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Volume control of the lower limb with graduated compression during different muscle pump activation conditions and the relation to limb circumference variation

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1 Type of Research: Single-center prospective crossover study.

2 Key Findings:

3 In healthy individuals below-knee 16-20 mmHg graduated compression stockings (GCS)
4 significantly reduce lower limb volume after 30 minutes of standardized walk (-4.4%), sitting (-
5 4.8%) and standing (-4.6%). Bioimpedance analysis demonstrated a significant extracellular
6 water reduction while walking with GCS ($p < 0.017$). The interface pressure variation between
7 ankle and calf values can become progressive rather than graduated based on the lower limb
8 circumference variation.

9 Take home Message: 16-20 mmHg below knee graduated compression stockings significantly
10 reduce healthy subjects lower limb volume after 30 minutes of sitting, standing or standardized
11 walk. Different B-B1 circumferences variations influence the interface pressure gradient
12 significantly.

13

14 Table of Contents Summary

15 This prospective crossover study demonstrates the lower limb volume reduction after 30 minutes
16 of standing, sitting or walking while wearing below knee 16-20 mmHg graduated compression
17 stockings.

18 Below-knee 16-20 mmHg can effectively control leg edema in standing, sitting and walking,
19 with a major effect in sitting, and independently the leg shape geometry influence on the
20 interface pressure profile.

21

22 **ABSTRACT**

23 **BACKGROUND:** Literature supports graduated compression stockings (GCS) use for leg

1 edema. Nevertheless, there is a paucity of data on the GCS effect related to sitting, standing and
2 walking on limb edema. Different limbs shapes data and their impact on GCS exerted pressure
3 are lacking. This investigation provides evidence-based information on GCS effect on edema
4 reduction and the limb circumference gradients impact on GCS pressure.

5 **METHODS:** Thirty healthy individuals (15M-15F, mean age 32 ± 5 years) were included. All
6 the subjects underwent lower limb volume (Kuhnke formula) measurement, before and after
7 sitting for 30 minutes, wearing below-ankle non-compressive socks. The same assessment was
8 repeated 7 days later, in the same subjects, but wearing a below-knee 16-20 mmHg GCS. At 7
9 days interval, one week with below-ankle non-compressive socks and one week with below-
10 knee 16-20 mmHg GCS, all the subjects repeated the same protocol including standing and
11 walking. Ten subjects underwent bioimpedance assessment (Biody Xpert IITM) before and after
12 sitting, standing and walking. In the same group, B and B1 interface pressure values were
13 measured.

14 **RESULTS:** All 60 limbs completed the data collection. Sitting or walking, without GCS, led to
15 no significant volume changes, while volume was decreased by the use of GCS (-4.8%,
16 $p<0.00001$; - 4.4%, $p<0.00001$, respectively). Standing up, without GCS, led to an increase in
17 volume (2.7%, $p<0.0001$), while limb volume was decreased (4.6%, $p<0.0001$) by use of
18 GCS. Biompedance showed an extracellular water reduction only while walking with GCS
19 (from $40.55\pm 1.66\%$ to $40.45\pm 1.71\%$, $p<0.017$). Mean interface pressure was 19 ± 5 mm Hg (B)
20 and 16 ± 5 mmHg (B1). The interface pressure variation from B to B1 was not homogenous
21 among participants (mean percentage variation of $-13\pm 25\%$, ranging from -54% to 16%). A
22 negative linear trend between pressure variation and circumference percentage increase was
23 found, the sub-analysis excluding the two outliers shows a strong negative linear correlation

1 (Pearson's coefficient: $r=-0.96$).

2 **CONCLUSION:** GCS lead to a significant limb volume reduction irrespective of limb position
3 and muscle pump function. However, extracellular fluid is only mobilized during muscle
4 contraction while walking with GCS. Interestingly, different lower limb circumferences
5 variations influence the interface pressure gradient, indicating the importance of proper fitting of
6 both B and B1 during prescription. These data provide a foundation to future investigations
7 dealing with GCS effect on fluid mobilization and with limb geometry impact on compression
8 performance.

9

10

11 **Keywords**

12 Compression, Volume, Bioimpedance, Edema.

13

14 **Conflict of interest** No conflict of interest to declare. No funding was provided for this
15 investigation. Graduate compression stockings were offered by MEDI GmbH & Co KG,
16 Bayreuth - Germany.

17

18 **INTRODUCTION**

19 GCS are classified according to the interface pressure exerted at the B point, which is defined as
20 the ankle point of minimum girth.¹

21 According to the international standards, in graduated hosiery the interface pressure should
22 decrease while moving from the ankle toward the knee.²

1 Literature has already shown that, in vivo, this graduated gradient is not always present and that
2 an inversion of the pressure profile can be found, presenting a higher pressure at the calf than at
3 the ankle (so called progressive compression).³⁻⁵

4 Importantly, whenever properly prescribed, both graduated and progressive compression
5 stockings have demonstrated to deliver a positive effect on the limb drainage, with the
6 progressive ones even improving the ejection fraction compared to the graduated hosiery.

7 In 2002, Aryal et al. assessed the interface pressure in healthy subjects wearing 23-32 mmHg
8 below knee GCS while lying supine and in standing. Data showed that the interface pressure
9 values at the ankle and below the knee correspond to the ones declared by the manufacturer, but
10 that in supine and even to a greater extent in the standing position, at the mid-calf, the interface
11 pressure was higher than at the ankle: a phenomenon that is much more evident at the medial
12 than at the lateral aspect of the leg.⁷

13 The finding of significant pressure variations along the leg based on the body position was
14 confirmed by Liu et al research.⁸ These investigations indicate how body postures may be one of
15 the most important factors influencing the skin pressure profiles.

16 However, homogeneous data collection reporting eventual differences in compression
17 performance in the sitting, standing, and walking position/activities are missing.

18 One of the few published reports on the topic is from De Godoy research group, and highlights
19 how GCS generate oscillatory pressure profiles during walking, with larger pressures producing
20 larger variations during muscle activity. Yet the investigation focused only on the walking
21 scenario, without comparison with the standing and/or sitting position.⁹

22 An evaluation of the postural impact on GCS pressure profiles was performed by Wildin,
23 assessing the same patient in the supine, sitting and standing positions. Only in the standing and

1 in the supine positions were appropriate median pressure profiles obtained. In sitting, the flexed
2 knee was associated with an interface pressure in excess of 28 mmHg at the popliteal level.
3 Moreover, progressive rather than graduated pressure was reported in up to 70% of cases.⁴
4 To the best of our knowledge, no investigations have correlated the lower limb circumferences
5 variations with interface pressure gradients along all of the different leg sectors, with a lack of
6 data regarding the different performance of GCS on different limbs conformations.¹⁰ Graduated
7 compression stockings (GCS) represent a fundamental tool in the management of subjects
8 affected by or at risk of lower limb edema.¹¹

9 The present work is aimed at evaluating the effect on lower limb volume variation of 16-20
10 mmHg GCS in the sitting, standing, and walking positions/activities, both by volumetry and
11 bioimpedance assessment.

12 Secondary endpoint is the correlation among the lower limb circumference variations and the
13 related interface pressure values every 4 cm along the leg (defined circumferential sectors
14 measured on the medial aspect of the leg).

15

16 **METHODS**

17 Thirty healthy individuals (15M-15F, mean age 32 ± 5 years) were included in the study.

18 Inclusion criteria were age from 18 to 75 years, body mass index <35 kg/m².

19 Exclusion criteria were cardiac comorbidity (e.g. congestive heart failure, cardiomyopathy,
20 coronary artery disease), chronic venous disease, lower limb arterial disease, use of drugs
21 affecting venous volume (e.g. diuretics, antihypertensives), lymphedema, previous varicose vein
22 treatments, moderate or severe biochemical alterations (e.g. diabetes mellitus, hypothyroidism),
23 chronic kidney disease, sport professionals, and postural musculoskeletal defects.

1 All the subjects underwent lower limb ultrasound evaluation to exclude venous, arterial, and
2 lymphatic impairment. Lymphatic disease exclusion was determined by clinical examination and
3 by ultrasound scanning reporting absence of the following findings: dilated lymphatic collectors,
4 thickened dermis, thickened and high-echoic subcutis, or reduced echo-contrast between the
5 dermis and subcuticular fat. A weight-bearing analysis excluded significant postural defects
6 potentially altering the limb drainage.¹²

7 All the subjects performed the following activity protocol, always in the same sequence, with
8 each activity separated by a one week period:

9 a. Sitting for 30 minutes, wearing below-ankle non-compressive socks.

10 b. Sitting for 30 minutes, wearing GCS.

11 c. Standing still for 30 minutes, wearing below-ankle non-compressive socks.

12 d. Standing still for 30 minutes, wearing GCS.

13 e. Walking for 30 minutes at a standardized pace, wearing below-ankle non-compressive socks.

14 f. Walking for 30 minutes at a standardized pace, wearing GCS.

15 The standardized pace was performed on a treadmill, under heart frequency monitoring, at a
16 speed related to the 70% of individual estimated maximal heart rate ($208 - 0.7 \times \text{age}$) according to
17 the Tanaka equation.¹² Each assessment was performed at 7 day intervals for all of the activities
18 (a-f above).

19 GCS used was a below-knee 16-20 mmHg (Mediven Elegance, MEDI GmbH & Co KG,
20 Bayreuth, Germany). The GCS were sized by one of the investigators (EM) at the enrollment
21 visit. Measures were taken between 8 and 9 am, with the subject standing up barefoot, measuring
22 the limb circumference at the ankle, at the largest point of the calf and the length from the
23 ground to the knee. The male population received 10 III, 4 IV and 1 V GCS sizes, while the

1 female population received 12 II and 3 III.
2 All of the tests were performed in the same room with controlled temperature set at 23 °C,
3 between 3 PM and 5 PM.
4 During the different activities, all of the subjects were instructed to always wear the same
5 comfortable sport shoes and to report eventual discomfort associated with GCS use.
6 Before and after all of the above reported activities (a-f above), in all patients, lower limb
7 volume was calculated by the mathematical truncated cone formula of Kuhnke ($V_{limb} = \sum X^2/\pi$)
8 assessing the leg circumference with a centimeter tape (Gulick Anthropometric Tape, Alimed),
9 starting from above the malleolar level all the way up to the knee every 4 cm, for a total of eight
10 segments (sectors).^{14,15}
11 Bioimpedance measurement (Biody Xpert II™) was performed before and after all of the above
12 reported activities (a-f above) in 10 subjects, the extracellular water rate was calculated
13 according to the following formula: (extracellular water/extracellular + intracellular water)*100.
14 At the beginning of the first session wearing GCS, the same 10 volunteer underwent also
15 interface pressure measurement at the B and B1 point (area at which the Achilles tendon changes
16 into the calf muscles).¹⁶
17 The protocol and the informed consent were approved by the Institutional Ethics Committee at
18 the University of Ferrara, all the individuals signed a proper informed consent.

19

20 ***Statistical analysis:***

21 InStat GraphPad (GraphPad Software, Inc. La Jolla, CA 92037 USA) was used for statistical
22 analysis. The data were expressed as mean \pm standard deviation, or percentage. Kolmogorov-
23 Smirnov test was used to assess the data distribution.

1 The differences between volume values in the different postural condition with and without GCS
2 were performed using Student's t-test, Wilcoxon Signed-Ranks Test when appropriate. Pearson's
3 correlation coefficient was used to calculate the linear correlation between interface pressure
4 variation and leg circumference percentage increase. The difference among the baseline volume
5 of each sessions and the volume reductions associated with GCS use were calculated using One-
6 way ANOVA test for repeated measures.

7 Statistical significance was defined as $p < 0.05$.

8

9 **RESULTS**

10 All 60 limbs presented neither vascular nor postural alterations and completed the data
11 collection.

12 Sitting or walking, without GCS, led to no significant volume changes (from 2534 ± 402 to 2547
13 ± 380 mL (0.5%) $P=.333$; from 2513 ± 406 to 2525 ± 413 mL (0.4%) $P=.096$) respectively, while
14 volume was significantly decreased by the use of GCS (from 2483 ± 400 to 2362 ± 406 mL (-
15 4.8%) $P<.00001$) in the sitting, and (from 2469 ± 432 to 2361 ± 416 mL (- 4.4%) $P<.00001$) in
16 the walking position/activity.

17 Standing up, without GCS, led to a significant increase in volume from 2493 ± 399 to $2561 \pm$
18 392 mL (2.7%, $P<.0001$), while limb volume was significantly decreased from 2497 ± 386 to
19 2381 ± 367 mL (4.6%, $p<0.0001$) by use of GCS during the standing position, (Table I).

20 The trend of the single cases of all the GCS sessions volume changes is reported in Figure 1.

21 The baseline lower limb volume showed no significant difference at the beginning of every
22 session ($P=.2541$) No significant difference was reported in the volume reduction associated with
23 GCS use in standing, sitting and walking ($P=.6971$).

1 Biopedance analysis showed a significant extracellular water reduction only while walking
2 with GCS (from $40.55 \pm 1.66\%$ to $40.45 \pm 1.71\%$, $P < .017$).

3 Mean interface pressure was 19 ± 5 mm Hg (B) and 16 ± 5 mmHg (B1).

4 The interface pressure variation from B to B1 was not homogeneous among participants (mean
5 percentage variation of $-13 \pm 25\%$, ranging from -54% to 16%).

6 Figure 2 shows a negative linear trend between pressure variation and circumference percentage
7 increase. The sub-analysis excluding the two outliers shows a strong negative linear correlation
8 (Pearson's coefficient: $r = -0.96$).

9 No complaints were reported after the GCS use in terms of discomfort.

10

11 **DISCUSSION**

12 The present work data demonstrated that without GCS lower limb oedema occurs after just 30
13 minutes in the standing position in normal healthy individuals, while during the same amount of
14 time the phenomenon is not observed in neither the sitting or walking conditions.

15 Interestingly, in standing, sitting, and walking, application of 16-20 mmHg GCS are able to
16 significantly reduce the lower limb volume, with the maximum effect been observed in the
17 sitting position.

18 This finding is of particular importance considering that a recent Cochrane review pointed out
19 the need of further data related to the use of non-pharmacological interventions for preventing
20 venous drainage impairment in standing and sedentary workers.¹⁷ In another published work
21 from our group, the use of 20-30 mmHg below-knee GCS in healthy subjects showed a
22 significant leg volume reduction by 7.7 and a decreased in perceived exertion after a 30 minutes
23 standardized walk.¹⁸

1 Castilho et al. tested the effect of 20-30 mmHg GCS on 10 healthy runners, focusing on the air-
2 plethysmographic parameters variation, showing a hemodynamic improvement. Also this
3 investigation points out the importance of further research in the evaluation of the relationship
4 between total limb volume, its different intra and extra-vascular components and the related
5 eventual edema.¹⁹

6 In the herein presented study 16-20 mmHg GCS were used and the lower limb volume decreased
7 by 4.4%, and with our previous work demonstrating a 7.7% volume reduction while wearing 20-
8 30 mmHg GCS, suggest a dose-dependent mechanism between compression values and oedema
9 reduction: a phenomenon in line with observed plethysmographic evidence of a dose-effect
10 mechanism of compression on venous emptying.²⁰

11 The clinical impact is not the endpoint of the herein reported investigation that is focused in
12 providing new evidence in graduated compression mechanism and related impact on lower limb
13 volume control. Yet, variations of few hundreds of milliliters in healthy leg volume have been
14 associated with an improvement of the perceived exertion after 30 minutes of standardized
15 walk.¹⁸

16 Previously published investigations demonstrated the possible utility of adequate compression in
17 prolonged standing up and/or sitting workers with minimal supporting evidence, yet, to our
18 knowledge, this is the first investigation assessing in the same subjects in homogenous
19 conditions, the effects of GCS in the sitting, standing, and standardized walking
20 position/activity.^{21,22}

21 The herein reported study population showed a homogeneous trend in lower limb variation in the
22 different conditions of sitting, standing and walking. A less homogeneous trend was reported in

1 an interesting paper by Goddard demonstrating that approximately two fifths of women
2 experience substantial pooling in the calf region whenever in a dependent position.²³
3 Apart the only female population, other significant differences characterize the Goddard
4 investigation by the herein presented one: Goddard measured the pooling by air
5 plethysmography focusing just on the calf part covered by the plethysmographer calf, while our
6 investigation used lower limb volumetry by validated Kuhnke formula.¹⁴ The different findings
7 of the two studies highlight also the importance of future investigations focused on the different
8 components of lower limb volume (intra vs extravascular compartment).
9 Interestingly this study shows a slightly more pronounced GCS effect on oedema formation in
10 the sitting position. The rationale could be associated with the smaller hydrostatic column
11 compared to the standing position, with consequent lower hydrostatic pressure to be counteracted
12 by GCS.²⁴
13 Yet no statistical significance was reached in the present study population, so making further
14 wider data collection on the topic needed.
15 The investigation also confirms that high pressure values are not needed to control lower limb
16 oedema formation.^{25,26}
17 Bioimpedance represents a useful and still underused evaluation tool in lower limb oedema
18 formation and GCS related control.^{27,28} The herein reported data demonstrated that only after
19 walking with GCS a significant decrease in extracellular fluid was reported, but not with
20 standing or sitting while wearing GCS. The possible interpretation is that the combined effect of
21 calf muscle pump activation and GCS is needed to generate a significant extracellular fluid
22 movement. Indeed, lower limb volume change does not overlap with venous ejection.
23 Future research lines will have to clarify the relationship of lower limb volume and extracellular

1 fluid components in the determination of the total volumetry during different limb activities (i.e.
2 sitting, standing, and walking).

3 Indeed, it can be hypothesized that in the sitting position GCS are acting more in the reduction of
4 the venous volume component, so that the lower hydrostatic load facilitates their action.

5 However, while walking, GCS could maximize their massage effect on the extracellular space,
6 so favouring extracellular fluid reabsorption, as indicated by the bioimpedance analysis. Further
7 investigations are needed in order to clarify this interesting finding.

8 The interface pressure assessment in B and B1 demonstrated that the mean pressure values
9 correspond to the ones declared by the manufacturer.

10 At the same time, a significant heterogeneity in the B-B1 pressure gradient was reported, ranging
11 from -54% to 16%. Interestingly, a linear trend has been noticed between the interface pressure
12 values and the leg circumferences, demonstrating that lower limb circumference variations can
13 impact the GCS pressure gradient profiles.

14 These data point out the importance of a proper lower limb sizing including not just the ankle
15 measurement but also the calf area and leg length, so to allow for a proper GCS prescription.

16 Moreover, such interface pressure variability urges future scientific data collection to always
17 include the report of how much pressure is exerted by the specific GCS both in B and in B1.

18 Lack of this information in future data collection could represent the bias of analyzing different
19 scenarios that are not reflecting homogenous conditions, and making data comparison difficult.

20 The importance of a better awareness and understanding of the interface pressure has been
21 recently reported also in sport compression stockings showing how in vivo and ex vivo pressure
22 profiles can present significant heterogeneity.²⁹

1 This has been also confirmed by Lurie et al. showing the significant variability in B1 interface
2 pressure with the use of different GCS brands;³⁰ similar differences among GCS brands were
3 reported also by Ma et al.³¹

4 Importantly, from the results of this study, it would be imperative for future data analysis related
5 to compression to report exactly what interface pressure is obtained on the specific patient, since
6 different patients with different circumference variations between B and B1, wearing the same
7 GCS could actually present different interface pressure values and gradients (i.e. graduated vs.
8 progressive).

9 As previously reported in the literature,^{3,4} the present investigation confirms that a significant
10 number of patients presents with a progressive rather than graduated profile moving from the
11 ankle up, while wearing a GCS. This finding doesn't diminish the value and efficacy of GCS in
12 lower limb oedema control and drainage facilitation. Indeed, previous investigations have
13 already shown that a progressive rather than graduated compression can be extremely beneficial
14 in terms of oedema reduction³² and calf ejection fraction.⁶ These data support the notion that
15 GCS are important in leg oedema reduction in a number of different postural positions and
16 activities, and that further research is required to understand the mechanism of interstitial fluid
17 (extracellular) mobilization induced by GCS while ambulating. Importantly, proper measurement
18 of the limb is required to maximize the effect of GCS, and that limb circumference variations
19 affect the interface pressure when measured during GCS wear at B and B1.

20

21 **CONCLUSIONS**

22 In conclusion, this investigation demonstrates that lower limb oedema is generated after just 30
23 minutes of standing position, and that 16-20 mmHg GCS are able to significantly reduce the

1 lower limb volume in the standing, as well as the sitting and walking conditions.
2 Walking with GCS is also associated with a significant decrease of the extracellular fluid, as
3 demonstrated by a bioimpedance analysis.
4 The leg circumference variations is a fundamental parameter to be taken into consideration in
5 GCS pressure profiles, with potential inversion of the gradient from graduated to progressive in a
6 significant number of cases, based on the different limb sectors circumferences. Further research
7 on the in vivo GCS performance and related fluids shifts is needed.

8

9

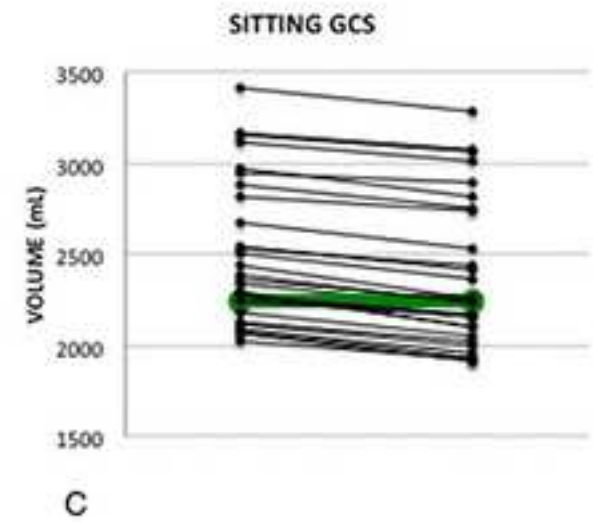
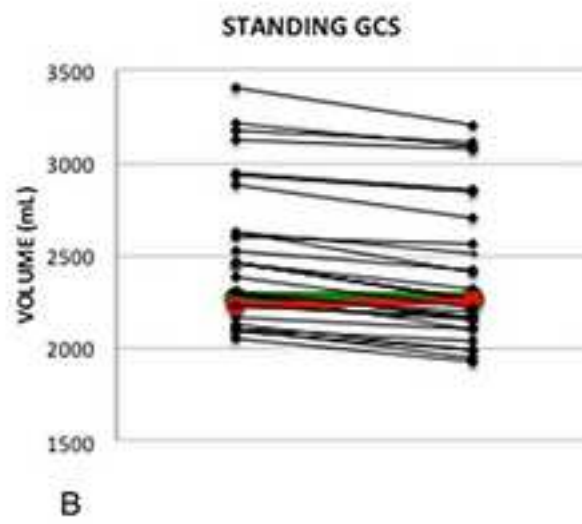
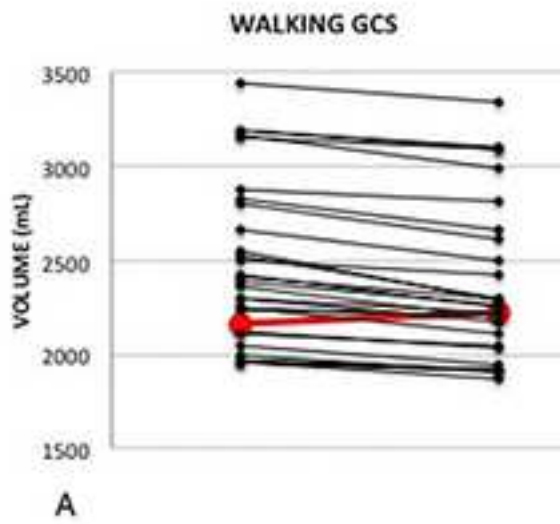
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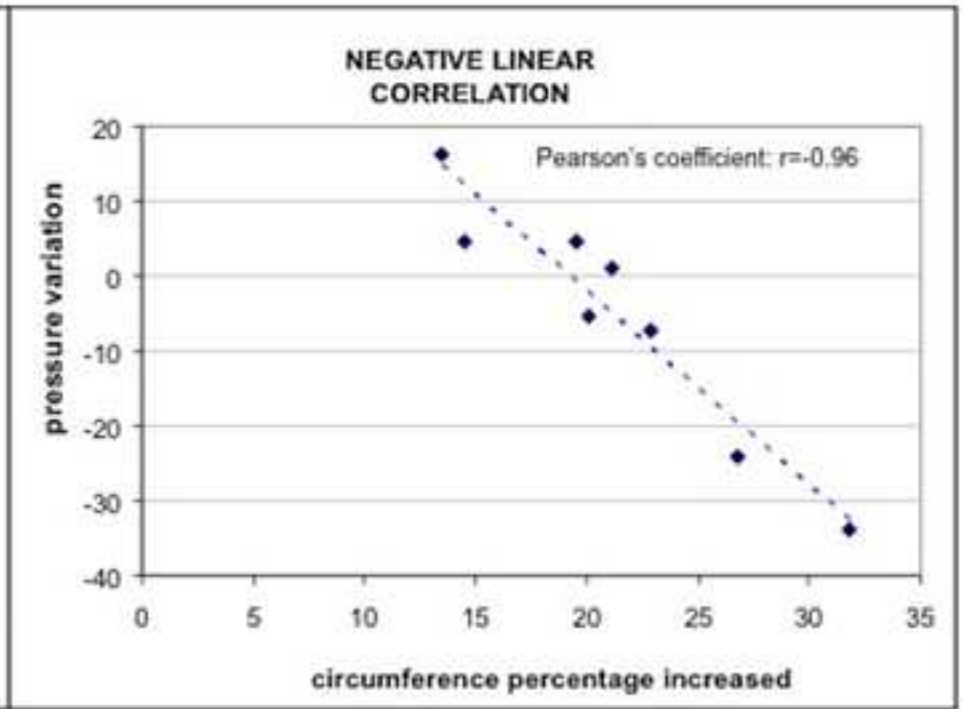
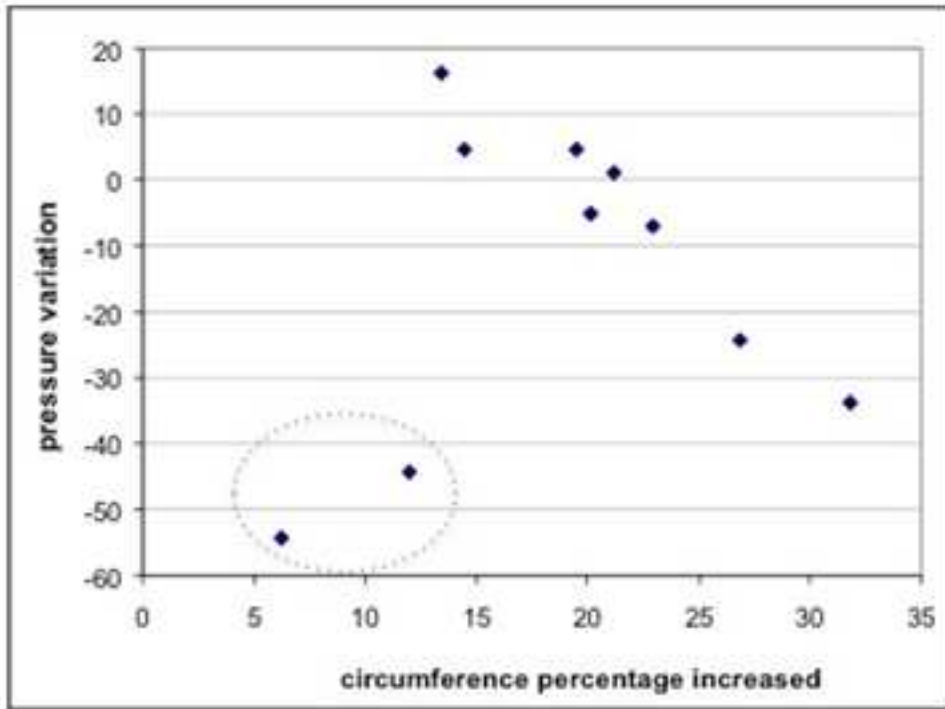


Table I.

| | Limb Volume (mL) Pre Sampling (mean±SD) | Limb Volume (mL) Post Sampling (mean±SD) | Mean variation (mL) (95% CI) | Mean % variation | P value | |
|-----------------------------------|--|---|---|-----------------------------|----------------|---|
| <i>WALKING NO GCS</i> | 2513 ± 406 | 2525 ± 413 | +10 (-2 – + 21) | 0.4% | .096 | — |
| <i>WALKING GCS</i> | 2469 ± 432 | 2361 ± 416 | -108 (-133 – -84) | - 4.4% | <.00001 | ↓ |
| <i>STANDING NO GCS</i> | 2493 ± 399 | 2561 ± 392 | +68 (+45 – + 90) | 2.7% | <.0001 | ↑ |
| <i>STANDING GCS</i> | 2497 ± 386 | 2381 ± 367 | -116 (-139 – -93) | - 4.6% | <.0001 | ↓ |
| <i>SITTING NO GCS</i> | 2534 ± 402 | 2547 ± 380 | +13 (-14 – +41) | 0.5% | .333 | — |
| <i>SITTING GCS</i> | 2483 ± 400 | 2362 ± 406 | -120 (-135 – -105) | - 4.8% | <.00001 | ↓ |

1 **Figure/Table Legend:**

2 **Figure 1:** The trend of the single cases of all GCS sessions volume changes. A) Single volume
3 changes in walking with GCS. In red the single case showing an increased volume. B) Single
4 volume changes in standing with GCS. In red the case showing an increased volume. In green
5 the case showing no volume change. C) Single volume changes in sitting with GCS. In green the
6 single case showing no volume changes.

7

8 **Figure2:** Negative linear trend between pressure variation and circumference percentage
9 increase. The sub-analysis excluding the two outliers shows a strong negative linear correlation
10 (Pearson's coefficient: $r=-0.96$).

11

12 **Table I:** Lower limb volume (mL) assessment by truncated cone formula (Kuhnke formula), pre
13 and post exercise (walking) or postural condition (standing and sitting), with and without
14 graduated compression stockings (GCS).