Homeostatic feelings – a novel explanation of vein symptoms derived from an experimental patient study

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Summary: *Background:* Vein symptoms (VS) entail diffuse leg discomfort and pain coinciding with a perception of weighty or swollen legs. Their traditional classification as a form of venous disease may be inaccurate as they occur in patients with no or any venous disorder. We hypothesized that VS would emerge from a primordially standing associated perturbation in the lower limbs which is not necessarily connected with a venous disorder. *Patients and methods:* Patients were sorted into groups according to the CEAP classification, VS only (C0s), primary varicose veins (C2p), varicose veins plus oedema (C2p and C3), and venous dermatopathy (C4). Patients completed questionnaires before and one week after they were exposed to a test of stationary standing. *Results:* Patients (N = 127) in the four groups differed by sex, age and body weight. The VS experienced in the preceding week scored the same in all groups at 3.1 on a numeric rating scale (range 0–10; SD 1.6). During standing, lower leg volume increased and symptoms emerged to the same extent across patient groups and were reduced similarly by compression (volume by 1.7 %, symptoms by 41.7 %). The emergence of symptoms was neither correlated with leg volume increase per se, nor with limiting this increase by compression. Symptoms recorded at baseline correlated with the symptoms provoked by the stress test with bare legs while the symptoms reported at follow-up, when stockings were worn regularly, correlated with the stress test with compression. *Conclusions:* VS, in terms of neuropsychology, reflect a homeostatic disturbance experienced in the presence and absence of venous disease. Thus, VS are not distinctive for the presence of venous disease insofar as they may reflect dynamic homeostatic feelings resulting from a standing-related disequilibrium in the legs' internal environment.

Keywords: Venous disease, vein symptoms, venous symptoms, homeostatic feelings, gravitational stress test, compression therapy

Introduction

Venous symptoms, or vein symptoms (VS) as they are termed now [1], are reported as diffuse leg discomfort and moderate pain coinciding with a perception of weighty or swollen legs [1–8]. Emotions, which often accompany VS, allude to the presence of disturbed vital feelings, including disturbed sleep, anxiety, depression, a low self-esteem and impaired quality of life [9–12]. VS are not reported as a persistent or chronic but rather as an intermittent condition, typically triggered by prolonged sitting or standing and worse in a warm environment and at the end of the day. Yet, VS also occur in the absence of such contexts, appearing and waning subtly and occasionally leading to a lasting bad background mood. In any case, they are readily alleviated by leg elevation or taking a walk and reliably

prevented by wearing graduated medical compression stockings (MCS) [13].

The prevalence of VS is very high in the general population, affecting 53 % of the 1800 subjects examined in the Bonn Vein Study II (BVS; 7) but their specificity for true venous disease is poor. Some phenomena are known for decades but are still unclear, among them the higher prevalence in women than men, the influence of patient's age and clinical manifestation of the venous disease. Separation of somatic from psychic components has been performed, yet the origin of the symptoms remained unexplained in the majority of subjects [6]. In a cross-sectional study, patients who had other conditions affecting the legs (e.g. osteo-arthritis, spinal disc herniation) reported VS almost as often as patients who had objectively diagnosed chronic venous insufficiency [11]. To the

contrary, a prior psychiatric study which used a comprehensive health questionnaire found that patients reporting VS in the absence of genuine venous disease did not show a higher prevalence of any other somatic or psychiatric symptoms [12].

When we applied the newly developed orthostatic stress test to healthy subjects, we confirmed that standing leads to a rapid increase in leg volume and observed that typical kinds of VS emerge concomitantly [14, 15]. We concluded that the healthy subjects' reaction to the clearly physiologic challenge might reflect a momentary disturbance to the legs' internal environment (Claude Bernard, 1813–1878: *Fixité du milieu intérieur*) and hypothesized that these complaints might occur during the stress test in humans with and without damaged venous anatomy and function. Therefore, we based subsequent investigations on the neurobiological concept elaborated by A.R. Damasio [16, 17]. He presented compelling evidence that the dynamic control of the bodies' internal environment is not limited to the compensatory or adjusting efforts of peripheral tissues but involves neuronal reactions which are perceived in the mind as feelings. Feelings are the highest manifestation of homeostatic control, a mental endeavour providing awareness of something potentially noxious which threatens the body from inside and out.

In the present study, we investigated whether patients with objectively diagnosed venous disease of varying degrees of severity would react differently when they undergo the gravitational stress test. We also examined whether the symptoms provoked by the stress test corresponded to the symptoms reported spontaneously. Finally, we studied the prophylactic benefit of wearing MCS both during the stress test and in everyday life.

Patients and methods

Study and patients

Invited to this investigator-initiated, prospective, cross-sectional study, were patients who consulted two Vein Centres during regular consultation hours for clarification of a venous disorder. Interested patients were informed in detail about the purpose of the study and what the implications of their participation were. For these candidate patients, the routine diagnostic work-up was supplemented with specific questionnaires, gravitational stress tests, both with bare legs and with MCS [14, 15], and the commitment to return a questionnaire which had to be completed at home after one week of wearing the MCS provided.

The study was performed at the Vein Centres in Wunstorf and Jena, both in Germany. The protocol was in accordance with the Helsinki Declaration and approved by the ethics commission of the Niedersachsen and Thüringen State Medical Chambers (*Landesärztekammer*), Germany (Study number 39524/2015/47) and registered with the

German Registry of Clinical Studies (*Deutsches Register Klinischer Studien*, No. DRKS00015116).

Methods

Candidate patients provided a health history and both legs were clinically examined for the presence of venous disorders using the Clinical, Etiologic, Anatomic, and Pathophysiologic (CEAP) classification. A duplex ultrasound exploration was performed of the common femoral, femoral, popliteal and posterior tibial veins, assessing compressibility and flow direction, with a reflux of longer than 1.0 sec considered pathological. The great and small saphenous veins were examined in their full length, the anterior accessory saphenous vein at its junction, and the perforating veins at the medial aspect of the lower legs. The same criteria were employed as for deep veins plus diameters at the junctions, and reflux evoked by manual compression of the calf, active toe elevation, and Valsalva manoeuvre in the groin region. Reflux of longer than 0.5 sec in the superficial veins was considered pathological [18]. When the clinical work-up found a patient eligible and written consent was granted, he/she was included in the study.

Two questionnaires were applied. The Psychic versus Somatic Venous Disease Questionnaire (PsySoVDQ), had been established in healthy volunteers [5, 8] and validated in the population-based Bonn Vein Study II [7]. Its psychic component includes questions related to anxiety, melancholy, and emotional inhibition (score 0–3), while its somatic component addresses the typical core VS (localized and diffuse pain, feelings of heaviness and swelling, score 0–3). Our patients' data were compared with the results of the Bonn Vein Study [7] whose participants were divided into those who reported symptoms and those who reported no symptoms. The published cohort had excluded C4-patients. For this study the 68 C4-patients were included. The short-term VS questionnaire (s-t VSQ) was developed for this study based on the items investigated previously [8] and evaluated eight sensations, namely pressure, tension, any clear pain, localized pain, diffuse pain, muscle pain, tingling and itching. These were recorded on a 0 to 10 numeric scale. Three dimensions could be found using factor analysis. Mean and peak (maximum of the individual symptoms) scores were calculated.

For the stress test, patients were positioned first for three minutes in a recumbent position with elevated legs in order to drain the veins. After having the patient stand up rapidly and positioned on the Bodytronic 600® (Bauerfeind, Zeulenroda, Germany), the patients stood still, and measurements of the lower legs' volume were started. Lower leg volume was defined as the volume measured between the lowest leg circumference (level B) and the circumference measured at the level of the tibial tuberosity (level D). Results were obtained for the first time after 50 seconds of standing still and subsequently six times within 10 minutes. After each measurement, the patient was asked to rate

Figure 1. Lower leg volume increase (left column) during the stress test with bare legs and wearing MCS (N = 224 legs with a venous diagnosis), and emergence of symptoms (right column) (N = 127 patients). All increases between the first (50 seconds after rise from recumbence) and the last measurements (10 minutes) were of statistical significance ($p < .001$). For further statistics see Table IV. NRS: Numeric rating scale (0–10).

any symptom experienced on one or both legs using a 0 to 10 numeric rating scale (NRS). Detailed information of the procedure, the measuring instrument, data processing, accuracy and reliability, and the necessity to correct the leg's volume since stockings themselves increase this measure have been presented previously [14, 15].

Below-knee MCS (Venotrain micro®) were provided in appropriate sizes by Bauerfeind, German class 1 (G1, ankle pressure 18–21 mmHg) for patients with CEAP C0s and C2, and German class 2 (G2, ankle pressure 23–32 mmHg) for patients with CEAP C2 & C3 and C4. Both legs were fitted with the same type of stocking, irrespective of the venous

Figure 2. Scatter plots and correlations between lower leg volume increase and symptoms after the stress test (N = 127 patients). NRS: Numeric rating scale (0–10).

findings on the less severely affected leg. Stockings were put on both legs immediately prior to the second stress test and from then on worn every day, morning to evening, for 1 week.

Protocol

Patients were assigned to one of four groups according to the clinical classification of the venous disease present on the more severely affected leg (leading leg). Reporting vein symptoms was mandatory for inclusion into group I but not for inclusion into the other groups.

Group I, C0s: VS only, meaning a negative history of a venous disorder, no clinical signs of venous disease and a normal ultrasound examination.

Group II, C2p: Primary varicose veins with reflux in the great saphenous vein and/or small saphenous vein and/or anterior accessory saphenous vein and/or perforating veins and visible tributaries.

Group III, C2 and C3: As in group II, but with clinically evident oedema.

Group IV, C4: Dermatologic signs of chronic venous insufficiency caused by primary varicose veins and/or deep venous reflux.

Each group had to include 30 patients, at least 10 per sex. When the number of inclusions was reached the assignment of patients to that group was halted.

Protocol sequence

- Patients completed two questionnaires, the PsySoVDQ and the baseline s-t VSQ.
- The stress test on the BT 600 was applied to both legs simultaneously without stockings.
- MCS were put on both legs.
- The stress test was repeated with MCS.
- MCS were used every day.
- After one week, the s-t VSQ was filled out and sent back.

The study's primary endpoint was the increase in the volume of the lower legs and the emergence of symptoms

while standing. Secondary endpoints were the type and intensity of symptoms reported at the baseline and at the end of one week with MCS and their relationship with the symptoms experienced during the stress tests.

Exclusion criteria were age younger than 18 or older than 75; weight over 120 kilos; pregnancy; presence of an acute venous condition (phlebitis, deep venous thrombosis, dermatitis) or a healed or florid venous ulceration (C5, C6); any health condition that could interfere with the study endpoints (i.e. a history or presence of pelvic venous disorders, oedema of other than venous origin, lymphedema, lipoedema, dermatopathy, arteriopathy, neuropathy, arthropathy, including spinal symptoms, and pharmacologic treatment with venotropic remedies, analgesics and anti-rheumatics); use of compression on the day of the consultation; inability to change rapidly from the recumbent to the standing position and to hold it for 10 minutes; inability to wear MCS or to complete the questionnaires.

Statistical analysis

Leg volume data are given in absolute values (mL) and in terms of change (mL %). The volume at time point zero shown in Figure 2 was extrapolated [13]. Symptoms are described in absolute values on the NRS and as absolute and percentage changes. To calculate volume and symptom prevention (or enhancement) attributable to MCS, differences were calculated between the values with and without MCS. To describe the total change of volume and symptoms, the differences between the first and the last measurements were calculated. To assess differences within a test series of the same subjects or between stockings and no stockings t-tests for paired comparison were calculated. To test between patient groups, ANOVA with post hoc analysis was performed. Pearson's correlations were calculated to test for the relationship between symptom and volume change in the stress tests and between symptoms at different time points. To find the dimensions of the symptoms' factors of the s-t VSQ, principal components analysis with varimax-rotation was used and the

Table I. Personal data and long-term symptoms assessed at baseline with the PsySoVDQ (Psychic versus Somatic Venous Disease Questionnaire) of the patients of this study (A) and of the subjects of the Bonn Vein Study (BVS, 7) who had reported symptoms (B) or no symptoms (C), assigned to diagnostic groups I to IV.

	C0 / C0s*	C2p	C2 & C3	C4	Total patients	P
a) Patients, this study						
N	32	30	35	30	127	
Male, N (%)	5 (16)	10 (33)	10 (29)	17 (57)	42 (33)	.007
Female, N (%)	27 (84)	20 (67)	25 (71)	13 (43)	85 (67)	
Age, mean (SD)	49 (15)	56 (12)	60 (12)	62 (8)	57 (131)	<.001
BMI, mean (SD)	25 (5)	26 (5)	29 (6)	29 (5)	27 (5)	.007
MCS worn before consultation, N (%)	1 (3)	6 (20)	13 (37)	19 (43)	39 (31)	<.001
PsySoVDQ, psychic component, mean (SD)	0.90 (0.39)	0.95 (0.51)	0.75 (0.48)	0.76 (0.4)	0.84 (0.45)	.208
PsySoVDQ, somatic component, mean (SD)	1.36 (0.69)	1.10 (0.54)	1.19 (0.73)	1.19 (0.73)	1.21 (0.68)	.488
b) Subjects BVS, symptoms reported						
N	541	231	190	53	1015	
Male, N (%)	189 (35)	88 (38)	71 (37)	25 (47)	373 (37)	.328
Female, N (%)	352 (65)	143 (62)	119 (63)	28 (53)	642 (63)	
Age, mean (SD)	54 (13)	58 (13)	63 (13)	68 (12)	58 (14)	<.001
BMI, mean (SD)	25 (4)	25 (4)	27 (4)	26 (3)	25 (4)	<.001
PsySoVDQ, psychic component, mean (SD)	0.83 (0.54)	0.73 (0.57)	0.74 (0.59)	0.58 (0.55)	0.78 (0.56)	.004
PsySoVDQ, somatic component, mean (SD)	0.62 (0.68)	0.67 (0.69)	0.90 (0.71)	0.81 (0.71)	0.69 (0.70)	<.001
c) Subjects BVS, no symptoms reported						
N	610	164	64	15	853	
Male, N (%)	320 (52)	78 (48)	34 (53)	10 (67)	442 (48)	.448
Female, N (%)	290 (48)	86 (52)	30 (47)	5 (33)	411 (52)	
Age, mean (SD)	49 (14)	55 (13)	60 (14)	66 (12)	51 (14)	<.001
BMI, mean (SD)	24 (4)	25 (4)	26 (3)	28 (4)	24 (4)	<.001
VS, psychic component, mean (SD)	0.77 (0.53)	0.63 (0.52)	0.69 (0.46)	0.25 (0.26)	0.73 (0.53)	<.001
VS, somatic component, mean (SD)	0.06 (0.23)	0.09 (0.31)	0.10 (0.29)	0.03 (0.13)	0.07 (0.25)	.268

BMI: Body mass index (weight (kg) / height (cm)²; MCS: Medical compression stockings; SD: Standard deviation. * Cohorts A and B: C0s; cohort C: C0

internal consistency of the factors estimated with Cronbach's alpha. As no differences between the diagnostic groups were found, patient data were combined for this factor analysis. Stepwise regression analysis was performed to test the multivariate influence of sex, age and CEAP classification on the PsySoVDQ scores. For all comparisons, $p < .05$ was considered statistically significant. Data were analysed using IBM SPSS Statistics for Windows, version 24.0.

Results

Patients

A total of 127 patients were enrolled, 85 women and 42 men, and assigned to one of the four groups according to the severity of the venous disease present in the leading leg. The study flow is shown in the electronic supplementary material (ESM) 1 and the participants' personal data are depicted in Table I. With increasing disease severity, the proportion of women decreased while the mean age, the body mass index (BMI) and the use of MCS increased. The patients of our study showed a comparable distribution

of sex, age and BMI as the reference Bonn Vein Study cohort [7] of symptomatic subjects.

The diagnosis made on the leading leg was compared with the diagnosis made on the non-leading leg (ESM 2). In group I (C0s), the non-leading leg received the same diagnosis in 91 % and the diagnosis C0 (no disease and no symptoms) in 9 %. In groups II (C2) and III (C2 & C3), the non-leading leg showed the same disease as the leading leg in 47 % and 66 %, and C0 in 23 % and 20 %, respectively. In group IV (C4), the non-leading leg showed the same disease in 23 % and C0 in 43 %.

Symptoms

The long-term VS with their psychic and somatic components were assessed at baseline using the PsySoVDQ (Table I). The psychic scores of the patients in our study and the subjects of both population cohorts revealed a stepwise decrease in the more severe diagnostic groups ($p < .001$ in the population cohorts). In a multivariate regression model, applied to the BVS cohort [7], the higher psychic scores were associated with female sex and younger age ($R^2 = 0.071$, $p < .001$) while the CEAP class had no additional relevance.

Table II. Single symptoms and symptom factors (F1–F3) assessed at baseline, encompassing the week before consultation (s-t VSQ (short-term VS Questionnaire), score range 0–10; mean, SD).

	C0s	C2p	C2 & C3	C4	Total patients
N	32	30	35	30	127
Pressure	3.7 (2.8)	3.1 (2.7)	3.0 (2.9)	3.2 (2.2)	3.3 (2.6)
Tension	3.8 (2.6)	3.1 (2.4)	3.1 (2.7)	3.5 (2.2)	3.4 (2.5)
Any net pain	3.5 (2.6)	3.2 (3.0)	3.2 (3.0)	3.8 (2.5)	3.4 (2.7)
Localized pain	3.5 (3.2)	3.2 (3.0)	3.2 (2.9)	4.3 (2.9)	3.6 (3.0)
Diffuse vague pain	3.4 (2.7)	2.8 (3.3)	2.8 (3.3)	3.1 (2.3)	3.0 (2.9)
Tingling	3.2 (3.2)	2.3 (2.4)	2.7 (2.9)	2.9 (2.5)	2.8 (2.8)
Muscle pain	3.1 (2.8)	2.3 (2.3)	2.4 (2.7)	2.8 (2.6)	2.7 (2.6)
Itching	2.1 (2.8)	1.9 (2.5)	2.6 (2.9)	2.9 (2.8)	2.4 (2.8)
F1) Pressure, tension, diffuse vague pain (Cronbach $\alpha = 0.77$)	3.7 (2.2)	3.0 (2.4)	2.9 (2.42)	3.3(1.9)	3.2 (2.2)
F2) Any net pain, localized pain (Cronbach $\alpha = 0.60$)	3.5 (2.4)	3.2 (2.6)	3.1 (2.6)	4.1 (2.2)	3.5 (2.4)
F3) Tingling, itching, muscle pain (Cronbach $\alpha = 0.47$)	2.8 (1.7)	2.2 (1.7)	2.5 (2.1)	2.9 (2.0)	2.6 (1.9)
Average symptom score (Cronbach $\alpha = 0.74$)	3.3 (1.6)	2.7 (1.7)	2.8 (1.7)	3.3 (1.6)	3.1 (1.6)
Peak symptom score	6.6 (1.7)	6.0 (2.7)	5.8 (2.9)	6.3 (2.2)	6.2 (2.4)

No comparisons were of statistical significance.

Table III. Increase of lower leg volume with a venous diagnosis and emergence of symptoms at the end of the stress test and their prevention by wearing MCS.

CEAP class	C0s	C2p	C2 & C3	C4	Total	
Type of stocking	G1 (18–21 mmHg)		G2 (23–32 mmHg)			P
Lower leg volume						
N (legs)	76	50	61	37	224	
First measurement mL, mean (SD)	2556 (740)	2587 (713)	2643 (637)	2703 (658)	2589 (679)	0.515
Increase prevented with stockings mL, mean (SD)	42 (44)	44 (48)	51 (60)	43 (50)	45 (52)	0.768
% increase prevented	1.6	1.7	1.9	1.6	1.7	
P increase prevented	<.001	<.001	<.001	<.001	<.001	
Symptoms						
N (patients)	32	30	35	30	127	
Bare legs, NRS (SD)	4.3 (2.8)	3.8 (2.9)	3.2 (2.8)	3.3 (1.9)	3.6 (2.6)	0.313
Stockings, NRS (SD)	2.4 (2.3)	2.2 (2.0)	1.9 (2.1)	1.9 (1.7)	2.1 (2.0)	0.690
Symptoms prevented with stockings NRS (SD)	1.9 (1.8)	1.6 (1.9)	1.3 (1.8)	1.4 (1.6)	1.5 (1.8)	0.577
% increase prevented	44.1	42.1	40.6	42.4	41.7	
P increase prevented	<.001	<.001	<.001	<.001	<.001	

G1: German class 1; G2: German class 2; NRS: Numeric rating scale (0–10); SD: Standard deviation.

The somatic scores were highest in the patients of our study, twice as high as in the population cohort of the subjects reporting symptoms and almost 20 times higher than in the population cohort reporting no symptoms. No significant differences were seen between the patient groups. In the multivariate regression model, applied to the BVS cohort [7], higher psychic scores were associated with female sex and higher CEAP class ($R^2 = 0.073$) while age had no additional relevance.

In the s-t VSQ at baseline, the mean average symptom score was 3.1 (SD 1.6). The mean peak score, i.e. the maximum score of each individual symptom, was 6.2 (SD 2.4) (Table II). Three clusters of symptoms were found:

subjective sensations (diffuse vague pain, pressure, tension; Cronbach α 0.79), localized and clear pain (Cronbach α 0.67), and other sensations (muscle pain, itching, tingling; Cronbach α 0.59). Differences between the patient groups were not statistically significant.

Stress test

At the time the first measurement was completed, the lower leg volumes had an average of 2622 mL per leg, with larger volumes in the groups with more severe disease (+ 147 mL in group IV) (Table III). The lower leg volume

Table IV. Symptoms experienced during the week before consultation when MCS were not or rarely worn and during the week after consultation when MCS were worn regularly. Presented are the factors of clustered symptoms and the average symptom scores of the s-t VSQ (short-term VS Questionnaire, range 0–10; mean, SD) of the patients who filled out the questionnaire on both occasions.

CEAP class	C0s	C2p	C2 & C3	C4	Total	P
N (patients)	25	25	28	24	102	
F1) Pressure, tension, diffuse vague pain (Cronbach α 0.79)						
Week before consultation (baseline)	4.0 (2)	2.5 (2.1)	3.1 (2.4)	3.3 (2)	3.2 (2.2)	.565
Week after consultation (follow-up)	1.2 (1.6)	1.3 (1.5)	1.6 (2.2)	2.0 (1.7)	1.5 (1.8)	.373
Improvement	2.8 (2.4)	1.2 (1.8)	1.5 (2.4)	1.3 (1.8)	1.7 (2.2)	.040 ^a
Percent difference	70	48	48	39	53	
P	< .001	< .001	< .001	< .001	< .001	
F2) Any clear pain, localized pain (Cronbach α 0.67)						
Week before consultation (baseline)	3.7 (2.3)	3.1 (2.5)	3.2 (2.4)	4.1 (2.5)	3.5 (2.4)	.412
Week after consultation (follow-up)	1.0 (1.7)	1.6 (1.9)	1.7 (2.3)	2.0 (2.3)	1.6 (2.1)	.366
Improvement	2.7 (1.9)	1.5 (2.6)	1.5 (2.6)	2.1 (2.7)	1.9 (2.5)	.262 ^b
Percent difference	73	48	47	51	54	
P	< .001	< .001	< .001	< .001	< .001	
F3) Tingling, itching, muscle pain (Cronbach α 0.59)						
Week before consultation (baseline)	2.9 (1.7)	2.0 (1.6)	2.4 (1.9)	3.0 (2.1)	2.5 (1.9)	.434
Week after consultation (follow-up)	1.1 (1.6)	0.9 (1.1)	1.3 (1.3)	1.6 (1.4)	1.2 (1.4)	.302
Improvement	1.8 (1.8)	1.1 (1.5)	1.1 (1.7)	1.4 (1.6)	1.3 (1.7)	.432
Percent difference	62	55	46	47	52	
P	< .001	< .001	< .001	< .001	< .001	
Average symptom score						
Week before consultation (baseline)	3.5 (1.3)	2.5 (1.4)	2.9 (1.8)	3.4 (1.8)	3.0 (1.6)	.362
Week after consultation (follow-up)	1.1 (1.3)	1.2 (1.2)	1.5 (1.6)	1.9 (1.4)	1.4 (1.4)	.241
Improvement	2.4 (1.5)	1.3 (1.5)	1.4 (1.8)	1.5 (1.6)	1.6 (1.6)	.063 ^c
Percent difference	69	52	48	44	53	
P	< .001	< .001	< .001	< .001	< .001	

^aC0s vs. other groups: $p = .004$; ^bC0s vs. other groups: $p = .076$; ^cC0s vs. other groups: $p = .008$.

increased rapidly during the first 2 min and slowly thereafter, with no difference between the patient groups (Figure 1). Wearing MCS prevented this increase by about 50 mL ($p < .001$) with no difference between the groups.

Symptoms emerged linearly in all groups, with no statistical difference between them (Figure 1 and Table III). The highest increase was observed in patients with C0s with bare legs (NRS + 4.3), the lowest increase in patients with C2p & C3 and C4 wearing stockings (NRS + 1.9). Wearing MCS significantly reduced the increase in reported symptoms, in a manner that was similar in all patients. Neither volume increase per se (without and with MCS), nor reduction of the increase with MCS, correlated with the emergence of symptoms (Figure 2).

Follow-up

One week after the consultation, patients completed the s-t VSQ a second time. The rate of return was 80 % (78–83 % per group) and most patients (86 %) had worn the stockings daily and all day. Wearing MCS reduced all symptoms in all patient groups by an average of about 50 %. The highest benefit was observed in patient group C0s (Table IV).

Correlations

The increase in reported symptoms during the stress test was correlated with the symptom scores of the s-t VSQ reported at baseline and one week thereafter (ESM 3). Significant correlations were found in all patient groups, on the one hand, between the symptoms reported at baseline and the stress induced symptoms with bare legs (overall $r = 0.53$), and, on the other hand, between the symptoms reported at the end of the week after the consultation and the stress-induced symptoms with wearing stockings ($r = 0.48$).

Discussion

Our study investigated the effect of gravitational stress on leg volume and symptoms in patients with various manifestations of venous disease. The venous findings and the personal characteristics of the patients separated into the four diagnostic groups were expectedly different whereas the prevalence and the type of VS were the same. The PsySoVDQ data were concordant with those of the

symptomatic subjects representing the general population [7] with the exception that the patients of our study showed a higher level of somatic symptoms. The difference is explainable, assuming most patients visiting a doctor's office do so because of their symptoms and, therefore, rate them higher than when they report them in a population survey. A significant though small increase of somatic symptoms was associated with more severe venous disease in the Bonn Vein Study [7]. In contrast, the psychic VS scores were the same in all three cohorts. Thus, healthy subjects and COs patients describe their symptoms in the same way as patients classified C2 to C4. This suggests the presence of a disease independent constant background perception of the legs' dynamic homeostatic situation which patients regularly describe with the terms common to VS.

The short-term incidence of VS showed the same average intensity of symptoms in all patient groups. The individual patients, however, showed different maximum scores in the different symptoms which reflect inhomogeneity. Thus, the assessment of individual VS adds little to the characterization of venous disease.

When exposed to the challenge of standing, patients in all groups experienced the same increase of leg volume and the same increase in symptoms. Both phenomena could be reduced alike by wearing MCS. However, as observed before in healthy subjects [8, 14, 15], the emergence of symptoms was neither correlated with leg volume increase per se nor with limiting this increase by wearing MCS with one exception that COs-patients with bare legs reported fewer symptoms although they had a greater leg volume increase ($r = -0.34$, $p = .054$). This finding is counterintuitive and needs further study.

The uniformity of the leg volume increase speaks for a consistent phenomenon which, we assume, is the filling of the legs' vein pools with blood not transported upward because of the inactivity of the muscle pump during quiet standing. The process showed a rapid first phase changing into a slower increase of volume after about 2 minutes. The venous capacity of the lower legs, measured here as leg volume increase, was the same in patients with COs to C4 disease and the same as in healthy subjects [14, 15]. In a pilot experiment using ultrasound to measure the filling of the femoral vein under the same experimental conditions, we found that the completely emptied femoral vein was filled to its maximum capacity after taking the upright position within about 15 seconds at the popliteal level and within about 45 seconds at the inguinal level [15]. Clearly, the Bodytronic system of measuring leg volume was too slow to monitor this early phase. However, the findings do not suggest that the results would have been different if we could have started measurements earlier.

The symptoms evoked during standing showed other dynamics, increasing linearly to the end. The symptoms reported with bare legs correlated strongly with the symptoms experienced during the week before the consultation when MCS were used infrequently. The result of the stress test with MCS correlated with the symptoms experienced during the week after the consultation when MCS were

used regularly. MCS showed the same efficacy in all patient groups under stress and everyday conditions with one exception: MCS were more effective in COs patients. This may be because COs patients perceive the physiologic consequences of standing greater than the patients with overt venous disease.

Previous studies which addressed vein volume and/or leg volume increase during short-time standing [19–21] had reported results like ours but did not assess symptoms. Clinical studies which compared leg volume changes and symptoms over a longer period had come to results corresponding with ours [5, 8, 22] but did not statistically compare volume increase with symptoms. The most recent reviews [23, 24] cited no additional studies addressing this correlation. The essential findings of this and previous studies emphasize the notion that standing is a strong physiologic challenge not only for the legs but for the entire subject. The reported VS are epiphenomena which reflect a disturbance of the legs' momentary homeostasis, its neuronal control and, ultimately, its impact on psychic processing [16, 17, 25, 26]. Altogether, our findings make it likely that the disturbance affects several tissues and not just the veins in their compartments [7, 8, 14, 15]. Compression modifies the vein capacity and reduces oedema. Inherently, stockings compress the skin where various tactile receptors are located, and this has the potential to modify the perception and neural reporting of the homeostatic changes that have occurred [27–29].

Limitations

The study has limitations and strengths. Its design intended to be as close to real life as possible. Therefore, we invited regular patients to take part. The patients underwent routine venous work-up supplemented by a test of standing and a period of wearing MCS the following week. To satisfy the statistical requirement of comparing groups of similar size, we had to stop including patients when the pre-set number of participants in each group was reached. The aim of including at least 10 men into the COs group was not reached because such patients were seen too rarely. Second, the stress test was performed with bare legs first and then with MCS. This order may have introduced bias. Third, we found it difficult to identify healthy subjects as concurrent controls who were naïve about venous disease and examine them in vein clinics using the patient-oriented protocol. For that reason, we drew on the data set of the Bonn Vein Study II [7]. Fourth, we used low-pressure stockings for patients in the COs and C2 groups and high-pressure stockings for patients in the C3 and C4 groups. This was a compromise between the fact that, in Germany, almost every patient is prescribed high pressure stockings [30] and the evidence indicating that subjects in groups COs and C2 are better served with low pressure stockings [13]. At last, our study intended to use the gravitational stress test as a diagnostic tool for venous disease. The

presence of such a connection was disproved and another role was attributed to VS. The strengths are the use of a standardized, well-tolerated and repeatable stress test, the use of well-established questionnaires, and the categorization of venous disease according to the CEAP classification. This study is the final step in a series of articles which produced increasing evidence that venous symptoms can be described as dynamic homeostatic feelings [16, 17].

Conclusions

Patients often and spontaneously describe their symptoms as feelings. Our neuropsychological considerations are in keeping with the patients' description. As Damasio's concept of the role of feelings has been used here for the first time, some practical hints might be added. One regards the therapeutic dilemma that may arise when patients report strong VS in the presence of minor venous pathology. Clearly, interventions may well have positive effects on symptoms [31, 32] as they can replace negative with positive feelings, allowing the peripheral structures to send signals of normality more often to the pertinent neural areas. Alternatively, they might repress the memory of the emotional stress which accompanied the symptoms. If VS are reported in the absence of a venous pathology or again when an intervention did not bring the expected result, they might be considered dynamic homeostatic feelings. In this case, one might first consider their background. In general, feelings appear to primarily fulfil a warning function. Worried individuals are thereby informed about potentially threatening homeostatic disequilibria – whether physical or psychic – and these feelings prompt them to take counter-measures. Regarding VS, the feelings often result from a psychic hindrance of locomotion. This might mean walking off in order to ease the sensations. In women, VS are often connected with an inability to attribute to the legs their libidinous role. Wearing light MCS can reduce the VS and the sequels of emotional stress [5, 8, 13, 23]. Clearly, the molecular biology of the local homeostatic disturbance and the mechanisms of its neuronal reprocessing remain to be discovered. The present work expands the concept of what VS mean and in so doing, might modify treatment strategies.

Electronic supplementary materials

The electronic supplementary materials (ESM) is available with the online version of the article at <https://doi.org/10.1024/0301-1526/a000807>.

ESM 1. Figure.

Study design, flow chart and number of patients.

ESM 2. Table.

Venous diagnosis of the leading and the non-leading leg (CEAP-class; N (%)).

ESM 3. Table.

Correlation of the symptoms (s-t VSQ, short-term VS Questionnaire).

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