Radboud Repository



PDF hosted at the Radboud Repository of the Radboud University Nijmegen

The following full text is a publisher's version.

For additional information about this publication click this link. http://hdl.handle.net/2066/118498

Please be advised that this information was generated on 2017-12-05 and may be subject to change.

Graduated Compression Stockings for Runners: Friend, Foe, or Fake?

H. Jorn Bovenschen, MD, PhD; Mariëlle te Booij, MD; Carine J. M. van der Vleuten, MD, PhD

Radboud University Nijmegen Medical Centre, The Netherlands

Objective: To assess the effect of graduated compression stockings (GCS) on lower leg volume and leg complaints in runners during and after exercise.

Design: Cross-sectional study.

Setting: Radboud University Nijmegen Medical Centre and an outdoor running track in Nijmegen, The Netherlands.

Patients or Other Participants: Thirteen Dutch trained recreational runners.

Intervention(s): Participants used a GCS on 1 leg during running.

Main Outcome Measures: (1) Lower leg volume of both legs was measured at baseline, directly after running, and at 5 minutes and 30 minutes after running using a validated perometer. (2) Leg complaints were reported on questionnaires at set intervals.

Results: (1) In both experiments, the legs with GCS showed a reduction in mean (\pm SEM) leg volume directly after running, as compared with the leg without GCS: -14.1 ± 7.6 mL (P=.04) for the 10-km running track and -53.5 ± 17.8 mL (P=.03) for the maximum exercise test. This effect was not observed at 5 and 30 minutes after running. (2) No differences in leg complaints were reported in either experiment.

Conclusions: The GCS prevented an increase in leg volume just after the running exercise. However, this result was not accompanied by a reduction in subjective questionnaire-reported leg complaints. The practical consequences of the present findings need further study.

Key Words: lower leg, leg volume, venous hemodynamics

raduated compression stockings (GCS) are gaining popularity among athletes in various sports disciplines, such as running. In athletes, increased arterial inflow in the legs may impair venous outflow, which may result in complaints of venous insufficiency. Furthermore, the feet of runners absorb 1.5 to 3 times body weight at every step. This may result in injuries such as cramps and medial tibial stress syndrome, impeding optimal muscle functioning during the next exercise.

Studies have demonstrated beneficial effects of GCS on venous hemodynamics. The GCS support and stimulate the calf muscle pump, increasing venous return and reducing leg edema.^{2,3} Recently, the use of GCS has become a growing trend among athletes, with the aim of improving venous return by applying graduated compression around the calves. This may increase end-diastolic volume, with an improvement of the cardiac output as a result, allowing athletes to perform at the same intensity with less cardiac stress or to increase their exercise intensity and performance.⁴ Furthermore, GCS may reduce muscular vibrations triggered by the contact of the feet with the ground, thereby reducing lateral movements of the gastrocnemius muscle, resulting in less traction on the Achilles tendon and less muscular damage.^{4,5}

Few authors have investigated the effect of GCS on performance and recovery after exercise among various sports disciplines. These show conflicting results.^{4–14} Three recent studies demonstrated the effect of wearing GCS during running in trained male runners.^{4–6} In 2 of these studies,^{4,5} the effect of wearing GCS on heart rate was measured; the hypothesis was that an increase in

venous return results in an increase in cardiac output and a decrease in heart rate. Leg volumes were not studied. Although these studies showed no evidence of the presumed beneficial effect of increased venous return, the authors^{4,5} highlighted the relevance of further research to study the effects of GCS on venous return. Furthermore, these studies demonstrated improved running comfort and decreased subjective leg complaints with the use of GCS during exercise.^{4,5} A decrease in leg complaints has been described in other sport disciplines as well, but these findings were not verified by objective data. Moreover, a reduction in leg complaints did not always correlate with better sport performances.^{8,12–14}

If the use of GCS in sports improves venous return and decreases leg complaints, it may be a protective factor against venous insufficiency and leg injuries. Furthermore, it may improve sport performance and recovery after exercise. Increase in leg volume is a physiologic and not a pathologic phenomenon. In general, leg edema after exercise or after a long working day results in leg complaints. Reducing this lower leg volume during sports seems an attractive way of optimizing physical condition and performance. Therefore, we conducted a randomized within-person, left-right comparative study to assess the effect of the use of GCS on lower leg volume and leg complaints in runners. Our hypothesis was that improved venous return may be reflected by reduced lower leg volume and eventually fewer exercise-related leg complaints. The placebo effect of new sport accessories may also be a factor, so we measured the effect of GCS on support of venous return objectively (by the perometer) and subjectively (by questionnaires).

METHODS

Participants

Fifteen trained recreational runners (8 men, 7 women) participated in the study. The runners were recruited from a local amateur running club by using flyers and approaching athletic trainers in an athletic club. Inclusion criteria were healthy men or women between 18 and 65 years of age who were trained recreational runners, training on average 2 times a week, for an average running distance of 12 km. Because we assessed the preventive effect of GCS in healthy participants and not the therapeutic effects, exclusion criteria were complaints of venous insufficiency in the last 2 weeks; a history of deep venous thrombosis, thrombophlebitis, or erysipelas; recent leg injury; joint pain; or relevant comorbidity. All participants completed questionnaires on physical and training characteristics, as well as subjective leg complaints during the last 2 weeks. Ethical approval was obtained from the university's review board, and written informed consent was obtained from all participants.

Procedures

Two experiments were designed to explore the effect of GCS on lower leg volume and leg complaints.

10-km Running Track. During the first experiment, all participants completed a 10-km run on a track wearing a GCS on 1 leg. The GCS were randomly assigned to either the left or the right leg. Lower leg volume and leg complaints were measured at predefined moments, using a perometer and questionnaires. This within-person, left-right comparative study design allowed each participant to serve as his or her own control. A field-based track rather than a treadmill protocol was chosen, because this best reflects regular running training. The participants exercised at a comfortable running speed; no maximum performance was required.

Maximum Exercise Test. In a second trial, participants completed a stepwise, speed-incremented maximum treadmill test until voluntary termination, again wearing a GCS on 1 leg. Here, the question concerned the extent to which the detected differences in the first trial were influenced by exercise intensity.

Four recreational runners who volunteered for the 10-km run on the track also participated in the maximum exercise test, and GCS were randomly assigned to either the left or the right leg. After a 10-minute warm-up, running speed was increased by 0.5 km/h every 3 minutes until a voluntary maximum was reached. The treadmill slope was 0%. The initial running speed depended on the average performance capacity of the participant.

Perometer

Lower leg volume of both legs was measured with a perometer before, immediately after, and at 5 minutes and 30 minutes after both the 10-km run on the track and the maximum exercise test. A perometer uses arrays of light switches made up of light-emitting diodes to illuminate,



Figure 1. Perometer. A perometer uses arrays of light switches made up of light-emitting diodes to illuminate, scan, and calculate the volume of an extremity in milliliters (mL). Lower leg volume was calculated from the medial malleolus to the tibial tuberosity and was measured with the participant in a standing position. Reprinted with permission from www.pero-system.de.

scan, and calculate the volume of an extremity in milliliters (Figure 1). A portable perometer was used (model 1000 M; Pero-System Messgeräte GmbH, Wuppertal, Germany). Lower leg volume was calculated from the medial malleolus to the tibial tuberosity and was measured with participants in a standing position. All measurements were done with the GCS absent. Between measurements, participants were seated. The validity of the perometer has been confirmed in several studies. 15-18 The volume circumference measurements taken by spring tape and by optoelectronic volumetry are both characterized by comparably high reliabilities. In another study, 18 a novel infrared optoelectronic system (Perometer) provided more accurate results than traditional indirect measurement of limb volume and potentially is a very useful clinical and research tool. Therefore, the perometer is as reliable as the criterion standard water volumetry. 15-18

Questionnaires

Leg complaints were reported on standardized questionnaires before, immediately after, and at 30 minutes and 2 days after completing both the 10-km run on the track and the maximum exercise test. Leg complaints were reported for each leg separately on a 5-point Likert scale, ranging from 1 (totally inapplicable) to 5 (maximally applicable). Fifteen items were scored: leg pain, heavy feeling, fatigue, blisters, swelling, muscle soreness, exhaustion, slipping of the foot, tightness, muscle vibrations, tingling, dull feeling, comfortable running, easy running, and fast recovery. The Physiology and Psychology Departments of the Radboud University Nijmegen provided support in developing the questionnaires.

Graduated Compression Stockings

Circular-knit GCS (25–35 mm Hg) were used. This type of GCS is presumed to be both effective in preventing venous insufficiency symptoms and comfortable for athletes to wear.⁴ The graduated compression is highest at

Table 1. Physical and Training Characteristics of Participants (n = 13)

	Mean \pm SD	Range
Age, y	40.5 ± 15.8	21.0-61.0
Height, m	1.73 ± 0.77	1.56-1.84
Body mass, kg	67.0 ± 9.1	49.0-78.0
Average training distance, km	12.3 ± 3.2	8.0-20.0
Average running speed, km/h	11.7 ± 1.3	10.0-14.5
Training sessions/ wk, no.	2.7 ± 1.0	0.5-4.5

the ankle and slightly decreases toward the top of the stocking. This graduated compression is important to prevent a tourniquet effect but still reach a maximum effect. Regular athletic socks lack this compression distribution and are therefore considered less effective.⁴ All GCS were custom made for each participant by Arion International BV (Geleen, The Netherlands) and distributed by Husselson VOF (Nijmegen, The Netherlands). The GCS was worn during both trials but never during the perometer measurements.

Outcome Measurements

The primary outcome was mean lower leg volume (mL), as measured by the perometer (mean \pm SEM). The secondary outcomes were subjective leg complaints, reported on the standardized questionnaires.

Statistics

Data were analyzed using SPSS (version 16.0; SPSS Inc, Chicago, IL). Means and SEMs were calculated. Repeated-measures analyses of variance were performed to detect statistically significant differences in leg volume change at set times.

Nonparametric Mann-Whitney U tests were performed to analyze all items on the questionnaires. All P values of <.05 were considered statistically significant.

RESULTS

Population

10-km Run on the Track. Of the original 15 participants, 13 individuals (6 men, 7 women) completed the 10-km run and were considered in the analysis. One participant dropped out due to a leg injury that happened between the measurement of the leg for correct GCS and the start of the 10-km run, and 1 participant was injured during the 10-km run. This injury was not considered GCS related.

Maximum Exercise Test. Four participants (3 men, 1 woman) with an average age of 53 years (range, 46–60 years) completed the maximum exercise test. Two participants used the GCS on the left leg and 2 on the right leg. The average running time until participants reached their maximum and stopped was 41 minutes (range, 37–49 minutes).

An overview of the physical and training characteristics of all 13 participants is provided in Table 1.

Leg Volume

10-km Run on the Track. No differences in volume were observed between legs before running. Mean lower

leg volume (\pm SEM) before running was 2341.5 \pm 121.5 mL for the leg with GCS and 2341.3 \pm 119.4 mL for the leg without GCS. The leg with GCS showed a mean volume change of -6.7 ± 9.4 mL immediately after running as compared with leg volume before running. At 5 and 30 minutes after the exercise, these differences were -17.6 ± 13.0 mL and -20.4 ± 13.4 mL, respectively. In contrast, the mean volume changes for the leg without GCS were 7.4 ± 7.4 mL immediately after running, -4.2 ± 8.2 mL at 5 minutes after running, and -14.6 ± 6.0 mL at 30 minutes after running (Figure 2).

Hence, the use of GCS led to a difference in volume of -14.1 ± 7.6 mL immediately after completing the 10-km run (P=.04). No differences were observed between legs at the other time points (Table 2).

Maximum Exercise Test. Mean lower leg volume before the test was 2253.5 \pm 225.0 mL for the leg with GCS and 2245.0 \pm 229.2 mL for the leg without GCS. The leg with GCS showed mean changes in volume of -26.3 ± 17.8 mL immediately after the test, -34.0 ± 16.3 mL at 5 minutes after the test, and -49.3 ± 11.4 mL at 30 minutes after the test as compared with baseline values. The mean volume changes for the leg without GCS were 27.3 \pm 23.5 mL immediately after the test, -18.5 ± 14.7 mL at 5 minutes after the test, and -51.8 ± 11.1 mL at 30 minutes after the test (Figure 3).

Thus, the use of GCS led to a difference in volume of -53.5 ± 17.8 mL immediately after completing the maximum exercise trial (P = .03). No differences were detected between legs at the other time points (Table 3).

Questionnaires

10-km Run on the Track. None of the participants reported a difference in leg complaints between the right and the left legs at baseline. The results of the questionnaires showed no differences in reported leg complaints between the leg with and the leg without GCS at all measuring moments, as reflected in Table 4.

Maximum Exercise Test. Baseline values were equal. All items on the questionnaires were scored comparably between groups, and no differences were detected, as shown in Table 4.

DISCUSSION

The aim of our study was to assess the effects of wearing GCS on lower leg volume and leg complaints in trained recreational runners during and after running sessions.

The main finding was a reduction in leg volume immediately after completing both the 10-km run and the maximum exercise test for the leg with the GCS as compared with the control leg. Analysis of the subjective data reported by questionnaires did not reveal any differences.

These findings may indicate that the effects of GCS on leg volume occur when the GCS are actively used. Although there was a statistically significant reduction in leg volume, the question remains as to what extent this finding is meaningful in daily running practice, because the questionnaire did not provide evidence of a subjective improvement for the leg with GCS.

The 10-km run and the maximum exercise track basically showed the same result: a difference in volume immedi-

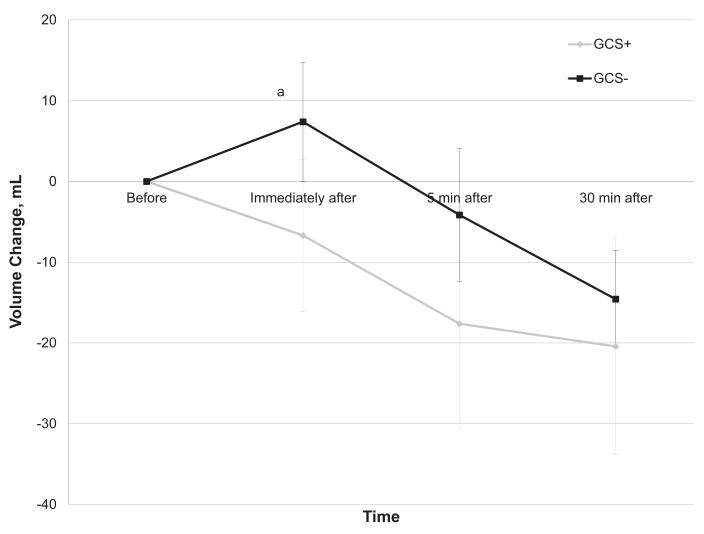


Figure 2. Mean volume change (mL), 10-km run. Mean volume change (\pm SEM) per time point, per leg compared with leg volume before running (n = 13, except for measuring moment 30 minutes, where n = 12). $^{\rm a}$ = statistically significant difference.

ately after running and no difference in subjective complaints. Statistical comparison between the tests is difficult, although the maximum exercise test seems to show larger absolute differences (not statistically tested) despite a lower number of participants. This might reflect a tendency toward a greater apparent effect of GCS with more intensive exercise.

In both tests, decreased leg volume was observed just after running in the legs with GCS but not in the legs without GCS. An increase just after running is probably caused by increased arterial inflow due to effort. Yet, in the legs with GCS, it is unlikely that the stockings

Table 2. Differences in Mean Absolute Volume Change (mL), 10-km Run

Measurement	n	Mean ± SEM	95% CI	P Value
Immediately after running 5 min after running 30 min after running		-14.1 ± 7.6 -13.5 ± 12.0 -5.8 ± 13.8	*	.04ª .14 .34

Abbreviation: CI, confidence interval.

diminished arterial inflow; therefore, the volume decrease is probably due to supported venous return and the calf muscle pump, as has been found before in walkers and athletes. ^{19,20}

Leg-volume measurements in healthy runners have not been previously reported. However, the effects of GCS on leg complaints and running comfort have been studied. Two studies^{4,5} among runners showed decreases in leg complaints or improvement in running comfort when wearing GCS during a 10-km run. The same results have been reported for other disciplines as well. Three studies (of cyclists and rugby players) showed decreases in leg complaints when wearing GCS during high-intensity exercise. 8,12,14 One group 13 reported a decrease in lateonset muscle soreness when wearing GCS during the dropjump exercise. We did not observe these results in runners. A traditional design was used in all studies: participants trained with GCS on both legs and repeated the experiment at a different time without GCS. 4,5,8,12–14 This time interval may have caused bias. Therefore, in our within-person, leftright comparative study, the participants filled out the questionnaires separately for both legs at the same time, which may have produced a more accurate report of leg

^a Difference between volume of the leg with and the leg without graduated compression stockings.

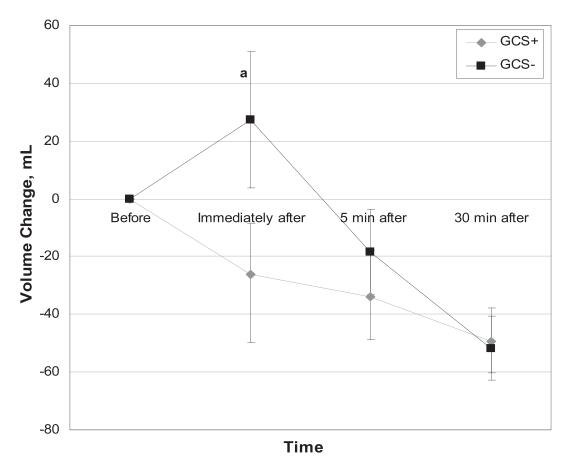


Figure 3. Mean volume change (mL), maximum exercise test.

complaints. However, the scoring form for subjective complaints is probably not sensitive enough to discriminate differences, and subjective complaints may be better measured in extended or repetitive exercise or training. Furthermore, the effects of GCS on leg complaints may be more explicit in untrained individuals. Future studies are needed to investigate this.

A strength of our study is that all participants completed the same type of exercise on the same day under the same circumstances. Also, all participants served as their own controls in this study design, so that a reliable comparison of intervention and control could be made.

Limitations include the use of a single type of GCS and the selection of trained recreational runners. Hence, the results cannot readily be extrapolated to other classes of GCS or other sport disciplines. The age range of the participants seems very broad, but this is mitigated by the

Table 3. Difference in Mean Absolute Volume Change (mL), Maximum Exercise Test

Measurement	n	$Mean \pm SEM$	95% CI	P Value
Immediately after running	4	-53.5 ± 17.8	-110.0, 3.0	.03ª
5 min after running	4	-15.5 ± 15.3	-64.1, 33.1	.19
30 min after running	4	2.5 ± 13.8	-41.3, 46.3	.43

Abbreviation: CI = confidence interval.

fact that the volunteers were healthy and by the left-right, within-person comparison. In this study, the only significant differences in leg volume with the use of GCS occurred immediately after exercise. The question arises as to whether this result is caused by a compression effect of the GCS or by decreased blood flow into the leg in contrast to increased venous return. However, because none of the participants had preexisting complaints of arterial insufficiency, their diastolic blood pressure should always have exceeded the pressure of the GCS and there should not have been decreased blood flow into the leg. All leg-complaint results were obtained by subjective measures on questionnaires, so it is possible that a placebo effect occurred. This possibility was minimized by the use of the within-person, left-right comparative study design.

Future studies, verifying these results in a broader context in larger groups of volunteers, should focus on the practical relevance of the effects of wearing GCS as well.

CONCLUSIONS

In summary, we are the first study to report leg-volume measurements in runners wearing GCS. The GCS prevented an increase in leg volume just after a running exercise. However, this result was not accompanied by a reduction in subjective leg complaints reported on a questionnaire. The practical significance and implications of the present findings remain to be established.

^a Difference between volume of the leg with and the leg without graduated compression stockings.

Table 4. Mann-Whitney U Test Results for Leg-Complaint Scores, 10-km Run

						Ë	Time					
		During Running	g	Imme	Immediately After Running	guiuur	30 1	30 min After Running	ing	2	2 d After Running	ū
	GCS +	GCS -		GCS +	GCS -		GCS +	GCS -		GCS +	GCS -	
Leg Complaint	Mean Rank	Mean Rank	Significance	Mean Rank	Mean Rank	Significance	Mean Rank	Mean Rank	Significance	Mean Rank	Mean Rank	Significance
Leg pain	12.42	14.58	.328	13.00	14.00	.317	13.12	13.88	.708	13.50	13.50	1.000
Heavy feeling	12.50	14.50	.429	14.62	12.38	.356	13.35	13.65	836	13.50	13.50	1.000
Fatigue	12.50	14.50	.361	13.73	13.27	.865	13.35	13.65	839	13.50	13.50	1.000
Blisters	14.00	13.00	.317	14.00	13.00	.317	14.00	13.00	.317	13.50	13.00	.317
Swelling	13.46	13.54	926	14.00	13.00	.317	13.50	13.50	1.000	13.50	13.50	1.000
Muscle soreness	NA	ΑN	ΑN	13.92	13.08	.682	13.38	13.62	.917	13.58	13.42	.935
Exhaustion	NA	ΑN	ΑN	14.35	12.65	0.531	13.50	13.50	1.000	13.50	13.50	1.000
Slipping of foot	15.00	12.00	.072	Ν	ΑN	ΝΑ	ΑN	ΑN	NA	Ϋ́	NA	ΥN
Tightness	15.23	11.77	.138	Ν	ΑN	ΑN	ΑN	ΑN	NA	ΑN	NA	ΥN
Muscle vibrations	13.50	13.50	1.000	13.54	13.46	.972	13.50	13.50	1.000	13.50	13.50	1.000
Tingling	14.00	13.00	.317	14.04	12.96	.518	14.50	12.50	.149	14.00	13.50	1.000
Dull feeling	13.00	14.00	.317	ΥN	ΑN	ΑN	ΑN	ΑN	NA	ΑN	NA	ΥN
Comfortable running	14.38	12.62	.470	ΑN	ΑN	ΑN	ΑN	ΑN	NA	ΑN	NA	ΑN
Easy running	13.46	13.54	626.	Ν	ΑN	ΑN	ΑN	ΑN	NA	ΑN	NA	ΥN
Fast recovery	N A	Ϋ́Α	ΑN	ΑN	ΑN	ΑN	13.50	13.50	1.000	13.50	13.50	1.000
Abbreviation: GCS, graduated compression stockings; NA, not app	graduated cor	mpression stoo	ckings; NA, not	t applicable.								

ACKNOWLEDGMENTS

We thank the participants in this study. We also acknowledge Arion International BV, Geleen, The Netherlands, and Husselson VOF, Nijmegen, The Netherlands, who supplied GCS for our participants. None of the authors have any conflicts of interest to declare.

REFERENCES

- Lieberman DE, Venkadesan M, Werbel WA, et al. Foot strike patterns and collision forces in habitually barefoot versus shod runners. *Nature*. 2010;463(7280):531–535.
- Ibegbuna V, Delis KT, Nicolaides AN, Aina O. Effect of elastic compression stockings on venous hemodynamics during walking. J Vasc Surg. 2003;37(2):420–425.
- Kraemer WJ, Volek JS, Bush JA, et al. Influence of compression hosiery on physiological responses to standing fatigue in women. *Med Sci Sports Exerc*. 2000;32(11):1849–1858.
- Creasy R. Performance, physiological, and perceptual effects of wearing graduated compression stockings during running [master's thesis]. Palmerston North, Auckland, New Zealand: Massey University, 2008. http://muir.massey.ac.nz/bitstream/10179/866/1/ 02whole.pdf. Accessed November 2, 2012.
- Ali A, Caine MP, Snow BG. Graduated compression stockings: physiological and perceptual responses during and after exercise. J Sports Sci. 2007;25(4):413–419.
- Kemmler W, von Stengel S, Kockritz C, Mayhew J, Wassermann A, Zapf J. Effect of compression stockings on running performance in men runners. J Strength Cond Res. 2009;23(1):101–105.
- Higgins T, Naughton GA, Burgess D. Effects of wearing compression garments on physiological and performance measures in a simulated game-specific circuit for netball. *J Sci Med Sport*. 2009; 12(1):223–226.
- 8. Duffield R, Edge J, Merrells R, et al. The effects of compression garments on intermittent exercise performance and recovery on consecutive days. *Int J Sports Physiol Perform.* 2008;3(4):454–468.
- Scanlan AT, Dascombe BJ, Reaburn PR, Osborne M. The effects of wearing lower-body compression garments during endurance cycling. Int J Sports Physiol Perform. 2008;3(4):424

 –438.
- Berry MJ, Bailey SP, Simpkins LS, TeWinkle JA. The effects of elastic tights on the post-exercise response. Can J Sport Sci. 1990; 15(4):244–248.
- 11. Bringard A, Denis R, Belluye N, Perrey S. Effects of compression tights on calf muscle oxygenation and venous pooling during quiet resting in supine and standing positions. *J Sports Med Phys Fitness*. 2006;46(4):548–554.
- Chatard JC, Atlaoui D, Farjanel J, Louisy F, Rastel D, Guézennec CY. Elastic stockings, performance and leg pain recovery in 63-yearold sportsmen. Eur J Appl Physiol. 2004;93(3):347–352.
- Davies V, Thompson KG, Cooper SM. The effects of compression garments on recovery. J Strength Cond Res. 2009;23(6):1786–1794.
- Duffield R, Cannon J, King M. The effects of compression garments on recovery of muscle performance following high-intensity sprint and plyometric exercise. *J Sci Med Sport*. 2010;13(1):136–140.
- Man IO, Markland KL, Morrissey MC. The validity and reliability of the Perometer in evaluating human knee volume. *Clin Physiol Funct Imaging*. 2004;24(6):352–358.
- Stanton AW, Northfield JW, Holroyd B, et al. Validation of an optoelectronic limb volumeter (Perometer). *Lymphology*. 1997;30(2): 77–97
- Labs KH, Tschoepl M, Gamba G, Aschwanden M, Jaeger KA. The reliability of leg circumference assessment: a comparison of spring tape measurements and optoelectronic volumetry. *Vasc Med.* 2000; 5(2):69–74.

- 18. Tierney S, Aslam M, Rennie K, Grace P. Infrared optoelectronic volumetry, the ideal way to measure limb volume. *Eur J Vasc Endovasc Surg.* 1996;12(4):412–417.
- 19. Sciacca V, Buonopera P, Mingoli A, Di Marzo L, Matteucci E. Evaluation of venous flow by light reflection rheography (LRR) in
- athletes performing track race. J Sports Med Phys Fitness. 1991; 31(2):265–271.
- Ibegbuna V, Delis KT, Nicolaides AN, Aina O. Effect of elastic compression stockings on venous hemodynamics during walking. J Vasc Surg. 2003;37(2):420–425.

Address correspondence to Carine J. M. van der Vleuten, MD, PhD, Department of Dermatology, Radboud University Nijmegen Medical Centre, PO Box 9101, NL- 6500 HB Nijmegen, The Netherlands. Address e-mail to c.vandervleuten@derma.umcn.nl.