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Original paper
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Stationary standing of healthy subjects provokes leg volume increase and unmasks emerging vein symptoms as homeostatic feelings.

La position debout de sujets en bonne santé provoque une augmentation du volume des jambes, révèlant les symptômes veineux, qui sont des perceptions homéostatiques.

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Abstract

Objective: Vein symptoms (VS) present as a conglomerate of discomfort and pain, and as sensations of swollen and heavy legs with poor sensitivity and specificity for true venous disease.

We investigated whether VS might reflect a neural monitoring function which responds to changes in the legs' homeostasis.

Methods: Healthy subjects were exposed to a 10 min gravitational stress with bare legs and compression stocking of different strength, length and garment finish.

Results: Volume of the two legs increased by 516 mL ($P \leq .001$) and typical VS emerged in each case with an intensity of 2.9 on a numeric rating scale (range 0 to 10, $P \leq .001$).

Compression stockings reduced both phenomena.

The effect on symptoms revealed a hierarchy: above knee stockings were better than below knee, low strength better than high strength, urea finish better than no finish (overall Spearman's rho = 0.17, $P = .046$).

Neither volume increase per se, nor limiting the increase, correlated with the emergence of VS.

Conclusions: Standing produces a time-dependent homeostatic disequilibrium epitomized as VS.

Résumé

Chez le sujet sain, le volume de la jambe augmente en orthostatisme, ce qui fait apparaitre des symptômes veineux, qui sont des perceptions sensorielles, des sensations, liées à l'homéostasie.

Objectifs : *La sensibilité et la spécificité des symptômes veineux (SV) sont peu fiables : inconfort et douleur, sensation de jambes gonflées et lourdes…*

Le but de ce travail est de déterminer si les SV correspondent à une fonction d'adaptation neuronale en réponse aux changements de l'homéostasie au niveau des jambes.

Méthodes : *Des sujets sains ont été exposés à un stress gravitationnel de 10 minutes, jambes nues, ou avec des bas de compression de différentes forces, longueurs et finitions textiles.*

Résultats : *Le volume des deux jambes a augmenté de 516 mL ($p \leq 0{,}001$) et des SV sont survenus chez tous les patients, d'une intensité de 2,9, sur une échelle numérique d'évaluation de 0 à 10 ($p \leq 0.001$).*

Le port de bas de compression a réduit ces deux paramètres.

Les effets sur les symptômes sont hiérarchisés :

- *les bas comprimant la cuisse étaient plus efficaces que ceux montant au-dessous du genou,*
- *les bas de faible compression étaient supérieurs à ceux de plus forte compression,*
- *les bas imprégnés d'urée exerçaient un meilleur effet que les bas usuels (corrélation de Spearman, rho = 0,17, $p = 0{,}046$).*

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Compression stockings exert a type-specific preventive effect.

This supports the concept of a neural monitoring function leading sensitive subjects to discontinue standing or move their limbs to rid themselves of their awkward feelings.

Keywords: *venous disease, vein symptoms, occupational leg swelling, homeostatic feelings, gravitational stress test, compression stockings.*

La survenue de SV n'était pas corrélée avec l'augmentation du volume, ni avec la limitation de cette augmentation par la compression.

Conclusion : *L'orthostatisme induit un déséquilibre homéostasique proportionnel à sa durée, qui se manifeste par la survenue de SV. Les bas de compression exercent un effet préventif spécifique sur ce phénomène. Cela confirme le concept de surveillance neuronale des membres inférieurs, incitant les sujets prédisposés à ne pas poursuivre une activité en orthostatisme ou à mobiliser leurs membres pour atténuer des symptômes désagréables.*

Mots-clés : maladie veineuse, symptômes veineux, sensation de gonflement, œdème gravitationnel, perception homéostasique, test de stress gravitationnel, compression, bas de compression.

Introduction

Some patients report symptoms of discomfort and awkward sensations in the legs [1-5], whether or not the origin of such symptoms lies in an empirically verified venous disorder.

Patients describe the sensations as feelings, as an ache or tingling, as diffuse or localized pain, or that their legs feel heavy, swollen, or tight [6-8].

While there is considerable variation in what individuals report, there is consistency when the components of pain and the sensation of swelling are considered together [6].

Vein symptoms (VS), as they are termed now [7], are quite prevalent and exist among 46% of those who show no signs of venous disease (CEAP classification C0 or C1), and among 65% of those with varicose veins with or without edema (C2 and C3) [8].

VS are particularly prevalent among those who sit or stand for long periods or who exercise a stationary profession, such as hairdressers [6, 7].

While VS themselves are benign and transient in nature, they are perceived to be annoying and can impair well-being and reduce the quality of life [9, 10].

Still, there is no proof they mark the first stage of an evolving venous disorder [1-3, 6-8], nor is there a statistical correlation between leg swelling and preventing vein symptoms by wearing compression stockings [6, 11, 12] even though felt (or observed) leg swelling often coincides with the expression of VS.

Studies conducted with healthy subjects suggest that during a gravitational stress test, leg volume increases [13-16] as a result of rapid filling of muscle sinus with blood not required for circulation – a physiological process. This can lead them to report the kinds of symptoms noted above [12].

Following AR Damasio, negative feelings are the mental expression of disturbed homeostasis in any tissue which trigger actions to restore the equilibrium [17].

In other words, reported vein symptoms may well reflect a disturbance to the homeostasis in the legs as a natural consequence of standing up from the supine position and standing still, rather than pain caused by some kind of damage [12, 19].

In clinical settings, VS can be mitigated by wearing low-strength medical compression stockings (MCS) as they may have the potential to prevent the homeostatic disturbance or to modify its perception [6, 11, 12, 19-21].

This study tested, in healthy subjects, for the differential effects on volume increase and symptoms of stockings of different strength, length, and garment finish. Its intent was not to search for the molecular basis of the disturbed homeostasis associated with standing but to eventually describe the VS as a neuropsychological response to the primarily physiological challenge.

In that, the study has the potential to improve the patients' and physicians' attitude toward VS, sensations which often remain clinically unexplained.

Methods

Research issues and study design

Our aim was to examine (and potentially confirm) specific hypotheses about the origins of VS. We made use of a newly developed instrument which allows exact measurement of leg volume during standing **(Fig. 1)** [12].

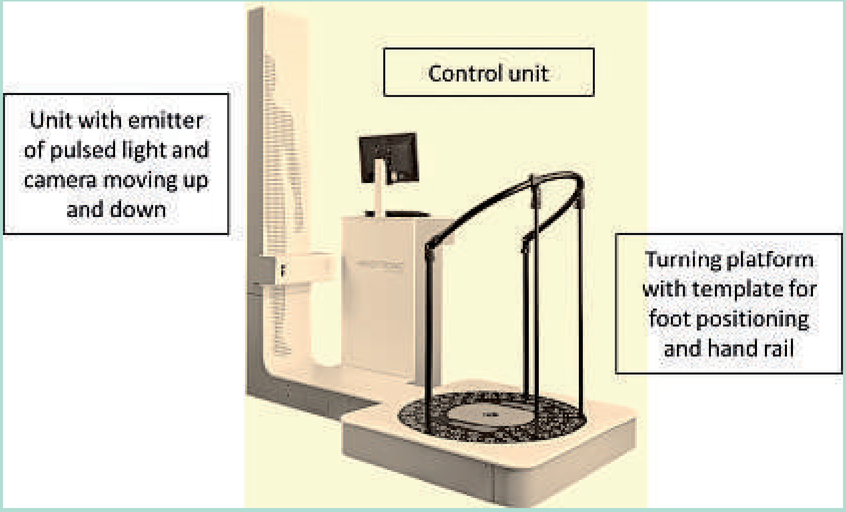


FIGURE 1 : Bodytronic® 600, the instrument to measure leg volume.

We wanted to establish whether healthy subjects, meaning those who show no evidence of venous disease, would nevertheless exhibit vein symptoms.

To that end, we developed a mild stress test in which subjects moved from a supine position (with legs elevated 30 degrees) to a standing position on the instrument, where measurements of leg volume and emerging symptoms were monitored [12].

In this study, we used the same tools for measuring both the volume of the lower leg and the thigh in mL, and the emergence of any symptoms using a numeric rating scale (NRS, range 0-10) seven times over a period of 10 minutes.

Our prior hypothesis, based on earlier work, was negatively formulated [12].

As healthy subjects regularly reported VS, one could rule out the possibility that such symptoms only occurred among those with verified venous disease conditions.

The corollary is that if healthy subjects did not report significant VS when subjected to mild stress, a case could be made that the symptoms were in some manner connected to or caused by venous disease.

One possibility was that the causes were not internal to the leg but instead reflected external sensations, presumably elicited in the skin, a part of the body largely ignored as a generator of sensations.

The fact that wearing compression stockings mitigates VS led us to hypothesize that there might be a correlation between garment and skin interaction (through touch, pressure, or massage) and prevention of VS.

Following this reasoning, applying pressure to the leg could simply modify perceptions or evoke comment about the area in question.

To this end, we tested a variety of compression stockings to establish whether there was such a correlation and compared these findings to measurements made when no stockings were worn.

It is of great practical importance to know whether the relief of vein symptoms necessarily requires tight stockings which reduce the pooling of venous blood, the physiologic phenomenon possibly responsible for the emergence of VS.

A rather different hypothesis is that the sensations are indeed internal – but are located more in nervous structures than in the leg.

That is, in order to verbally express that one's legs feel heavy or swollen, the brain must process something that is then articulated as discomfort, whether or not the underlying site of this discomfort can be localized.

This is not far-fetched: the 'phantom limb' phenomenon – a painful sensation in the missing limb reported by a majority of amputees – is a stark illustration of this type of disjuncture between articulated discomfort and a cause which can be physiologically verified.

By analogy, our hypothesis here, which is based on what healthy subjects report, is that the articulation of discomfort is instead in response (even in anticipation) to a more general change in the homeostasis of the legs.

This could help explain why VS are so often articulated as diffuse feelings rather than a clearly localized sensation as would be the case if it were in response to a noxious stimulus to pain receptors.

	Series 1			Series 2		
	Men	Women	Total	Men	Women	Total
N (%)	10 (42)	14 (58)	**24 (100)**	10 (42)	14 (58)	**24 (100)**
Age, yrs	33.1 (11.0)	35.3 (8.6)	**34.4 (9.5)**	37.0 (12.4)	40.2 (8.4)	**38.8 (10.2)**
Height, cm	181.0 (5.9)	168.3 (6.4)	**173.6 (8.8)**	182.8 (6.2)	168.7 (6.6)	**174.6(9.5)**
Weight, kg	82.3 (7.9)	70.4 (9.3)	**75.4 (10.4)**	83.3 (9.0)	74.1 (9.5)	**77.9 (10.2)**
BM	25.1 (2.2)	24.9 (3.5)	**25.0 (3.0)**	24.9 (2.4)	26.1 (3.5)	**25.6 (3.1)**

TABLE 1 : Personal data of participating volunteers (mean, SD).

The present study, therefore, was exploratory, both in the sense of exploring hypotheses and in the sense of exploring specific 'remedies' – such as graduated compression stockings – for the reported VS.

The study was performed at the Medical Science Laboratory of Bauerfeind AG (Zeulenroda, Germany) and the vascular laboratory of the Venenpraxis Wunstorf.

The protocol used followed the guidelines of the Helsinki Declaration and was approved by the ethics commission of the Thüringen State Medical Board (study number 39524/2015/47).

The subjects were orally informed and granted consent at the outset and again before each test series was started.

Measurement of leg volume

The lower leg and thigh volumes of both legs were measured simultaneously with the Bodytronic® 600 (Bauerfeind AG) **(Fig. 1)**, an instrument which makes it possible to take frequent and highly accurate measurements of leg volume.

Test subjects stand on a platform holding a support frame, and the platform makes one entire rotation (360 degrees) in 50 seconds.

During this time, both legs are profiled and measured using a visible light camera with stripe projection.

A cloud of dots is thereby generated which is converted into a three-dimensional model of the lower extremities.

The leg circumferences are divided into layers and that data is added together to generate volume.

The lower leg is defined as the volume measured between the smallest circumference above the ankle (B-level) and the circumference measured at the level of the tibial tuberosity (D-level).

The thigh is defined as the volume measured between the D-level and the largest thigh circumference (G-level).

Data on the accuracy of measurement of the leg circumference and on the effects compression stockings have been presented previously [12].

Protocol

Two cohorts of 24 healthy volunteers were selected from a pool of 63 who had participated in a previous test [12].

The selection criterion was whether they had experienced at least one symptom (e.g., received a score of 2 or more on the numeric rating scale (NRS) in the course of this earlier test).

The absence of venous, including C1, or other leg disorders was established by an angiologist, who took a history and conducted a clinical examination, a duplex ultrasound scan of all leg veins, and a photoplethysmography test.

Subjects provided personal data **(Table 1)** and agreed not to wear any compression stockings until all studies were completed.

Subjects were prepared in the supine position on a bed with their legs elevated 30 degrees on a foot rest for three minutes.

They then moved to the adjacent platform of the BT600, placed their feet on the template painted on the platform, put their weight equally on both legs, and took a comfortable stance, holding firmly to the handrail.

The platform began rotating immediately and the first volume measurement was completed 50 seconds later.

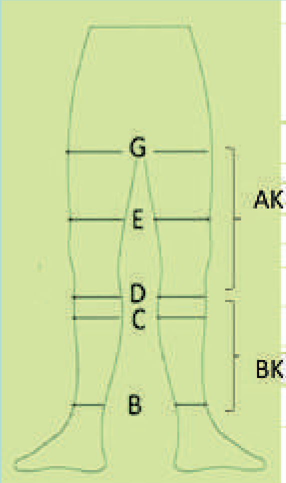
Leg volumes were measured 7 times, from 50 seconds to 10 minutes, both simultaneously and separately for each leg, and these measurements were averaged for all analyses.

The average interval between subsequent measurements was 95 seconds (SD 7.3).

Subjects in test series 1 performed 2 tests with bare legs and 4 tests with stockings;

Subjects in test series 2 performed 1 test with bare legs and 2 tests with stockings **(Fig. 2)**.

Each test was performed on a separate day at approximately the same time of day.



	F1[1] Discretion™	G1[2] Venotrain™	G1[2] Venotrain™ with urea	G2[2] Venotrain™
G	7-8	7-8	7-8	9-10
AK	(light green)	(light green)	(dark green)	(dark green)
E	7-8	7-8	7-8	10-13
D	7-9	9-10	9-10	12-14
C	8-9	12-13	12-13	16-18
BK	(light green)			(medium green)
B	13-14	18-21	18-21	25-28

AK = above knee, BK = below knee
[1] French class 1, norm AFNOR [2] German classes 1 and 2, norm RAL

FIGURE 2 : Details of the 6 MCS used: trade names, interface pressures (mmHg) and designation of colors used in Figures 4, 6 and 7.

All compression stockings were regular products of Bauerfeind, provided in appropriate sizes and put on both legs immediately before the subjects lay on the bed. The subjects did not know which stockings they wore for a given test.

At the end of each rotation of the platform, subjects were asked whether they had experienced any leg symptoms.

While standing on the platform, and in order that subjects would remain still while answering, they were shown a numeric rating scale (NRS) with numbers ranging from 0 to 10.

Zero denoted no symptoms while ten denoted very strong symptoms; detailed analyses of symptoms have been previously reported [12, 18].

We wondered, as we became aware that below-knee compression was leading to an increase in thigh volume, how this could occur.

The popliteo-femoral axis is the major pathway draining the lower leg, and the normal femoral vein has no connection with thigh muscle veins up to the inguinal junction, we examined the femoral vein using ultrasound.

A member of the study staff (male, 73, BMI 24.5) underwent two series of measurements with bare legs, below knee (BK) German class 1 (G1) and above knee (AK) G1 stockings.

We measured femoral vein cross-sections and determined blood volumes at the end of the preparation period when the legs were elevated, immediately after the subject stood, and took multiple measurements at brief intervals for the next five minutes, as feasible.

Vein cross-sections were measured proximal to the short saphenous vein junction (site A) and 14 cm below the great saphenous vein junction (site B).

Measurements at the great saphenous vein junction are only feasible with bare legs, since the ultrasound does not penetrate the grip top of the stockings.

Vein circumference was measured using the function integrated in the ultrasound scanner, and femoral vein volumes were calculated using the truncal-cone model.

Data analysis and statistics

Leg volume data are given in absolute values (mL) and in terms of percentage change. Symptoms were described in absolute values on the NRS.

To calculate volume and symptom prevention (or enhancement) attributable to compression stockings, differences between values with and without them were calculated.

To describe the total change of volume and symptoms, the difference between the first measured value after rising from the bed (after 50 seconds) and the mean of the two last measurements was calculated.

To test for differences of the same subjects within a test series, or between different treatment conditions (different stockings), t-tests for paired comparison were applied for volume data and Wilcoxon signed rank tests were conducted for the data on symptoms. Spearman's correlations were used to check the relationship between volume and NRS changes.

	Series 1									Series 2				
	Bare legs	BK F1		BK G2		AK F1		AK G2		Bare legs	AK G1 micro		AK G1 micro balance	
Volume (mL)	Mean (SD)	Mean (SD)	P	Mean (SD)	P	Mean (SD)	P	Mean (SD)	P	Mean (SD)	Mean (SD)	P	Mean (SD)	P
Lower leg	2613 (393)	2572 (392)	<.001	2558 (389)	<.001	2573 (373)	.002	2548 (390)	<.001	2670 (396)	2604 (400)	<.001	2607 (387)	<.001
Thigh	4285 (881)	4387 (910)	.091	4368 (914)	.138	4259 (887)	.562	4206 (830)	.151	4396 (934)	4313 (944)	<.001	4307 (932)	<.001
Entire leg	6898 (1198)	6959 (1238)	.326	6926 (1239)	.629	6832 (1195)	.174	6754 (1166)	.027	7065 (1241)	6918 (1256)	<.001	6914 (1224)	<.001
Symptoms (NRS)	2.94 (1.43)	2.23 (1.76)	.038	2.33 (1.28)	.015	1.9 (1.25)	.004	2.08 (1.19)	.004	2.88 (1.62)	2.08 (1.56)	.028	1.67 (1.63)	.001

Paired t-tests for volume, Wilcoxon signed rank tests for symptoms between bare legs and MCS.

TABLE 2 : Leg volume and symptoms after 10 minutes of stationary standing with bare legs and with MCS.

In this correlation matrix, volume data were calculated from the end of the preparation period to the first measurement at 50 seconds, under the assumption that the veins were empty after 3 minutes of 30 degrees elevation.

To correct for the subjects' different statures, individual blood volume was estimated using body weight (60 mL/kg of body weight for women, 70 mL/kg of body weight for men).

The calculated initial volume increase and the subsequently measured increase were added together. For all comparisons, P<.05 was considered statistically significant.

Results

Tests with bare legs

While standing for 10 minutes with bare legs **(Table 2, fig. 3)**, lower leg volume increased by 96 mL in the 1st series (SD 40; 3.6%; P<.001) and by 88 mL (SD 31; 3.3%; P<.001) in the 2nd series.

The thigh volume increased by 174 mL in the 1st series (SD 52; 3.9%; P<.001), and by 161 mL (SD 45; 3.6%; P<.001) in the 2nd series.

The volume increases of each entire leg averaged 263 mL (SD 5; 3.7%, P<.001).

It took place in two phases.

After standing for about 140 seconds, the rapid increase changed to a slower rise; at this point, about 80% of the increase observed over a 10-minute period had occurred.

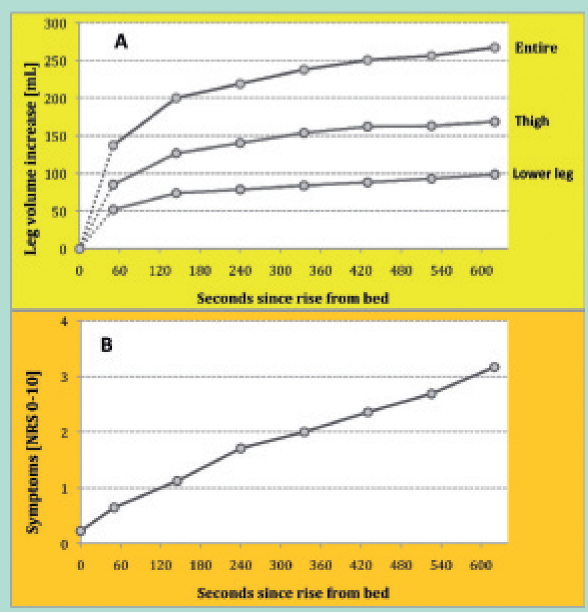


FIGURE 3 : Increase of leg volume and emergence of symptoms during stationary standing with bare legs (for statistics, see Table 2).

The ultrasound study of the femoral vein **(Table 3, fig. 4)** showed that the vein was empty of blood in its lower part (cross-section <0.1 cm²) and almost empty in its proximal part (cross-section 0.4-0.7 cm²) at the end of the preparation period.

Upon standing up, with no stockings worn, the cross-section at the distal site increased to 0.7 cm² within 20 seconds and at the proximal site to 1.5 cm² within 50 seconds, respectively.

	A Distal FV	B Proximal FV	C Subinguinal FV	Volume A - B (mL)	Volume B - C (mL)	Volume A - C (mL)
	Area (cm²)	Area (cm²)	Area (cm²)			
Bare leg	0.86	1.66	1.79	37.1	24.7	61.9
BK G2	0.93	2.07		43.9		
AK G2	0.79	1.79		37.7		

*TABLE 3 : Increase of the femoral vein blood volume during standing.
Cross sectional surface of the FV measured after leg elevation and during 5 minutes of stationary standing.
Site A, proximal to the junction of the short saphenous vein;
site B, 14 cm distal to the great saphenous junction;
site C, great saphenous junction (bare legs only).
The FV volume was calculated for the segments A-B (length = 30 cm), B-C (length = 14 cm) and A-C.*

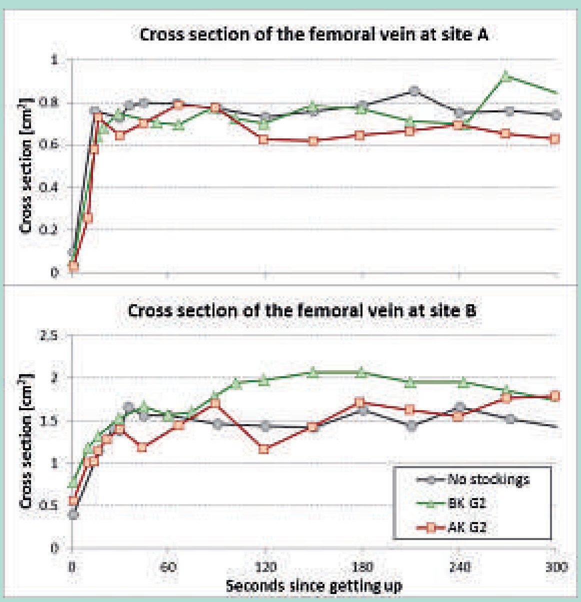


FIGURE 4 : Cross-sections of the femoral vein measured after lying for 3 minutes with elevated legs and after taking the standing position.

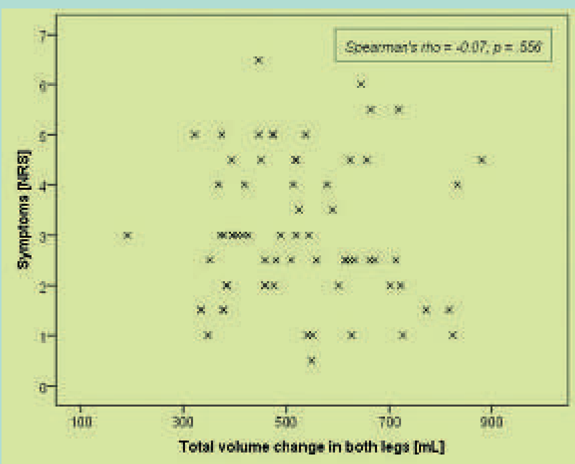


FIGURE 5 : Correlation between volume increase (mL) and NRS (scale points) after standing for 10 minutes with bare legs.

The femoral vein volume reached 60 mL after 60 seconds and did not increase further until the fifth minute.

Symptoms began to emerge immediately after subjects took their position on the platform, increased continuously and linearly with time, and reached 2.94 NRS points (SD 1.43; P<.001) at the end of the test period **(Table 2, fig. 3)**.

No correlation was found between volume increase and the intensity of emerging symptoms **(Fig. 5)**.

Tests with MCS

Stockings of different length, strength and garment finish exerted different effects on lower leg and thigh volumes **(Tables 2 and 4, fig. 6)**.

Lower leg volume increase was reduced with all stockings, as compared with bare legs, by between 40 mL and 65 mL (P<.001).

AK F1 stockings were less effective than AK G2 stockings (P = .043).

Thigh volume changes showed a two-sided effect.

As compared with no stockings, BK stockings increased the thigh volume, F1 by 101 mL and G2 by 83 mL.

Conversely, AK stockings reduced the thigh volume increase, F1 by 26 mL, G1 and G2 between 79 mL and 89 mL, respectively.

The differences between BK and AK stockings were significant (P = .01 and .002, respectively).

At the entire leg, AK stockings prevented the volume increase by 66 mL (F1) and 144-152 mL (G1 and G2), respectively, whereas BK stockings enhanced volume increase by between 27 mL (G2) and 60 mL (F1).

The differences between BK and AK stockings were significant (P = .002).

	Series 1								Series 2		
	Below knee stockings			BK F1 vs. AK F1	BK G2 vs. AK G2	Above knee stockings			Above knee stockings		
	BK F1		BK G2			AK F1		AK G2	AK G1 micro		AK G1 micro balance
Volume [mL]	Mean (SD)	P	Mean (SD)	P	P	Mean (SD)	P	Mean (SD)	Mean (SD)	P	Mean (SD)
Lower leg	−41 (41)	.190	−56 (56)	.908	.418	−40 (55)	.043	−65 (55)	−65 (54)	.799	−63 (47)
Thigh	+101 (283)	.576	+83 (266)	.001	.002	−26 (216)	.196	−79 (260)	−82 (82)	.730	−89 (97)
Entire leg	+60 (295)	.361	+27 (277)	.002	.002	−66 (230)	.086	−144 (299)	−148 (108)	.879	−152 (107)
Symptoms [NRS]	−0.71 (1.58)	.595	−0.61 (1.06)	.508	.182	−1.05 (1.56)	.477	−0.86 (0.86)	−0.79 (1.67)	.133	−1.21 (1.5)

Plus-minus signs: + = enhancement, − = prevention.
Paired t-tests for volume, Wilcoxon signed rank tests for symptoms between different MCS.

TABLE 4 : Leg volume and symptoms prevented or enhanced by MCS.

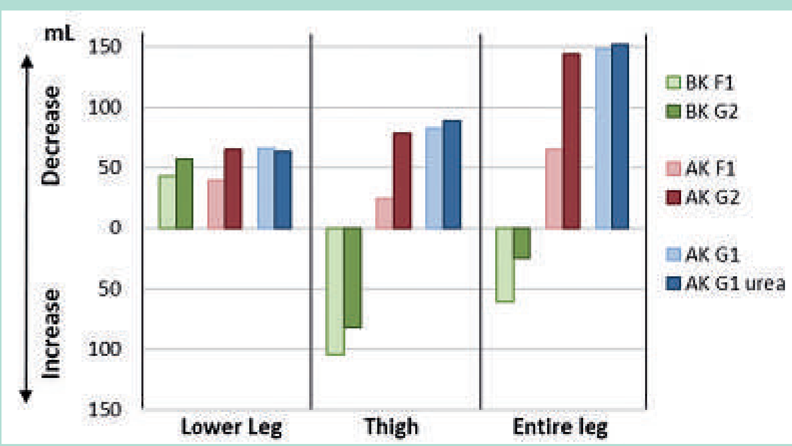


FIGURE 6 : Change of volume observed when wearing 6 different MCS as compared with bare legs (for statistics, see Table 4).

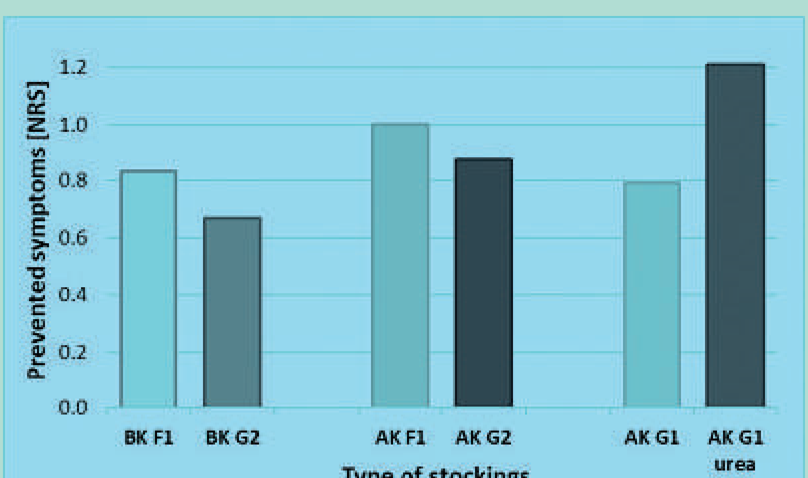


FIGURE 7 : Symptoms prevented by wearing 6 different MCS as compared with bare legs (for statistics, see Table 4).

The volume increases of the femoral vein **(Fig. 4, Table 3)** was not modified by wearing AK G2 stockings but slightly enhanced by BK G2 stockings in its proximal part, beginning after about 60 seconds.

The increase of symptoms showed the same dynamics with bare legs and with stockings: immediate beginning, steady increase, and a linear course.

All stockings reduced the symptom increase as compared with bare legs by 0.61 to 1.21 NRS-points (P = .038 to .001; Table 2, fig 7).

Sort sequence comparisons of the effect of stockings on symptoms showed these differences: AK was better than BK, urea finish better than no finish, F1 better than G1 and G1 better than G2 (overall Spearman's rho = 0.17, P = .046, single comparisons not significant).

As demonstrated in the test with no stockings **(Fig. 5)** there were no significant correlations between symptoms and volume changes in any of the stockings used (Spearman's rho between −0.36 and −0.07, P between .088 and .756).

Discussion

We developed a gravitational stress test as a surrogate for the VS encountered in real life.

The tests involved having healthy subjects with a verified lack of venous disease stand up from a supine position with leg elevation (30°, 3 min) and measuring their leg volumes during stationary standing (7-times over 10 minutes) [12].

In all subjects, these tests consistently provoked an increase in leg volume with bare legs (by 500 mL in 10 minutes in the two legs together), the physiological result of standing up. It can be explained by the filling of veins and sinus with blood which at that point is not required for circulation.

The muscle sinus serves as the reservoir when standing upright; the increase in volume also results from relative muscle inactivity while standing still.

The axial veins of the lower leg do not take up much volume during standing [11].

In contrast, the popliteo-femoral vein, which is the main conduit draining the lower leg, has a high capacity, allowing the inclusion of about two-thirds of blood displaced from the lower leg when BK stockings are worn.

Subjects, however, also reported VS (intensity 2.9 on an NRS from 0 to 10).

This is more difficult to explain, as it seems unlikely that standing for 10 minutes would produce any injury and elicit a sensation of pain as a result.

The phenomenon is universal [1-5], though with varying severity [8] and the terms used to describe it are selective [6, 8].

Were it related to risk, the type of sensations could warn of an impending emotional or psychic stress rather than tissue damage [18].

Our suggestion is that subjects are responding to a disturbance (real, impending, or imagined) in the homeostasis of the legs.

Following the fundamental work of AR Damasio on the neurobiology of feelings [17], we think VS are an expression of a neural signaling or control mechanism.

As such, the signal will vary by the strength of the challenge, the feasibility of ending the symptoms or changing the homeostasis further (by walking, putting on a compression stocking, shaking out a leg, and so forth), and possibly even the memory of, or emotional response to, previous burdening situations.

The nexus of feelings can be derived from information patients offer spontaneously or when asked by an attentive physician taking their history.

The hypothetical mechanisms which may trigger the homeostatic disturbance and elicit the response to it have been reviewed [22] but data from investigations are lacking.

We infer from evidence in other fields that activation of specific neural networks occurs in response to various challenges, with information captured, decoded, diagnosed, monitored and ultimately sent to specific areas of the brain [23, 24].

In our research, standing up and then standing still was the challenge, the filling of veins the physiological consequence, and the emergence of symptoms an epiphenomenon. Compression stockings modify the vein capacity, depending on their length and strength, and this influences how great the increase in leg volume will be, as our test results show.

However, our findings speak against the notion that volume increase per se, or even limiting that increase, might be the cause of the symptoms.

Indeed, variations in individual physiology may also account for the differences in symptoms or sensations reported – even to the point where no symptoms at all are reported.

In this context, we focused on the skin and considered that compression stockings, or garments more generally, might modify the reporting of symptoms.

It has been shown that fast-adapting skin receptors are particularly sensitive to new, repetitive and light tactile stimuli, and any movement of a fine garment on the skin may activate these receptors.

Monotonous strong pressure as exerted by high-strength stockings may predominately activate slow-adapting receptors [25].

So, one possibility is that reported sensations are externally generated, meaning not necessarily in the environment of veins located deep in the legs but rather within the skin. This notion is supported by a few studies.

Low-pressure bandages, but not regular strength bandages, were found to improve pain and postural sway in subjects with knee osteoarthritis [26].

Light pressure applied to the skin, but not strong pressure, improves the cutaneous microcirculatory activity and increases cutaneous thermal conductivity [27, 28].

Another study compared the effect of compression applied to the foot only, the foot plus the lower leg, and the entire leg, on experimentally induced pain inflicted on an upper limb, and found that the larger the area of leg compression the more analgesia was produced on the arm [29].

This finding is in accord with our data showing that AK stockings are more effective in preventing symptoms during standing than BK stockings.

The finding that stockings finished with urea reduce the symptoms more than crude stockings may be due to the urea's softening effect on the skin [30].

Still, as garments are often perceived as pleasant to wear, this cannot readily explain the effect of compression in subjects or patients who report painful or unpleasant VS.

In sum, our findings fit well into the concept of dynamic control of homeostasis through its cognitive representation as feelings [31].

For some subjects, this neural monitoring may send a 'function: normal' signal, reflecting how it usually feels when standing up from a supine position and standing or sitting still for a certain time.

For other subjects or patients, there may be an acute awareness or sensitivity (including from external stimuli) to the challenge of standing, which leads to the perception of symptoms associated with it: discomfort, heaviness, fullness, tingling, itching, restlessness, an urgent need to get up, etc.

Elderly persons anticipate problems when standing and take precautions, including not getting up rapidly from bed or a chair. Some subjects, seven percent in the general population [8], experience emotional stress and even may develop psychic conditions in association with VS [32].

Wearing compression stockings not only precipitate a reduction of VS but can improve disturbed sleep, depressive states, and leg-related self-esteem [6].

The asset of this study is to produce novel information that VS are fundamentally natural (if not neural) homeostatic feelings rather than sensations of disease.

Clearly, the molecular or micro-environmental mechanism involved in the control of the legs' homeostasis was not the topic of this study.

The drawback of the study is that we did not include patients with objectively proven venous disease. Therefore, it remains unknown whether patients with a venous disease react in the same manner as healthy subjects when exposed to the stress test.

A study with such patients could allow for the necessary comparison.

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Data collection took place, in part, at Bauerfeind with employees of the company.

Nevertheless, the company was not involved in the study design, analysis and interpretation of data, manuscript writing, or the decision to submit the manuscript for publication.

Conflict of interest statement

WB and FA are consultants for Bauerfeind AG, D-07937 Zeulenroda-Triebes, Germany. EM & JB report no conflict of interest.

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