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	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.

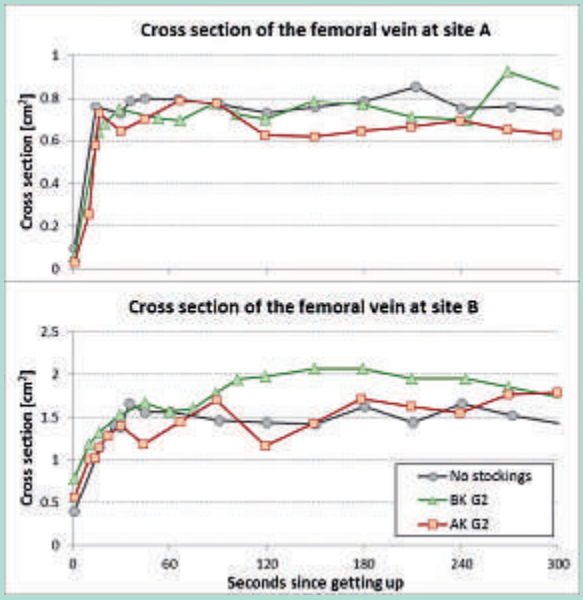

FIGURE 4 : Cross-sections of the femoral vein measured after lying for 3 minutes with elevated legs and after taking the standing position.

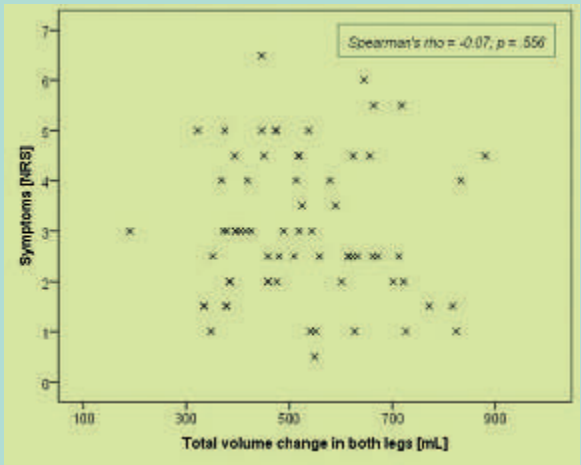

FIGURE 5 : Correlation between volume increase (mL) and NRS (scale points) after standing for 10 minutes with bare legs.

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).

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	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.

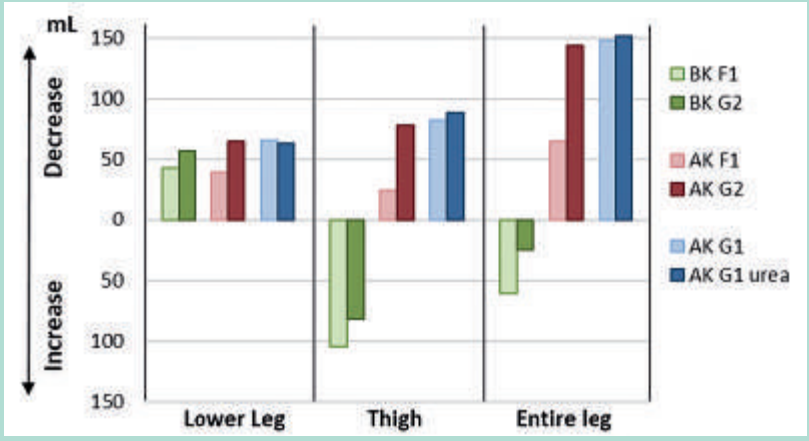

FIGURE 6 : Change of volume observed when wearing 6 different MCS as compared with bare legs (for statistics, see Table 4).

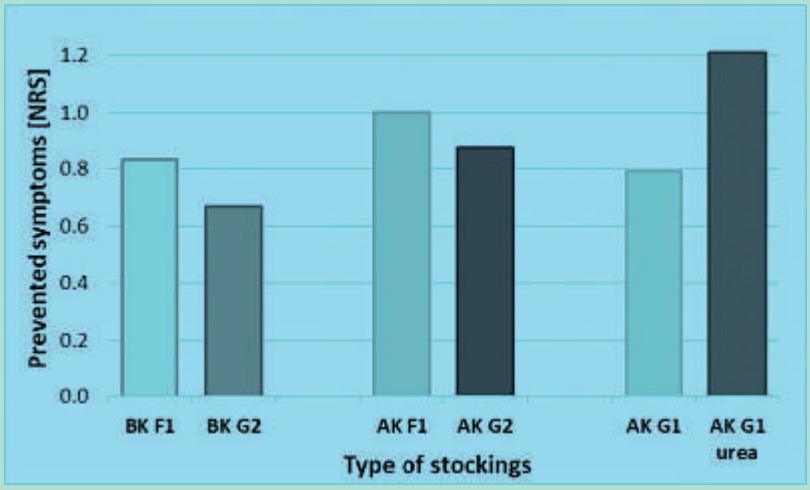

FIGURE 7 : Symptoms prevented by wearing 6 different MCS as compared with bare legs (for statistics, see Table 4).

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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.

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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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