weeks of sleeping on an active mattress, and after an 8 week washout period (at week 16).

Results: Ten healthy participants were recruited (4 male, age 52.7 ± 8.5 years, 6 female age 51.8 ± 17.5 years). Following active mattress use RBF, PORH and BskT at the hallux pulp increased by 336%, 197% and 3.5^{o}C, respectively; mean values increased from 24.3 ± 38.3 pu to 106.0 ± 100.3 pu (p=0.021) and from 13,456 ± 10,225 pu.s to 40,252 ± 23,995 pu.s (p=0.003) and from 22.9 ± 2.5 ^{o}C to 26.4 ± 1.9 ^{o}C (p=<0.001), respectively.

Conclusion: Active mattress use for 8 weeks leads to significant improvements in RBF, PORH, and BskT. These results suggest that active mattress use can improve endothelial function. Future research is required to explore the potential of active mattress (AM) use in the treatment and management of diseases and conditions that would benefit from an improved endothelial function.

Introduction

The role of an effective support surface is to facilitate the natural flow of blood[1] and lymphatic fluid.[2] This is achieved through dissipating interface pressures between the skin and the support surface.[3] Blood flow can also be stimulated through an active massage, one that applies and relieves pressure exerted on tissues.[4] For this reason, active mattresses (AM) that mimic the natural repositioning regime of sleeping humans whilst in bed,[4] are widely used to aid in the prevention and treatment of pressure ulcers.[1,5]
Despite evidence that AM can stimulate localized blood flow during short term use <60 minutes,[5,6] no studies have explored the long term use of an AM on vascular endothelial function. This function is essential for multiple processes such as angiogenesis, repair of damaged tissues, regulation of vascular tone and permeability, and prevention of inappropriate clotting.[7,8,9,10]

Intermittent pneumatic compression (IPC) devices are used to stimulate blood flow by sequentially inflating and deflating pneumatic air chambers.[11,12,13] In addition to the pressure exerted on deeper tissues to simulate the natural 'venous pump,' IPC alters the interface pressures exerted on the skin tissues improving vascular endothelial function through increased hemodynamic shear.[11,14]

IPC devices have been used to treat fractures and soft tissue injuries,[15] peripheral arterial disease,[16] venous ulcers, lymphoedema,[11] deep vein thrombosis;[17] improvements in blood lactate,[18] skin blood perfusion and $TcpO_2$ have also been observed.[19] Whilst IPC is considered to be clinically effective;[11,12,17] the device, which is prescribed for 30 to 120 mins daily use,[13] encompasses entire limbs and impedes physical activity.[11,17]
Stevens and Woller[17] reported that whilst IPC was useful in preventing deep vein thrombosis amongst stroke patients, the devices were hard to keep on, and compliance to IPC therapy occurred in less than one-third of the 118 stroke patients, despite being under the supervision of trained nurses.

Active mattresses (AM) are also designed to apply alternating pressure and pressure relief to the skin, using a similar method to IPC.[1] Goossens & Rithalia,[5] demonstrated that the application and release of pressure by a single pneumatic air cell within an active mattress, exerted on the heels of healthy subjects, is sufficient to stimulate a significant acute endothelial response in terms of increased blood flow. Their findings for AM concur

with Sheldon *et al.*[14] who found that within the first 5 minutes of IPC there was a two-fold increase in mean blood flow compared with baseline. AM could therefore provide similar beneficial outcomes to IPC, yet with the potential for greater compliance due to ease of use. However, no studies have investigated the effects of long term use of AM on endothelial function.

Post Occlusive Reactive Hyperaemia (PORH) refers to the increase in skin blood flow caused by a brief period of arterial occlusion.[20] PORH provides a simple, non-invasive method for examining microvascular endothelial function and is frequently used to evaluate structural changes to blood vessels and vascular endothelial health.[20] The PORH test is used to assess endothelial function in a wide range of diseases, including peripheral arterial disease,[21] hypertension,[22] peripheral sensory neuropathy[23] and endothelium-dependent vasodilation in aging humans.[24] Other uses of PORH include assessing athletes' ability to recover from injury and delayed onset muscle soreness.[25,26] Microvascular assessment of endothelial function, by PORH with LDF monitoring, is considered more appropriate than flow-mediated dilatation (FMD, to assess arterial diameter, by ultrasound probe, in response to brachial artery occlusion and release). Paricularly as the FMD technique is poorly related to tissue perfusion and microvascular assessment of endothelial function.[27,28]

IPC therapy stimulates endothelial function[11] and IPC and AM have similar indications for use. Both IPC and AM are effective aids in the treatment of skin tissue injuries, for which improvements in blood flow are known to be a primary factor.[6] However, the long term effects of AM use on vascular endothelial health has yet to be explored. Therefore, the aim of this study was to assess the longitudinal use of AM on RBF, PORH and BskT measures.

Materials and Methods

Participants

The study included healthy participants. On arrival at the laboratory, all participants were provided with verbal and written information on the study protocol prior to providing informed consent and completing a PAR-Q (Physical Activity Readiness Questionnaire). Participants were excluded from participation in the study if they reported any conditions known to influence vascular function. Ethical approval to conduct the study was obtained

from the University of St Mark & St John Ethical Approval Committee (Reference No: EPO33).

Design

Participants were required to visit the laboratory on three occasions, each separated by a period of 8 weeks. The first visit (week 0) was used to establish baseline measures of RBF, PORH and BskT, blood pressure, capillary blood markers, and body composition. The second visit was after an 8 week period sleeping on an active mattress (Dreemflow® mattress, Dreamflow Ltd, Plymouth Science Park, Plymouth, England) (week 8). The final visit (week 16) followed an 8 week washout period whereby participants returned to sleeping on their own mattress. All measures recorded at baseline were repeated on each subsequent visit.

Baseline Testing

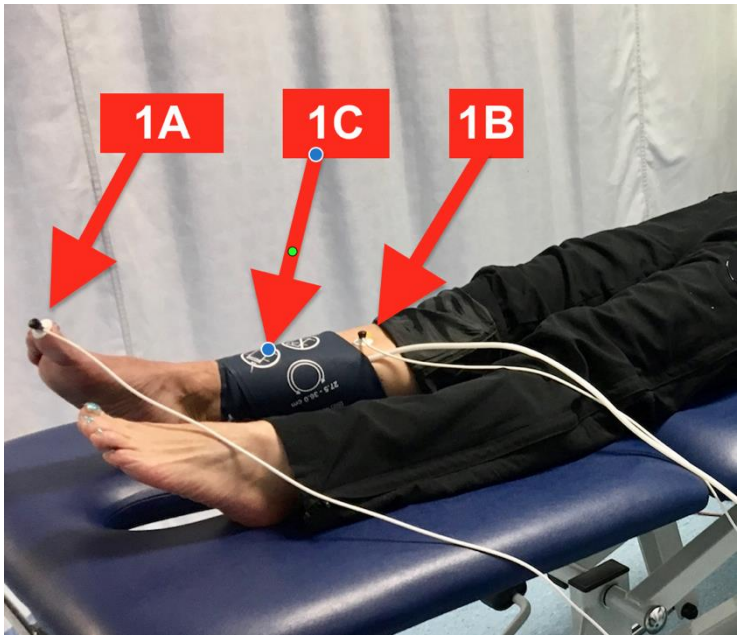
Participants were asked to undertake a 10-hour glucose fasting diet (overnight) to include refraining from beverages other than water before attending the laboratory at the University of St Mark and St John. Due to the risks of headaches and fatigue associated with fasting, all laboratory studies commenced at 7.00am and were completed by 11.45am. All participants were assessed between approximately 1.5 - 6 hours after waking. Apart from this restriction, participants were asked to maintain the same diet and lifestyle throughout the study. On arrival, participants were familiarised with the study environment, the staff and the study schedule; this period also enabled participants to feel safe, relaxed and to acclimatise. Blood and other tests were completed prior to a further 10 minutes of acclimatisation, lying supine, before the start of PORH testing, about 40 minutes after arrival. Laboratory temperature was measured by digital thermometer (Big-Digit Thermometer, Fisher Scientific, Bishop Meadow Road, Loughborough, Leicestershire, UK). Participants wore loose, comfortable clothing during each laboratory visit.

Participants' blood pressure, heart rate (MX2 Basic, Omron, Kyoto, Japan) and body composition (including total body water, extra cellular water, and inter cellular water) were assessed (Tanita Multi-Frequency Body Composition Analyser, MC-180MA, Tanita Corporation, Tokyo, Japan). Following this, fingertip capillary blood samples were taken

for, resting blood glucose and cholesterol (CardioChek, Polymer Technology Systems, Inc., Indianapolis, USA) and haemoglobin (Hemocue AB, Angelholm, Sweden).

Participants then moved onto a bed where they rested in a supine position for 10 minutes to allow for plasma volume stabilisation. For measurement of PORH, participants were instrumented with a pressure cuff and controller (MoorVMS-PRES, Moor Instruments, Axminster, UK) applied to the ankle of the right leg. A laser Doppler and temperature (LD/T) monitor and probe (MoorVMS-LDF2 dual Channel Laser Doppler with VP1T-V2 probe, Moor Instruments, Axminster, UK) was attached to the hallux pulp of the big toe of the right leg (Figure 1; 1A) for the PORH test; a second LD/T probe was attached approximately 1.5 cm above the pressure cuff (1C in figure 1) for the determination of peripheral blood flow. The combined LD/T probe was attached at the start of the final 10 minute acclimatisation period so that the stability of measurements could be verified before starting the PORH test. All blood flow measures were recorded as laser Doppler perfusion units (PU) and analysed using MoorVMS-PC v4.1 PC Software (Moor Instruments, UK). The participants were asked not to move or speak during blood flow measures.

Figure 1: Image of participant undergoing post occlusive reactive hyperaemia (PORH), resting blood flow (RBF) & baseline skin temperature (BskT) assessment. Labels 1A & 1B show the laser Doppler and temperature (LD/T) monitor and probe probe attachments, and 1C is the pressure cuff.



Following the 10-minute plasma volume stabilisation period RBF and PORH were measured. RBF was recorded as a 30s mean value. The PORH protocol entailed inflation of the ankle pressure cuff to a supra-systolic pressure of 180 mmHg and held for 3 minutes; the pressure cuff was then released, and the hyperaemic response was recorded over a 5 minute period.[29] BSkT at the Hallux Pulp was recorded throughout as an indirect estimate of blood flow changes.[30,31]

Data Analysis

PORH responses were assessed as the area under the skin blood flow response curve (AUC) after release of occlusion. Data was input and stored in a Microsoft Office Excel (version 16.19) spreadsheet (Microsoft Corporation, USA). Statistical software package SPSS (version 22.0, SPSS, Chicago, Illinois) was used for all statistical analyses. Parametric results were statistically compared using one-way repeated measures analyses of variance (ANOVA) with a Bonferroni adjustment. Where differences were indicated, post hoc pairwise comparisons were used to compare means. Probability values of <0.05 were considered statistically significant, and all tests were two-sided. All results are expressed as means (SD) unless otherwise stated.

Results

Ten healthy participants (six females and 4 males) aged 52.2 ± 13 y with a body mass of 76.3 ± 11.1 kg, were recruited into the study. The laboratory temperature remained between 22.6 and 23.8 °C. Participants confirmed there had been no significant changes to diet or lifestyle during the whole study period.

Laser Doppler mean RBF increased from 24.30 ± 38.26 PU at week 0 to 106.02 ± 100.34 PU at week 8 (p=0.021), a 336% increase. Mean RBF decreased after returning to the domestic mattress for 8 weeks to near pre-intervention levels at week 16 (table 1).

Vascular endothelial function, as asssessed by PORH (AUC), increased from 13,546 ± 10,225 PU.s at week 0s to 40,252 ± 23,995 PU.s at week 8 (p=0.003), a 197% increase. It decreased to near pre-intervention levels after returning to the domestic mattress for 8 weeks (Figure 2). Maximum hyperaemic LD blood flow showed a similar response (results not shown). BSkT at the hallux pulp, increased by 3.5°C between pre (week 0) and post-active mattress use (week 8), from 22.9 ± 2.5 ^{o}C to 26.4 ± 1.9 ^{o}C (p=<0.001); after the 8 week washout period, BSkT returned to 22.0 ± 2.3^{o}C . There were no significant changes in skin temperature pre and post PORH testing at each visit; this confirmed temperature stability of participants.

Blood pressure showed a trend towards improvement with active mattress use: 120/77, pre-active mattress use; 115/75 post active mattress; 124/83 post 8 weeks washout. Diastolic blood pressure fell post active mattress use (p=0.022) and showed a trend towards deterioration following the 8 week washout period (p=0.059).

Resting Heart Rate, Glucose and cholesterol remained stable throughout the 16-week study. Several small changes to body composition, including fat-free mass and basal metabolic rate, were statistically significant but these changes were within the margins of error of the assessment techniques used.

Table 1. Dynamic physiological measures assessed at each visit.

		Week 0	P (0-8)	Week 8	P (8-16)	Week 16	P (0-16)
Resting Blood Flow	Mean (PU)	24.30 ± 38.26	0.017	106.02 ± 100.34	0.021	28.53 ± 41.62	
PORH	Area U C (PU.s)	13,546 ± 10,225	0.001	40,252 ± 23,995	0.003	11,583 ± 9,212	
BskT	Hallux Pulp (°C)	22.9 ± 2.5	<0.001	26.4 ± 1.9	<0.001	22.0 ± 2.3	
	Leg (°C)	28.7 ± 1.3		29.4 ± 0.5	<0.001	28.7 ± 0.4	0.001
Blood Pressure	Systolic (mmHg)	120 ± 11	0.059	115-± 10	0.053	124-± 13	
	Diastolic (mmHg)	77-± 12		76-± 12	0.022	83 ± 14	0.059
Heart Rate	Heart Rate (BPM)	67 ± 7		66 ± 8		68 ± 9	

Mean ± SD values for resting blood flow (RBF), post occlusive reactive hyperaemia (PORH) and baseline skin temperature (BskT) at baseline, following an 8 week intervention period sleeping on an active mattress and following an 8 week washout period. Significant differences are shown for P<0.05 and where a trend is indicated (P<0.6): between week 0 versus week 8, P(0-8); week 8 versus week 16, P(8-16) and week 0 versus week 16, P(0-16). Abbreviations: RBF (resting blood flow), PORH (post occlusive reactive hyperaemia) BskT (baseline skin temperature), BP (blood pressure), Resting HR (resting heart rate).

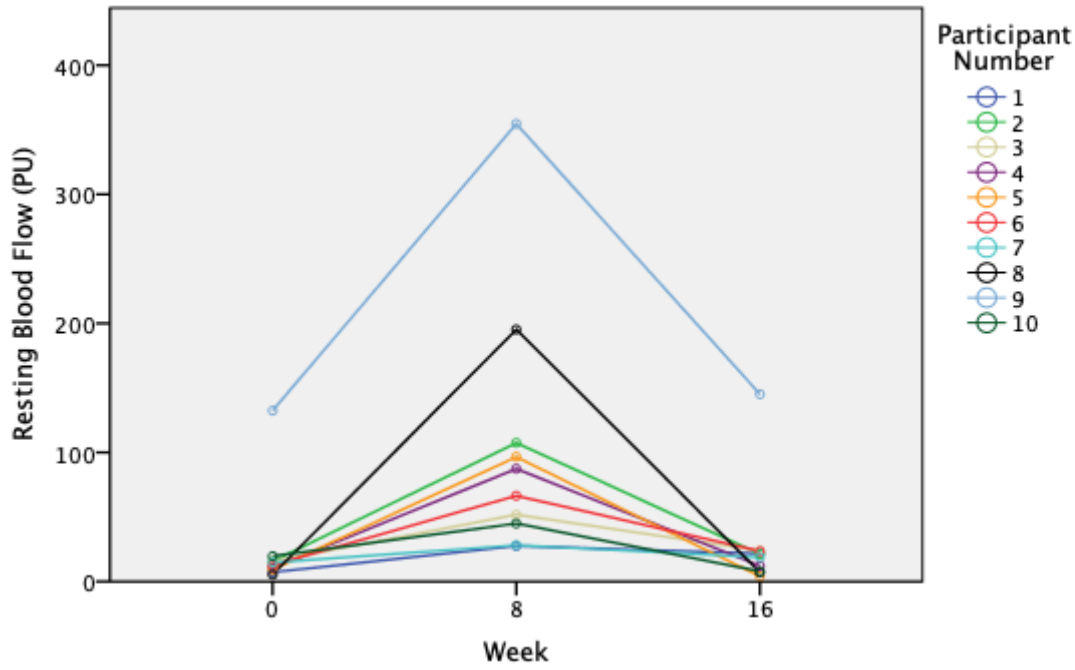
Table 2. Chronic physiological performance measures assessed at each visit

	Week 0	P(0-8)	Week 8	P(8-16)	Week 16	P(0-16)
Blood Glucose (mmol/l)	4.9 ± 0.2		4.9 ±0.1		4.9 ±0. 4	
Total Cholesterol (mg/dl)	4.5 ± 1.3		4.8 ±1.1		4.9 ±0.3	
HDL (mg/dl)	1.4 ± 0.5		1.5 ±0.4		1.4 ±0.4	
TC/HDL (mg/dl)	3.2 ±1.1		3.1 ±1.1		3.4 ±1.1	
Body Mass (kg)	73.4 ±18.0		73.5 ±18.1		72.7 ±18.2	0.047
Fat Free Mass (kg)	53.95 ±14.25	0.033	54.47 ±14.14	0.003	53.17 ±14.02	0.014
Basal Metabolic Rate (Cal)	1592 ± 403	0.024	1604 ± 402	0.001	1570 ± 397	0.006

Table 2. Mean ± SD values for resting heart rate, blood glucose, cholesterol and body composition following an 8 week intervention period sleeping on an active matress and following an 8 week washout period. Significant differences are shown for P<0.05: between week 0 versus week 8, P(0-8); week 8 versus week 16, P(8-16) and week 0 versus week 16, P(0-16).

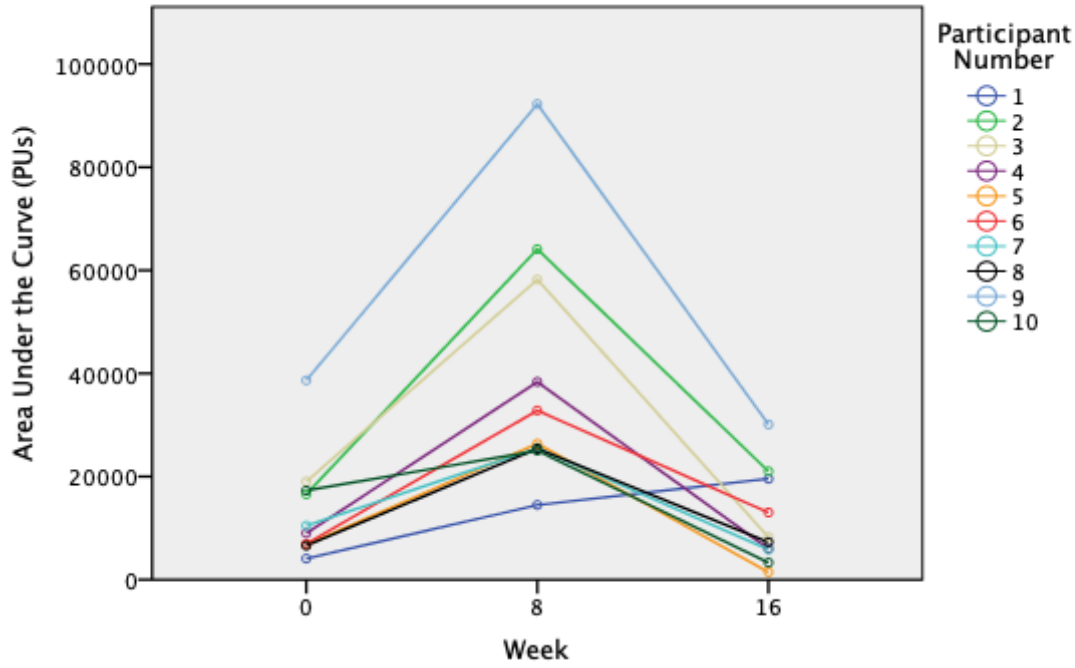
Abbreviations: HDL (high density lipoprotein), TC/HDL (total cholesterol / high density lipoprotein).

Figure 2: Schematic description of the analysis of Resting Blood Flow (PU)



All participants experienced an increase in resting blood flow following the use of the active mattress (p=0.021) and returned to near baseline (p=NS) following the 8-week washout.

Figure 3: Schematic description of the analysis of Area Under the Curve (PU's)



Participants experienced an increase in post occlusive reactive hyperaemia (PORH) area under the curve (AUC) PU.s (p=0.003), following the use of the AM, most returning to near baseline (p=NS) following the 8 week washout.

Discussion

The main finding of this study was that sleeping on an AM for 8 weeks, significantly improved vascular endothelial response as measured by PORH (197%), and indirectly by RBF (336%) and BSkT (3.5°C). Previous studies have demonstrated that the use of support surfaces can lead to changes in endothelial function,[5] BSkT[32] and RBF. [6,33] Goossens and Rithalia[5] demonstrated that heels placed on three different types of AM, resulted in one AM having significantly greater increases in PORH than the two other AM types. However, these measurements were taken for periods of less than 60 minutes, during AM use, and taken from the heels where skin tissue and LDT probe were in direct contact with the support surface, and therefore subject to the influences of interface pressure. Our study was the first to investigate the physiological effects of long-term use of AM, without acute influence of interface pressure. This has demonstrated that the effect of active mattress use is systemic, showing improvements in BSkT, RBF and endothelial function.

For the PORH test, occlusion at the ankle, with monitoring at the pulp of the hallux was considered appropriate, rather than brachial occlusion, as used for FMD, following observations by Roustit et al, 2008,[27] who demonstrated that microvascular impairment can exist in the absence of any impairment to macrovascular impairment. FMD with ultrasound or PORH with LDF, assessed at the brachial artery, could be a more appropriate assessment for many cardiovascular diseases. However, the skin sites most relevant to current AM use are the lower limbs and feet; due to the prevalence, pain and morbidity associated with pressure ulcers, leg ulcers and diabetic foot ulcers.

All participants on each of the 3 measurement occasions were assessed within 6 hours of using the AM. Following the 8 week washout period endothelial function, BSkT and RBF returned to near baseline, although at what time point this occurred requires further investigation. Givi[34] demonstrated that manual lymphatic massage amongst pre-hypertension females can alter blood flow for up to seventy-two hours post-intervention. They also reported significant reductions in both mean systolic and diastolic blood pressure compared to the control group.

The use of healthy, mature adults, to assess the long term effects of AM on endothelial function has not been previously reported but this group is more prone to age-related

vascular deterioration than the healthy, younger adults, as used by Goossens and Rithalia [5] ; (age 23.9 ± 2.1 / BMI 21.0 ± 2.4 kg/m^2).

As one of the primary roles of the endothelium is to regulate blood flow,[7,11] and as improvements in RBF are used to discern improvement in endothelial function,[14] the current finding that RBF improved post active mattress use is the first indication that use of the AM can lead to an improvement in endothelial function.

PORH is an established method of testing endothelial function.[35,20,25] PORH assessments are an effective means of assessing endothelial health because the rate, duration, and extent of endothelium-dependent vasodilation affects the rate and quantity of returning blood flow following the period of arterial occlusion. The reproducibility of PORH has been found to be fair to good.[20] PORH responses are significantly reduced in patients with cardio-metabolic diseases, compared to healthy subjects[36] and significantly reduced amongst healthy sedentary participants versus highly trained athletes.[25]

This study noted a highly significant,196% increase in PORH following the use of the AM ; 13,456 ± 10,225 pu.s (wk 0) versus 40,252 ± 23,995 pu.s (wk 8) before declining to near baseline at week 16. The PORH result confirms a significant improvement in endothelial function post active mattress use.

The changes to endothelial function as a result of AM intervention is hypothesised to be similar to that of IPC therapy. Previous studies on IPC devices have shown that air cell inflation results in a pressure gradient that accelerates RBF by over 200%, distending the lumen, whilst exerting up to a 20% increased shear stress on the endothelial cells.[11]

Chen *et al.,* [11] reported that improvements in vascular tone, the healing of damaged blood vessels and an increased capillarization of tissue are all attributable to improved endothelial function. Future studies may, therefore, benefit from observing potential changes in angiogenesis and vascular healing with AM use. The increase in peripheral blood flow is particularly important because it is known to decline with age and poor lifestyle.[38]

Healthy adults have been shown to reposition every 11.6 minutes whilst asleep in bed,[4] in order to stimulate reactive hyperemia naturally, which is the body's way of ensuring

adequate blood flow and tissue regeneration. Our data suggest that following use of AM, this natural cycle can be augmented to improve blood flow and endothelial function. This has exciting possibilities as a means of offsetting, delaying or potentially reversing vascular disease associated with endothelial dysfunction.

Our observation of improved endothelial function suggests potential therapeutic effect of AM use in a wide range of conditions where endothelial dysfunction has been observed, including hypercholesterolaemia,[37,38] heart failure and exercise capacity,[39.40] diabetic neuropathy[23] and hypertension,[22] although future research would be needed to explore these potential benefits of AM use.

Blood pressure in this study remained stable and within the healthy range; it trended towards improvement following 8 weeks of AM use, but there was an unnexplained increase in BP at 16 weeks versus baseline, so the suggested improvement at week 8 also requires further investigation.

Resting heart rate remained stable throughout the 16-week study indicating a minimal impact from other potential influences on cardiovascular function. Future research on the effects of AM use in hypertension is required. Glucose remained stable throughout the study. Similarly, there were no significant changes to cholesterol levels. Whilst endothelial cells maintain cholesterol homeostasis by down-regulating cholesterol synthesis,[41] significant changes were not anticipated due to the healthy population sampled. Previous studies have shown massage therapy and moderate exercise effective in treating hypercholesterolemia through mechanisms of action similar to those augmented through AM.[42,43,44] Therefore further research should explore the affects of AM use in cardiovascular diseases. There is evidence that improved endothelial function can improve basal metabolic rate and help to reduce body fat.[45]

Changes to body composition that are related to endothelial function, such as basal metabolic rate [46] were improved with AM use, but given the tolerance variability of the body composition monitor used, the 3% changes identified in our data fall within this margin suggesting measures associated with body composition and hydration remained essentially stable over the 16 weeks. The absence of significant changes to body composition, glucose and cholesterol levels were a further indication that diet and lifestyle did not change significantly during the study.

Limitations

This pilot study included a small cohort of healthy participants, and there were no objective assessments of compliance or hours of AM use; subjectively, participants confirmed, via questionnaire, that sleep habits were unchanged although, anecdotally, many reported feeling better and free from morning stiffnes after AM use. Objective assessments of AM use should be considered in a future study but must avoid excessive intrusion into the personal lives of participants. AM use was in participant's homes, therefore additional factors were uncontrolled: mattress underlying the AM, room temperature and dietary routine. However, the lack of significant differences in body composition and blood markers indicate that these factors were likely to be constant over the 16-week duration of the study for each participant.

The baseline LD recording period was limited to 30 seconds. Although this period is long enough to average over cardiac and respiratory oscillations, a longer period would be required to cover lower frequency oscillations (Stefanovska et al, 2001).[47] The practical limitations on duration of clinical testing also needs to be considered.

This study has only assessed the use of one AM; whilst AM that apply and relieve interface pressures may stimulate endothelial function, the degree by which the endothelium responds to these pressures will depend on several variables. These include the duration and intensity of pressure (at the application and at relief) and the subject's tissue tolerance to pressure.[48] Further research is required to establish the effects of these three variables on endothelial function, BSkT, RBF. Further studies are also needed to establish the duration of AM use to elicit beneficial improvement to endothelial function and to establish the duration of benefit following cessation of AM use in clinical populations. It will also be important to assess the health economics of AM use and how provision might be funded. For many, personal, domestic purchase and use will be a practical option for self management of disease.

Conclusions

This study found significant improvement in RBF, PORH, and BskT over the 8 weeks of AM use which returned to normal following the 8 week washout period. This has been

attributed to stimulation by the application of pressure as well as pressure relief. We suggest that AM use might have a wide range of applications where the promotion of blood flow and improved endothelial function would be beneficial. AM use as an aid to the treatment of conditions where endothelial dysfunction has been identified are areas for future research.

Conflict of Interest.

Gary Baker is the clinical director with Squirrel Medical® Ltd and co inventor of the Dreemflow mattress. Dr Rodney Gush is an employee of Moor Instruments, the company that manufactured the blood flow monitoring equipment.

References

1. Phillips, L., Goossens, R., Takahashi, M. and Clark, M. Defining active pressure redistribution. Wounds International. 2012; 3: 1, 52 - 56.
2. Gunther, R., Clark, M. The effect of a dynamic pressure-redistributing bed support surface upon systemic lymph flow and composition. Journal of Tissue Viability. 2000; 10: 3, 10 -15
3. Ovens, L. Selecting a support surface how to guide. Wound Essentials. 2012; 7: 2, 2 - 4
4. Keane, F. The minimum physiological mobility requirements for a man supported on a soft surface. Paraplegic. 1978; 16: 383-389
5. Goossens**,** R., Rithalia, S. Physiological response of the heel tissue on pressure relief between three alternating pressure air mattresses. Journal of Tissue Viability. 2008; 17: 1, 10 - 14.
6. Bergstrand, S., Kallman, U., Ek, A. et al. Microcirculatory responses of sacral tissue in healthy individuals and inpatients on different pressure-redistribution mattresses. Journal of Wound Care. 2015; 24: 8, 346 - 358.
7. Biddle, C. Like a slippery fish, a little slime is a good thing: The glycocalyx revealed. AANA Journal. 2013; 81: 6, 473 - 480.
8. Celermajer, D.S. Endothelial dysfunction: Does it matter? Is it reversible? Journal of the American College of Cardiology. 1997; 30: 2, 325 – 333
9. Khazaei, M., Moien-afshari, F., Laher, I. Vascular endothelial function in health and diseases. Pathophysiology. 2008; 15: 1, 49 - 67.
10. Widmer, J., Lerman, R. Endothelial dysfunction and cardiovascular disease. Global Cardiology Science and Practice. 2014; 3. 291-308
11. Chen**,** A., Frangos, S., Kilaru, S., Sumpio, B. Intermittent pneumatic compression devises - Physiological mechanisms of action. European Journal of Vascular and Endovascular Surgery. 2001; 21: 5, 383 - 392.
12. Martin, J., Martin**,** A., Mumford, P. et al. Unilateral application of an external pneumatic compression therapy improves skin blood flow and vascular reactivity bilaterally. *Peer J*. 2018; 29: 6, 1-18
13. Alvarez, O., Wendelken, M., Markowitz, L., Comfort, C. Effect of High-pressure, Intermittent Pneumatic Compression for the Treatment of Peripheral Arterial Disease and Critical Limb Ischemia in Patients Without a Surgical Option. Wounds. 2015; 27: 11, 293 – 301.

14. Sheldon R., Roseguini B., Thyfault J. et al. Acute impact of intermittent pneumatic leg compression frequency on limb hemodynamics, vascular function, and skeletal muscle gene expression in humans. Journal of Applied Physiology. 2012; 112: 12, 2099 - 2109.
15. Khanna, A., Gougoulias, N., & Maffulli, N. Intermittent pneumatic compression in fracture and soft-tissue injuries healing. British Medical Bulletin. 2008; 88: No. 1, 47-56.
16. Mohamed, F., El-deen, H. Effect of Intermittent Pneumatic Compression Therapy on Healing of Diabetic Foot Ulcer. International Journal of Diabetes Research. 2015; 4: 4, 67 -72.
17. Stevens, S., Woller, S. Intermittent pneumatic compression in patients with stroke. The Lancet. 2013; 382: 9891, 484 - 486.
18. Hanson, E., Stetter, K., Li, R., Thomas, A. An Intermittent Pneumatic Compression Device Reduces Blood Lactate Concentrations More Effectively Than Passive Recovery after Wingate Testing. Journal of Athletic Enhancement. 2013; 2:3, 1-4.
19. Pawlaczyk, K., Gabriel, M., Urbanek, T. et al. Effects of intermittent pneumatic compression on reduction of postoperative lower extremity edema and normalization of foot microcirculation flow in patients undergoing arterial revascularization. Medical Science Monitor. 2015; 21: 21, 3986 - 3992.
20. Agarwal, SC, Allen J, Murray A and Purcell IF. Comparative reproducibility of dermal microvascular blood flow changes in response to acetylcholine iontophoresis, hyperthermia and reactive hyperaemia. Physiol. Meas. 31 (2010) 1–11..
21. Wahlberg, E., Jörneskog, G., Olofsson, P. et al. The influence of reactive hyperemia and leg dependency on skin microcirculation in patients with peripheral arterial occlusive disease (PAOD), with and without diabetes. Vasa. 1990; 19: 4, 301 - 6.
22. Farkas, K., Nemcsik, J., Kolossváry, E. Impairment of skin microvascular reactivity in hypertension and uraemia. Nephrology Dialysis Transplantation. 2005; 20: 9, 1821 - 1827.
23. Barwick, A., Tessier, A., De Jonge J. Peripheral sensory neuropathy is associated with altered post-occlusive reactive hyperemia in the diabetic foot. British Medical Journal Open Diabetes Research and Care. 2016; 4: 1, 1 - 6.
24. Kirby, B., Brett S., Voyles, W. et al. Endothelium-dependent vasodilatation and exercise hyperaemia in aging humans: Impact of acute ascorbic acid administration. Journal of Physiology. 2009; 587: 9, 1989 - 2003.

25. Heylen, E., Simon, B., Guerrero, F. et al. Reactive hyperaemia in the forearm skin of highly trained windsurfers. International Journal of Sports Medicine. 2005; 26: 10, 822 - 826.
26. Durand**,** M., Gutterman, D. Exercise and vascular function: How much is too much?. Canadian Journal of Physiology and Pharmacology. 2014; 92: 7, 551 - 557.
27. Roustit, M., Simmons, G., Baguet, J. et al. Discrepancy between simultaneous digital skin microvascular and brachial artery macrovascular post-occlusive hyperemia in systemic sclerosis. Journal of Rheumatology. 2008; 35: 8, 1576 - 1583.
28. Ibrahimi, K., De Graaf, Y., Draijer, R. et al. Reproducibility and agreement of different non-invasive methods of endothelial function assessment. Microvascular Research Journal. 2018; 117: 50 - 56
29. Jarm, T., Kragelj, R., Liebert, A. et al. Postocclusive Reactive Hyperemia in Healthy Volunteers and Patients With Peripheral Vascular Disease Measured by Three Noninvasive Methods. In: Dunn J.F., Swartz H.M. (eds) Oxygen Transport to Tissue XXIV. Advances in Experimental Medicine and Biology. 2003; 530: 661 - 669. Springer, Boston, MA.
30. Rubinstein, E., Sessler, D. Skin-Surface temperature Gradients Correlate with fingertip blood flow. Anesthesiology. 1990; 73:3,541-545.
31. Joly, H., Weil, M. Temperature of the Great Toe as an Indication of the Severity of Shock. Circulation. 1969; 39:1, 131 - 138.
32. Posada-Moreno, P., Iglesias, M., De Bengoa Vallejo, R. et al. Influence of different bed support surface covers on skin temperature. Contemporary Nurse. 2011; 39: 2, 206 – 220.
33. Rothenberger, J., Krauss, S., Held, M. et al. A quantitative analysis of microcirculation in sore-prone pressure areas on conventional and pressure relief hospital mattresses using laser Doppler flowmetry and tissue spectrophotometry. Journal of Tissue Viability. 2014; 23: 4, 129 – 136
34. Givi, M. Durability of effect of massage therapy on blood pressure. International Journal of Preventive Medicine. 2013; 4: 5, 511- 516.
35. Carasca, C., Magdas, A., Tilea, I., Incze, A. Assessment of Post-Occlusive Reactive Hyperaemia in the Evaluation of Endothelial Function in Patients with Lower Extremity Artery Disease. Acta Medica Marisiensis. 2017; 63: 3, 129 -132.

36. Cordovil, I ., Huguenin, G., Rosa, G. et al. Evaluation of systemic microvascular endothelial function using laser speckle contrast imaging. Microvascular Research. (2012) Vol. 83, No. 3: 376–379.
37. Steinberg, H. O., Bayazeed, B., Hook, G. et al. Endothelial dysfunction is associated with cholesterol levels in the high normal range in humans. Circulation. 1997; 96: 10, 3287 - 3293.
38. Jani, B., Rajkumar, C, Ageing and Vascular Ageing. Postgraduate Medical Journal. 2006; 82: 968, 357 - 362.
39. Andreassen, A., Gullestad, L., Holm, T. et al. Endothelium-dependent vasodilation of the skin microcirculation in heart transplant recipients. *Clinical Transplantation*. 1998; 12: 4, 324 – 332
40. Hambrecht, R., Fiehn, E., Weigl, C. et al. Regular physical exercise corrects endothelial dysfunction and improves exercise capacity in patients with chronic heart failure. Circulation. 1998; 98: 24, 2709 - 2715.
41. Hassan, H., Denis, M., Krimbou, L. et al. Cellular cholesterol homeostasis in vascular endothelial cells. The Canadian Journal of Cardiology. 2006; 22: 35 - 40.
42. Hur, M., Oh, H., Lee, M. et al Effects of aromatherapy massage on blood pressure and lipid profile in Korean climacteric women. *International Journal of Neuroscience*. 2007; 117: 9, 1281 - 1287.
43. Franklin, N., Ali, M., Robinson, M. et al. Massage therapy restores peripheral vascular function after exertion. Archives of Physical Medicine and Rehabilitation. 2014; 95: 6, 1127 - 1134.
44. Chatzizisis, Y., Coskun, A., Jonas, M. et al. Role of Endothelial Shear Stress in the Natural History of Coronary Atherosclerosis and Vascular Remodeling Journal of the American College of Cardiology. 2007; 49: 25, 2379 - 2393;
45. De Moraes, R., Van Bavel, D., Gomes. et al. Effects of non-supervised low-intensity aerobic excise training on the microvascular endothelial function of patients with type 1 diabetes. A non-pharmacological interventional study. BMC Cardiovascular Disorders. 2016; 16: 1, 1–9.
46. Olive, J. L., Ballard, K. D., Miller, J. J., Milliner, B. A. Metabolic rate and vascular function are reduced in women with a family history of type 2 diabetes mellitus. Metabolism: Clinical and Experimental. 2008; 57: 6, 831 - 837
47. Stefanovska, A., Luchinsky, D.G., McClintock, P.V.E. Modelling couplings among the oscillators of the cardiovascular system. Physiological Measurement. 2001; 2: 3, 551-564

48. Kruger, E.A., Pires, M., Ngann, Y. et al. Comprehensive management of pressure ulcers in spinal cord injury: Current concepts and future trends. The Journal of Spinal Cord Medicine. 2013; 36: 6, 572 - 585.