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ORIGINAL ARTICLE

Compression socks and the effects on coagulation and fibrinolytic activation during marathon running

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Abstract

Purpose Compression socks are frequently used in the treatment and prevention of lower-limb pathologies; however, when combined with endurance-based exercise, the impact of compression socks on haemostatic activation remains unclear.

Objectives To investigate the effect of wearing compression socks on coagulation and fibrinolysis following a marathon.

Methods Sixty-seven participants [43 males (mean ± SD: age: 46.7 ± 10.3 year) and 24 females (age: 40.0 ± 11.0 year)] were allocated into a compression (SOCK, $n = 34$) or control (CONTROL, $n = 33$) group. Venous blood samples were obtained 24 h prior to and immediately POST-marathon, and were analyzed for thrombin–anti-thrombin complex (TAT), tissue factor (TF), tissue factor pathway inhibitor (TFPI), and D-Dimer.

Results Compression significantly attenuated the post-exercise increase in D-Dimer compared to the control group [median (range) SOCK: + 9.02 (− 0.34 to 60.7) ng/mL, CONTROL: + 25.48 (0.95–73.24) ng/mL]. TF increased following the marathon run [median (range), SOCK: + 1.19 (− 7.47 to 9.11) pg/mL, CONTROL: + 3.47 (− 5.01 to 38.56) pg/mL] in all runners. No significant post-exercise changes were observed for TAT and TFPI.

Conclusions While activation of coagulation and fibrinolysis was apparent in all runners POST-marathon, wearing compression socks was shown to reduce fibrinolytic activity, as demonstrated by lower D-Dimer concentrations. Compression may reduce exercise-associated haemostatic activation when completing prolonged exercise.

Keywords Compression · D-dimer · Tissue factor · Tissue factor pathway inhibitor · Thrombin–anti-thrombin complexes

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Abbreviations

DVT	Deep vein thrombosis
ELISA	Enzyme-linked immunosorbent assay
TAT	Thrombin–anti-thrombin complex
TF	Tissue factor
TFPI	Tissue factor pathway inhibitor

Introduction

While physical activity and exercise appear to protect against thromboembolic episodes (Posthuma et al. 2015), exercise has long been recognized to induce transient activation in blood coagulation (Prisco et al. 1998), platelet aggregation (Kestin et al. 1993), and fibrinolytic activity (Molz et al. 1993), increasing the potential for deep vein thrombosis (DVT). The degree to which these systems are activated is often dependent upon the duration and intensity of the exercise, together with the study population investigated (ElSayed et al. 1995). Evidence for the activation

of the coagulation system following strenuous endurance exercise (i.e., marathon distance, 42.2 km) is reflected by specific markers of in-vivo thrombin generation such as thrombin–anti-thrombin complexes (TAT) (Parker et al. 2011; Prisco et al. 1998) and prothrombin fragment 1 + 2 (Bartsch et al. 1995; Kupchak et al. 2013; Sumann et al. 2007). TAT has been widely used as a valuable marker of activated blood coagulation during exercise, with significant increases in TAT reported immediately POST-marathon (Parker et al. 2011; Prisco et al. 1998; Sumann et al. 2007), and also following endurance exercise of shorter duration (Bartsch et al. 1995; Weiss et al. 1998).

The fibrinolytic system is activated in unison with the coagulation system, presumably to preserve haemostatic balance (Parker et al. 2011). This has been demonstrated by elevated measures of D-Dimer, a marker of in-vivo fibrin degradation, in addition to TAT, immediately upon marathon completion (Hilberg et al. 2003; Prisco et al. 1998). However, the regulation and activation of haemostasis is complex and involves many factors other than TAT and D-Dimer.

While 1 in 1000 athletes will experience a post-exercise thromboembolic event (Hilberg et al. 2002), exercise-induced haemostatic activation may not be detrimental to most participants. However, the risk of an adverse event is compounded by underlying and acquired risk factors associated with hypercoagulability such as oral contraceptive use and long-haul travel, dehydration (Para et al. 2015). Several case studies documenting the occurrence of deep vein thrombosis in otherwise healthy athletes following endurance-based exercise have been documented (Hull et al. 2015; Theiss et al. 2011), highlighting the potentially detrimental effects of athletic training that may in the worst case scenario, result in a fatality.

Compression socks are frequently used for the treatment and prevention of lower extremity clinical pathologies, including DVT, with compression socks shown to maintain the coagulation and fibrinolytic balance through increases in both venous and arterial blood flow (Benko et al. 2001). The use of clinical compression garments has been transferred to the sporting industry, and continues to grow in popularity due to the anticipated enhancement of exercise performance and recovery (Kraemer et al. 2001), despite a lack of clear scientific evidence of their effects on physiology. The impact of compression socks on haemostatic activation during endurance exercise has rarely been investigated, with only one previous study with a small sample size ($n = 20$) reporting a decrease in overall haemostatic activation following a marathon when compression socks were worn (Zaleski et al. 2015a). It was hypothesized that when worn during a marathon, compression socks will reduce haemostatic activation. Therefore, the aim of this study was to investigate the effect of compression socks on exercise-induced activation of the coagulation and fibrinolytic systems when worn during strenuous endurance exercise.

Methods

Participants

Forty-three males (mean ± SD: age: 46.7 ± 10.3 year, height: 1.80 ± 0.1 m, body mass: 77.7 ± 13.1 kg) and 24 females (age: 40.0 ± 11.0 year, height: 1.60 ± 0.1 m, body mass: 58.0 ± 9.3 kg) were recruited to participate in the study through an email sent to all registered marathon runners ($n = 6216$), with runners also recruited the day before the 2016 Gold Coast Marathon (Gold Coast, Queensland, Australia) at the Gold Coast Exhibition Centre. All consenting study participants (recruited via email and the day prior to the marathon) who were screened by the primary researcher to ensure all participants were non-smokers, with no known history or clinical signs of metabolic conditions or coagulation disorders. Participants were excluded from the study if they had a previous history of thromboembolism. Female participants were excluded if they were taking the oral contraceptive pill, with all participants required to be illness and injury free, while avoiding the use of anti-coagulant (i.e., aspirin, heparin, and warfarin) and non-steroidal anti-inflammatory medications for at least 2 weeks before, and throughout the testing period. Furthermore, participants were to avoid the use of all types of compression garments while traveling to the Gold Coast and in the lead up to the marathon itself. Participants were provided with a written description of the risks and benefits of the study and provided signed informed consent prior to their inclusion within the study. Details that may disclose the identity of the subjects have been omitted. All human studies have been approved by the appropriate ethics committee and have, therefore, been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Study overview

This was a randomized control trial investigating the effects of compression socks on strenuous exercise-induced activation of coagulation and fibrinolysis. All participants recruited were randomly assigned using a computer generated code to either the control [CONTROL, 21 males and 12 females ($n = 33$)] or the compression sock [SOCK, 22 males and 12 females ($n = 34$)] group. Foot-to-knee compression socks were provided by 2XU (24/7 Compression Socks, 2XU North America LLC, Carlsbad, CA, USA) to participants within the SOCK group, with sock size dependent upon shoe size and self-reported lower leg circumference.

Marathon characteristics

The marathon began at 07:30 h and was completed on a flat terrain with no elevation, at an average temperature of 16.4 ± 4.3 °C and 69.0 ± 20.4% relative humidity.

PRE-marathon venous blood sample

Twenty-four hours prior to the marathon, all participants reported to the Gold Coast Exhibition Centre between 10:00 and 14:00 h for the collection of a PRE-marathon venous blood sample. During this visit, participants within the SOCK group received their compression socks and were instructed to wear their socks to the marathon, during the marathon and following the marathon until the POST-marathon blood draw (immediately POST: ~ 10–20 min). Participants within the CONTROL group were instructed to refrain from wearing any type of compression garment prior to the first venous blood sample (PRE-marathon), and throughout the duration of the marathon and the recovery period (i.e., marathon completion until POST-marathon venous blood sample collection).

POST-marathon venous blood sample

A second venous blood sample was collected immediately within 10–20 min upon completion of the marathon (POST) in a medical tent, less than 100 m from the finish line between ~ 10:00 and 14:00 h.

Blood sample collection

Blood samples were drawn without stasis by venepuncture from the antecubital fossa from participants in a supine position. Blood samples for determining markers of coagulation and fibrinolysis were collected into 3.8% sodium citrate Vacutainers® (Becton Dickinson, New Jersey, USA). Within 4 h of collection, citrated blood samples were centrifuged at room temperature for 15 min at 2000*g*. Plasma supernatant samples were aliquoted and stored at − 80 °C until required for analysis.

Blood sample analyses

Tissue factor (TF), tissue factor pathway inhibitor (TFPI), thrombin–anti-thrombin complexes (TAT), and D-Dimer were determined by enzyme-linked immunosorbent assay (ELISA) kits (Abcam, Melbourne, Australia) according to manufacturer's instructions. Inter-assay coefficients of variation were below 6.2% and Intra-assay coefficients were below 5.9% and. The minimal detectable dose for TF, TFPI, TAT and D-Dimer were ~ 4 pg/mL, 14.9 pg/mL, ~ 0.5 ng/mL, and 71 pg/mL, respectively. All samples were measured in duplicate. Absorbance for each marker was read using an infinite 200 PRO Spectrophotometer (Tecan Trading, AG, Männedorf, Switzerland). Changes in plasma volume were calculated for TF, TFPI, TAT, and D-Dimer as described in the literature according to the method of Dill and Costill (1974).

Statistical analysis

A Shapiro–Wilk test was used to assess normality of distribution, with all markers of haemostasis (TAT, TF, TFPI, and D-Dimer) non-parametrically distributed. All statistical analyses were performed using GraphPad Prism version 5.03 for Windows (GraphPad software, La Jolla California, USA). Baseline participant characteristics (age, weight, BMI, training volume), overall marathon finishing time, differences between groups in PRE- and POST-marathon measures of haemostasis (TAT, TF, TFPI, and D-Dimer), along with differences in the magnitude of change (PRE–POST), were analyzed using a Mann–Whitney *U* Test. Cohen's effect sizes (*d*) were calculated from PRE–POST blood values within and between conditions (CONTROL versus SOCK), calculated as $d_{NP} = Z/\sqrt{N}$ where $_{NP}$ is non-parametric, Z is the z-score calculated from Wilcoxon signed-rank test, and N is the number of participants, and interpreted as small < 0.2, moderate > 0.5 or large > 0.8 (Cohen 1992). Results are presented as median (range), unless otherwise stated.

Results

Participant characteristics

There were no significant differences in baseline characteristics between groups for age, mass, body mass index (BMI), and training volume (h wk^{1}) (all $p > 0.05$) (Table 1).

Coagulation and fibrinolytic responses

PRE- and POST-marathon coagulation and fibrinolytic results for CONTROL and SOCK groups are presented in Table 2. Plasma concentrations of TAT, TF, TFPI, and D-Dimer did not differ between groups at baseline ($p = 0.328$, $p = 0.063$, $p = 0.278$ and $p = 0.807$, respectively). Significant increases in PRE- to POST-marathon measures of TF and D-Dimer were observed in both the CONTROL ($p = 0.001$) and SOCK groups ($p < 0.05$), while no significant changes in TAT and TFPI were observed (all $p > 0.27$) (Table 2). The magnitude of post-exercise increase in D-Dimer was smaller in the SOCK group (9.03 (− 0.34 to 60.8) ng/mL) compared to the CONTROL group (25.5 (0.95 –73.2) ng/mL; $p = 0.008$, $d_{NP} = 0.43$) (Fig. 1). The difference

Table 1 Mean (±SD) baseline measures of physical and performance characteristics for the SOCK versus CONTROL participants

Variable	CONTROL ($n=33$)	SOCK ($n=34$)	P value
Age (years)	45.2 ± 11.5	43.5 ± 10.5	0.662
Body mass (kg)	69.6 ± 15.6	71.4 ± 14.9	0.512
Body mass index (kg m^{-2})	23.2 ± 3.5	23.8 ± 3.1	0.379
Training volume (h min wk^{-1})	5:02 ± 2:13	4:39 ± 1:58	0.147

Table 2 Thrombin–anti-thrombin complex (TAT), tissue factor (TF), tissue factor pathway inhibitor (TFPI), and D-Dimer measured PRE- and POST-marathon for the CONTROL and SOCK groups

	CONTROL ($n=33$)				SOCK ($n=34$)			
	PRE	POST	P value	d_{NP}	PRE	POST	P value	d_{NP}
TAT (ng/mL)	3.19 (0.16–6.28)	3.09 (0.56–7.31)	0.272	0.14	2.47 (0.34–7.31)	2.48 (0.99–7.78)	0.400	0.10
TF (pg/mL)	3.86 (0.00–5.53)	7.41 (2.16–42.5)	< 0.001*	0.54	5.06 (0.13–14.2)	5.84 (0.84–17.1)	0.040*	0.26
TFPI (ng/mL)	24.85 (0.29–77.33)	22.70 (0.28–88.50)	0.840	0.03	17.9 (0.50–48.5)	17.3 (0.41–72.6)	0.490	0.09
D-Dimer (ng/mL)	5.22 (0.00–24.14)	33.71 (5.27–88.00)	< 0.001*	0.70	5.50 (0.05–33.3)	16.7 (1.02–78.2)	< 0.001*	0.43

Data are presented as median (range)

*Significant difference between PRE- and POST-marathon values within group. d_{NP} = effect size

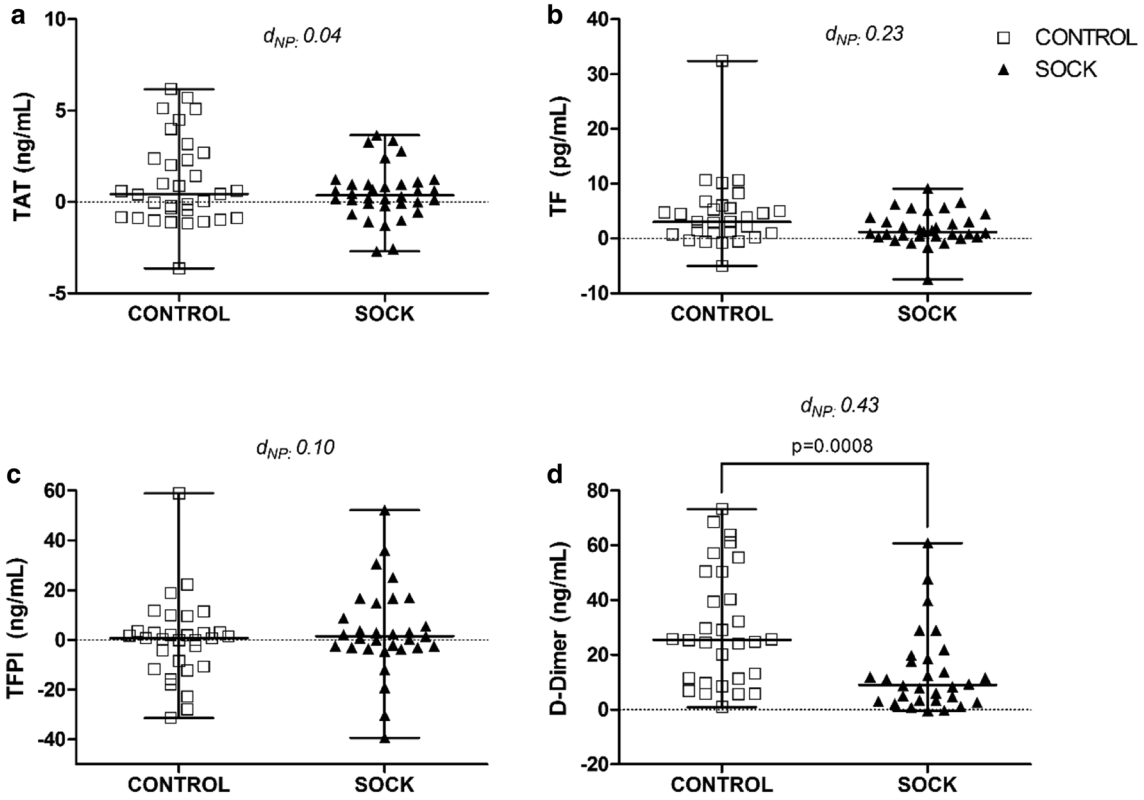

Fig. 1 Median (range) magnitude of change (Δ) between PRE–POST measures of **a** thrombin–anti-thrombin complexes (TAT), **b** tissue factor (TF), **c** tissue factor pathway inhibitor (TFPI), and **d** D-Dimer for the CONTROL and SOCK groups. d_{NP} = effect size

between the CONTROL and SOCK groups in the magnitude of post-exercise change was small for TAT, TFPI, and TF (all $d_{NP} < 0.23$) (Fig. 1).

Marathon finish time

No significant differences ($p = 0.106$) were observed in official marathon finishing times when comparing the SOCK and CONTROL groups (4:29:23 ± 1:17:19 and 4:27:26 ± 1:16:15, respectively).

Discussion

The aim of this study was to investigate the effect of compression socks on strenuous exercise-induced activation of the coagulation and fibrinolytic systems of haemostasis following a marathon. Wearing compression socks during a marathon attenuated the post-exercise increase in D-Dimer concentration. In addition, acute activation of coagulation and fibrinolysis was observed immediately POST-marathon, as reflected by significant increases in plasma concentrations of TF and D-Dimer, regardless of whether SOCKS were worn.

Within the present study, and in line with previous research (Kupchak et al. 2013; Parker et al. 2011; Siegel et al. 2001), marathon running was associated with elevated concentrations of D-Dimer. Indeed, our findings are similar to those of Siegel et al. (2001) in which a significant increase in POST-marathon concentrations of D-Dimer (177 ± 137 to 29 ± 279 ng/ml; $p < 0.001$) was observed within 4 h of marathon completion. When worn during a marathon, compression socks were shown to reduce the magnitude of increase in POST-marathon concentrations of D-Dimer (Fig. 1), contrasting the findings of Zaleski et al. (2015a) in which concentrations of D-Dimer did not differ between when compression socks were worn versus not worn at any given time point (i.e., PRE-, POST- + 24 h POST-marathon). However, Zaleski et al. (2015a) failed to present the PRE- and POST-marathon data for D-Dimer itself; therefore, these findings should be interpreted with caution. Compression socks and pneumatic calf compression devices appear to increase fibrinolytic activity (Tarnay et al. 1980) through inhibiting components associated with Virchow's Triad (i.e., venous stasis, hypercoagulability, and vessel wall damage), ultimately reducing the risk of thrombosis formation. Indeed, in a case study by Zaleski et al. (2015b), plasma concentrations of D-Dimer were reported to be ~ 30% lower in a single runner with a genetic pre-disposition to blood clotting (i.e., F5 1691 A risk allele, Factor V Leiden mutation) when compression socks were worn versus not worn over two marathon runs. Therefore, when worn during a marathon, compression socks may reduce the potential for clot formation, as indicated by reduced D-Dimer (clot fibrinolysis) formation. However, research on the use of compression socks to maintain the balance of both the coagulation and fibrinolytic systems during prolonged strenuous exercise is limited; therefore, further investigations are required to verify the findings of the present study and those of Zaleski et al. (2015a, b).

In agreement with previous research (Bartsch et al. 1995; Parker et al. 2011; Sumann et al. 2007), simultaneous activation of the coagulation system was observed in all participants as indicated by significant increases in TF [the primary activator of the TF-coagulation pathway (El-Hagracy et al. 2010)], regardless of whether compression socks were worn (Table 2). The present findings are in contrast to those of Weiss et al. (2002) who failed to demonstrate a significant increase in post-exercise concentrations of TF (205 ± 43 to 218 ± 47 pg/ml; $p > 0.05$, $d = 0.29$) albeit in a shorter duration (1 h) maximal run, suggesting the duration of the exercise itself may be a factor in exercise-induced activation of coagulation. In addition, when comparing the magnitude of change between the CONTROL and SOCK groups, a non-significant difference with a small ES was observed within plasma concentrations of TF (Fig. 1), suggesting compression socks do not "dampen" the activation of the coagulation system when completing a marathon run. However, in order to confirm these findings, further research investigating a more extensive range of well-known markers of coagulation activation are therefore required.

When combined with muscular activity, compression socks reduce venous stasis, while increasing the volume and velocity of blood flow in the deep venous system, resulting in decreased blood pooling in the distal calf veins (i.e., posterior tibial vein, anterior tibial vein, and peroneal vein), reducing haemostatic activation and increasing fibrinolytic potential (Benko et al. 2001; Zaleski et al. 2015b). Indeed, with a greater range of participants wearing compression socks ($n = 34$) versus a control group ($n = 33$) within the present study, our findings are in contrast with those of Zaleski et al. (2015a), who reported POST-marathon plasma concentrations of TAT to be 17% lower ($p = 0.07$) in runners assigned to the SOCK group when compared to the control group. In addition, when worn during the 2013 Hartford marathon, compression socks were shown to reduce the magnitude of change in POST-marathon concentrations of TAT ($d = 3.00$) (Zaleski et al. 2015b). Several published studies have demonstrated significant POST-marathon increases in plasma concentrations of TAT (Parker et al. 2011; Prisco et al. 1998; Sumann et al. 2007), however, this was not the case within the present study despite similar runner characteristics (age, training volume and marathon finish times), blood collection, and sample analysis procedures. The absence of a post-exercise increase in TAT within the CONTROL and SOCK groups is unusual; however, our findings are similar to those of Parker et al. (2011) in which no significant

increases in TAT were observed POST-marathon within a control group, when investigating the effects of travel and marathon running combined. However, Parker et al. (2011) found a significant increase in TAT was observed after the marathon in the runners that had traveled more than 5 h to compete (TRAVEL: 5.0 ± 4.0–12.9 ± 15.6 µg/L versus CONTROL: 4.0 ± 1.2–6.1 ± 1.2 µg/L; $p = 0.04$, $d = 0.81$). Therefore, the impact of air travel in combination with endurance-based exercise is of particular interest, with an upsurge in national and international participation in varying duration endurance-based events (i.e., triathlons, marathons, and Iron Man competitions), highlighting the need for further research, especially with an aging population.

When completing prolonged strenuous exercise (i.e., 42.2 km marathon), runners are exposed to 'running-specific' risk factors increasing the risk for venous thrombosis generation through repetitive micro-trauma resulting in foot strike haemolysis, dehydration, and endothelial damage (Para 2015; Telford et al. 2003). Increased thrombosis risk may be a direct result of an upsurge in haemodynamic forces, increasing laminar shear stress (Millar-Craig et al. 1978), and exposing TF to the blood stream, initiating the coagulation cascade, and resulting in an increased concentration of TAT complexes (Versteeg et al. 2013). Indeed, an increase in markers indicative of tendency for coagulation activation following the marathon was observed in both the CONTROL and SOCK groups, as demonstrated by the relatively similar effect sizes (CONTROL, small to moderate and SOCK, small to large, respectively) for plasma concentrations of TF. Therefore, within the present study, coagulation and fibrinolytic activation was observed within both the CONTROL and SOCK groups, with lowered activation observed within the runners assigned to the SOCK group.

Practical applications

While compression socks are frequently used within the sporting industry to enhance exercise performance and aid recovery, the use of compression socks within endurance-based exercise may reduce the potential for thrombosis development. When compression socks are not worn when completing a marathon run, our results demonstrate an increase in plasma concentrations of D-Dimer, suggesting an increased potential for thrombin generation. Therefore, the use of compression socks when completing a marathon run may benefit endurance-based athletes. To date, investigations into the use of compression socks and haemostatic activation in prolonged strenuous exercise is limited, thus further research is required to confirm the findings of the present study and those of Zaleski et al. (2015a).

Limitations

This study was not without limitations. While participants were excluded from participating if they had a known and previous history of thromboembolism, participants were not screened for genetic mutations for thrombophilia including Factor V Leiden mutation. The influence of travel on markers of haemostasis were not controlled for within the present investigation; however, previous investigations have identified that air travel augments haemostatic activation immediately following a marathon (Parker et al. 2011, 2012). Therefore, further investigations should account for the influence of travel on markers of haemostasis following a marathon run. In addition, we did not control the volume of training or nutritional intake for the participants within the present study. This can be controlled for in future investigations by providing participants with food and training guidelines leading up to the event itself.

Conclusions

While activation of coagulation and fibrinolysis was apparent in all runners following the marathon, our results suggest an increase in fibrinolytic activity as reflected by an increase in D-Dimer, when compression socks were not worn throughout a marathon run. Therefore, compression socks may assist in the reduction of exercise-associated coagulation and fibrinolytic activation when completing prolonged strenuous exercise; however, further research is required to make firm conclusions regarding the beneficial effects of compression socks.

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design and revision of the manuscript. JWF contributed to the concept of the study design, data interpretation and analysis, and the revision of the manuscript.

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