

On physiological edema in man's lower extremity

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Summary. To examine whether the so-called musculo-venous pump counteracts the development of interstitial edema in the lower extremities of man in the upright position, the volume changes in the calf which occurred during twenty minutes of rhythmic muscular exercise were measured in twenty-three subjects by impedance-plethysmography. The results were compared with the volume increase found during quiet relaxed standing for the same length of time. Contrary to the hypothesis, and edema-protective effect of the musculo-venous pump could only be shown in about half the number of the subjects. In the others, muscular exercise led to increases in calf volume which were higher than those measured in the normal upright position. These results show that the calf muscle pump does not generally have an edema-protective effect but rather that muscle contractions also activate mechanisms which stimulate the extravasation of fluid.

In a second test-series with twenty subjects, changes in calf volume were measured during the course of the day. In nearly all cases, the calf volume was greater in the evening than in the morning. It could be shown that the volume increases in the evening are caused by an increase in extravascular fluid. Compared to the increase in extravascular volume occurring during twenty minutes, in a normal upright position, the accumulation of extravascular fluid during the day is, however, remarkably low. Although it is still unknown how interstitial edema in man's lower extremities is prevented during the day, these findings lead to the hypothesis that the edema-preventing mechanisms, for instance the muscle-lymph pump, do

not become maximally effective until a certain volume has accumulated in the interstitial space.

Key words: Edema-preventing mechanisms — Orthostasis — Muscle pump — Interstitial fluid — Transcapillary filtration

Introduction

Changes of body posture from a horizontal to a standing position in man cause rapid blood volume changes in the vessels of the lower extremities (Asmussen et al. 1939a, 1939b; Asmussen 1942; Krug and Schlicher 1960; Rieckert 1970; Marées 1974; Kirsch et al. 1980) due to hydrostatic effects. The resulting pressure increases also lead to rises in the effective filtration pressure. According to Starling's hypothesis (Starling 1886), these cause an increased net filtration of fluid into the interstitial space, and can be demonstrated during continued orthostasis as slow volume increases after initial rapid vascular filling (Atzler and Herbst 1923; Looke 1936; Hörig 1976).

According to numerous studies (Pollack and Wood 1949; Henry and Gauer 1950; Höjensgard and Stürup 1953; bibliography cf. Kriessmann 1975), the increased venous pressure in the lower extremities in a normal standing position is reduced by activating the muscle pump: during contraction, the skeletal muscles induce venous compression, which causes a rapid emptying of the respective venous segments. Due to the function of the venous valves, this emptying takes an exclusively centripetal direction. During muscular relaxation, the closed valves prevent reflux from proximal to distal sections of the venous system. Thus, the rate of renewed filling of the veins is re-

latively slow and depends solely on the arterial flow via the capillaries. Furthermore, with closed venous valves, the blood column is divided into various short segments, thus reducing the local hydrostatic pressure to the level of the individual segments. Thus, considering the temporal mean, the venous pressures in the lower extremities decrease at varying rates. The pressure reductions retroactively also cause a decrease of pressure in the venous section of the capillaries, which, in turn, supposedly lowers the effective filtration pressure and lessens the increased filtration in the normal upright position (Henry and Gauer 1950; Gauer 1972). To our knowledge, conclusive proof of these hypothetical "edema-protective-effects" of the musculo-venous pump in man has yet to be established.

Standard plethysmographic methods are only partially suited for measurement of filtration-induced volume changes during muscle contraction and during the regular course of the day. Difficulties in obtaining totally identical samples of tissue sections for repeated measurements are one reason for the inadequacy of this method. However, this requirement is met by an impedance-plethysmographic procedure (Stick 1981). The present study utilizes this procedure in order to measure volume changes in the lower leg during 20 min of relaxed standing and 20 min of standing with rhythmic muscle contraction, and during the regular daily activities of the subjects.

Subjects and methods

Impedance plethysmography is an indirect method of recording volume changes in a section of an extremity by measuring the variations in electrical impedance. With the aid of two exterior electrodes, a constant alternating current (4 mA, 100 kHz) is led through a segment of the body. Based on the potential differences between another two electrodes, which are located between the outer electrodes and form the boundaries of the measured segment, the instrument (IfM impedance cardiograph Model 304) computes the initial impedance and the changes of resistance in the measured segment. These data, displayed digitally, can be taken off as analogue signals at the instrument's output. Within a certain range, the change in resistance ΔZ is proportional to the change in volume ΔV of the measured segment. According to Nyboer (1970) ΔV can be computed as follows:

$$\Delta V = \frac{L^2}{Z_0^2} \varrho(\Delta Z) \quad (1)$$

Z_0 = initial resistance

L = length of the measured segment

ϱ = specific resistance of the fluid inducing volume changes.

Particulars and sources of error of this method have been detailed elsewhere (Stick 1981). If experimental conditions are

identical and certain requirements are met, the method seems to be suitable for observing volume changes caused by capillary filtration. Compared to measurements using mercury-in-silastic strain gauges, the volume changes are underestimated by impedance plethysmography by a factor of about 1.3.

In relation to other plethysmographic methods, this procedure offers the following advantages: identical segments can be measured repeatedly over long periods of time, while subjects can move about freely since the electrodes are securely attached to the skin by adhesive tape. Furthermore, the sensor cannot slip during muscular exercise, as may occur in other procedures. When using this method, no exterior pressure is exerted on the tissue and volume changes are recorded without inertia.

The tests were conducted on healthy volunteers aged 20 to 35, who showed no evidence of venous valvular incompetence. (Test series 1: $n=23$, 6 women, 17 men; test series 2: $n=20$, 6 women, 14 men). Each subject participated in one series only.

The electrodes were attached circularly around the lower leg using strips of aluminium foil with an adhesive tape backing. Their position was not altered during the respective tests. The pair of electrodes at the boundaries of the measured segment included the largest circumference of the calf of each subject. The length L of the measured segment was 15 cm. The total volume of the measured segment was determined plethysmographically by water displacement.

In test series 1, the subjects lay on a tilt-table in the horizontal position for half an hour during the preparatory stage, and were then moved into a 70° upright position. After standing relaxed for 1 min, the subjects stood on their toes every 10 s following the rhythm of a time signal. This exercise lasted for 20 min, after which the subjects were once again tilted into a horizontal position. After about 30 min, the initial conditions were once again attained, i.e. approximately the same initial impedance Z_0 of the measured segment as at the end of the preparatory stage. Continuing the test, the subjects were brought into an upright position and remained standing supported and relaxed for 21 minutes in this position. Room temperature was in the range of $25^\circ\text{C} \pm 1^\circ\text{C}$.

In test series 2, the subjects drove to the laboratory immediately after getting up in the morning. After attaching the electrodes, impedance was measured every minute for 5 min while standing in a 70° upright position on a tilt-table, followed by a change into a horizontal position which lasted for 5 min as well. The leg position chosen by each subject was registered by a measuring system attached to the tilt-table, thus ensuring that the joints were positioned in exactly the same fashion during later measurements. These tests were repeated at an average of 9 h later in the afternoon of the same day, and in the morning of the following day. In the intervals, the subjects (students) pursued their normal activities.

Statistic evaluation

The arithmetic means and the medians of the measured values were computed for evaluation. In test series 1, these values did not show major differences. In test series 2, however, their quotient was not within the range of the values 0.9 and 1.1. Therefore, preference here was given to the median in order to describe the central tendency (Immich 1974). In order to determine whether the observed differences were statistically significant, the Wilcoxon matched pairs signed rank test was applied. The quality of paired variances was checked with the t -test (Sachs 1974). The straight lines in figure 5 were computed by means of the Gaussian least square method.

Results

a) Test series 1

In the first stage (rhythmic muscular exercise), all 23 tests could be carried through to the 21st minute. In the second stage, however, 8 tests had to be stopped prematurely since the subjects showed early signs of collapse while standing motionless.

Figure 1 shows original recordings of changes in impedance.

Immediately after the subject had been placed in the upright position (arrows), impedance rapidly dropped in both stages of the test (upward deflection). Equation (1) shows that these decreases in impedance correspond with the volume increase of the measured segment caused by the influx of blood into the capacity vessels of the lower extremities due to the change of position. After the first minute the measuring bridge is balanced again ($\Delta Z = 0$). Following the rapid decline in impedance a flattening can be observed during the upright position, which, in turn, is followed by further steady drops in impedance due to increased transcapillary filtration. The upper curve (relaxed standing) shows slight variations expressing the volume pulse and variations of vascular filling due to respiration.

In contrast to this, the recording of the first test stage (lower part of Fig. 1) is influenced by the effects of muscular exercise. Steep and marked rises in impedance (downward deflections) exceeding the range of the recordings can be observed during the contraction of the calf muscles while the subjects are standing on their toes. As soon as the muscles are relaxed, impedance once again approaches the initial value. On the one hand, these rapid changes in impedance during muscular contractions have to be regarded as artefacts due to muscular movement. On the

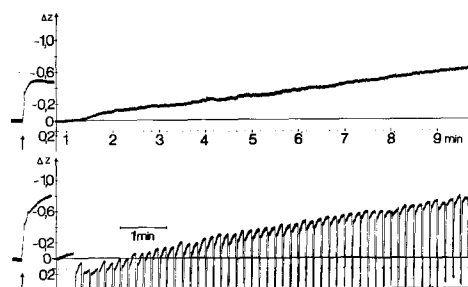


Fig. 1. Part of the original recording of changes in impedance during the upright position. Upper part: quiet standing; lower part: rhythmic heel rising

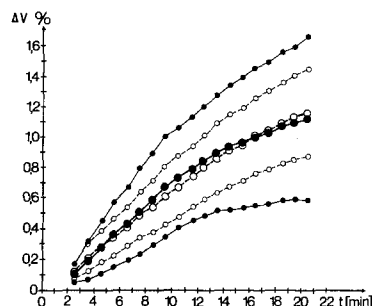


Fig. 2. Arithmetic means (large symbols) and standard deviations (small symbols) of calf volume changes recorded in all subjects during quiet standing (open circles) and heel rising (dots). While the arithmetic means differ only slightly between the two stages, considerable differences in variability can be observed

other, they express fluctuations in blood volume effected by the musculo-venous pump. During contraction, blood is expressed from the vessels of the muscles surrounded by fascia. Upon relaxation, blood once again flows from the arteries into the capacity vessels of the measured section. At the same time, the recorded line broadens due to variations in volume pulse. By plotting the recorded peaks, one arrives at a curve which represents the volume changes induced by transcapillary filtration. This curve is based on 6 values per minute due to the rhythm of muscle contraction. In order to reduce the effect of accidental variations, arithmetic means were computed for every minute. The reference value ($\Delta Z = 0$, $Z = Z_0$) for calculating the slow filtration-induced volume changes in the calf was taken from the respective arithmetic mean of the second minute after the subject had been brought into an upright position. Later variations in impedance may be considered as mainly caused by changes in extravascular volume (Schnizer et al. 1978). According to Nyboer's derivation of equation (1), the specific impedance of the interstitial fluid ($\rho = 60 \Omega \cdot \text{cm}$), therefore, has to be considered when computing this volume change (Stick 1981).

Figure 2 shows the mean volume changes of all subjects in both stages of the test. On average, the calf volume increase is identical in both test stages. However, the variability in volume increases was markedly greater during muscular exercise.

For the 15 subjects who completed 20.5 min in a relaxed upright position, the arithmetic mean of the volume changes in stated as a percentage of the initial volume [ml/100 ml] amounted to $\bar{x} = 1.13\%$ (medium $\bar{x} = 1.16\%$), the minimal value was 0.56%, the maximum value was 1.63%, the

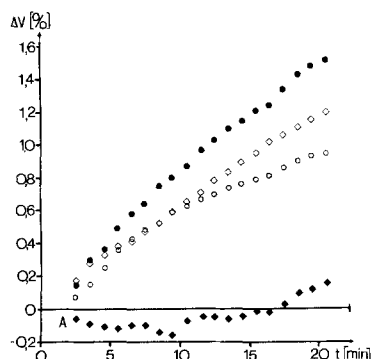


Fig. 3. Calf volume changes during muscular exercise (solid symbols) and the increases in calf volumes during quiet standing (open symbols). While in one subject (squares) the volume of the calf during muscular exercise remains nearly unchanged, in the other subject (circles) the calf volume during rhythmic heel rising increases faster and more markedly than during motionless standing, where the increase in calf volume is similar in both subjects

standard deviation was 0.28%. The comparable arithmetic mean $\bar{x} = 1.09\%$ ($\bar{x} = 1.08\%$) computed for muscular exercise did not show a significant statistical difference. The mean difference as only $\bar{x}_d = 0.04\%$ ($\bar{x}_d = 0.05\%$). In contrast to this the variance differed markedly. After 20.5 min of rhythmic muscular exercise, the minimum increase in volume was 0.16%, maximum change reached 2.34%, and the standard deviation amounted to 0.54%.

The variances of values recorded at 5.5 and 20.5 min after the subjects had been moved into an upright position showed statistically significant differences between the two stages:

$$5.5 \text{ min: } \hat{t} = 2.899 > 2.831 = t_{21}; \alpha = 0.01$$

$$20.5 \text{ min: } \hat{t} = 2.644 > 2.160 = t_{13}; \alpha = 0.05$$

The extreme values of the differences computed for every subject ranged from a minimum of 0.65% to a maximum of 1.04% after 20.5 min.

Figure 3 shows the measured values of the tests with this extreme pattern. In one subject (squares), the muscle pump has a marked edema-protective effect as expected from the hypothesis stated in the introduction. In relaxed standing (open squares), a slow, continual increase in calf volume occurs due to increased transcapillary filtration. However, with rhythmic muscle contractions (solid squares), lesser volume increases can be observed, with the calf volume even reducing at the beginning of the test. In the other subject (circles), the increase in volume during rest (open circles) is similar to that of the first subject. Dur-

ing muscular exercise (dots), however, all values exceed the comparable values during rest, with the rate of volume increase always greater than that during rest. At the end of the test periods, the muscular exercise caused a reduction by 87% in the first case, and an increase by 62% in the second case as compared to the values measured during relaxed standing.

b) Test series 2

Figure 4 shows the results of the second test series for all 20 subjects. With exceptions in 2 cases, the calf volume had increased in the evening when compared to the initial morning value ($\Delta V = 0$) and once again approximated the initial values on the following morning. In the evenings, volume changes recorded while the subjects were supine on average amounted to:

median: $\bar{x} = 1.7\%$ (arithmetic mean $\bar{x} = 1.6\%$). The 95% confidence interval for the median was within 1.5% and 2.1%. The median of the volume changes measured in an upright position amounts to $\bar{x} = 1.8\%$ and is almost identical with that computed in lying. The average volume change on the second morning was rather low compared to the initial value observed on the first morning: median $\bar{x} = 0.1\%$ ($\bar{x} = 0.2\%$). The 95% confidence interval of the median comprises zero: $-0.14\% < \bar{\mu} < 0.34\%$. The increases in calf volume

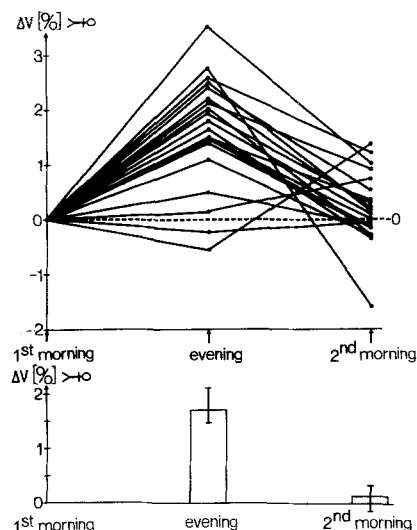


Fig. 4. Volume changes in the calf during 24 h. The upper part shows the individual volume changes of all 20 subjects in the evening and the following morning, the lower one illustrates the medians and their 95%-confidence intervals. All changes are related to the initial volumes measured on the first morning

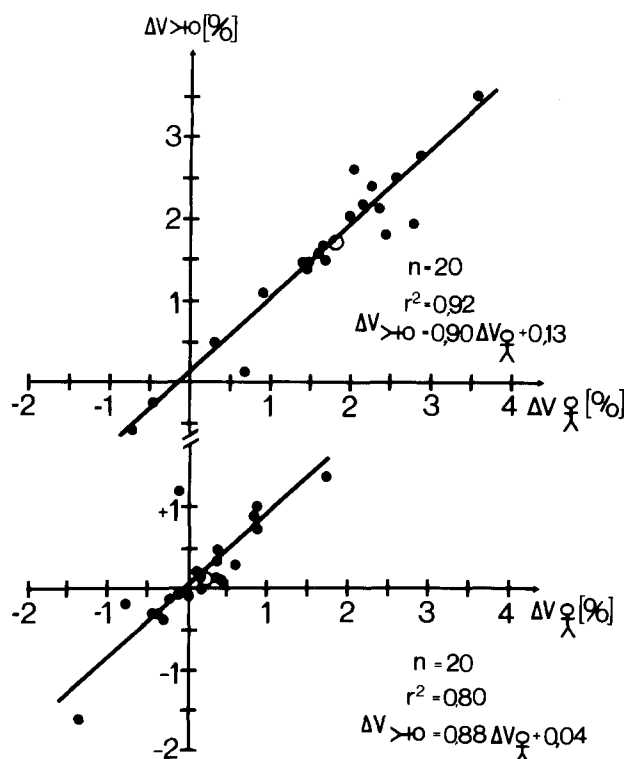


Fig. 5. Correlation of changes in calf volumes measured both in the standing position (*abszissa*) and when lying down (*ordinate*). The upper part represents values measured in the evening, the lower part the corresponding values recorded the following morning

in the evening were statistically significant ($P \leq 0.001$), while the deviations on the second morning do not differ significantly from zero ($P > 0.05$).

Since the measurements (first morning, evening, second morning) were always recorded both for an upright and horizontal position, one might assess to what extent the measured volume changes are caused by shifts in the intra- or extravascular volume. While the capacity vessels are engorged after 5 min of standing, they are almost empty when lying down.

In Fig. 5, the corresponding changes in volume are plotted in a coordinate system. The volume changes measured in different stages of vascular filling both in the evening (upper part) and the next morning (lower part) correspond well. The differences measured in the upright position are only slightly larger than the values measured when lying down. The marked difference in vascular filling in standing and lying down obviously have only very little impact on the volume changes measured during the same posture. Hence, one can deduce that the changes in calf

volume described above are caused by changes in extravascular volume.

Discussion

Volume increases in the lower extremities caused by increased filtration when standing have been measured with various methods by different authors (Atzler and Herbst 1923; Waterfield 1931; Looke 1936; Asmussen et al. 1939a, 1939b; Ludbrook and Loughlin 1964; Mellander et al. 1964; Hörig 1976). Basically, volume changes in the intra- and extravascular spaces can only be summarized recorded when applying exterior plethysmographic procedures, as, e.g., impedance plethysmography. However, given certain experimental conditions, it is possible to differentiate the rapid changes in vascular filling from the slow changes in extravascular, mainly interstitial, volume due to the different rates with which these volume changes occur (Ludbrook and Loughlin 1964; Mellander et al. 1964).

Thus, at first there is a very rapid increase in calf volume when the subject is moved into an upright position, as is shown in Fig. 1. This process, caused by an increased filling of the capacity vessels, is more or less complete after 1 to 2 min, and is followed by a slow, frequently almost linear increase in volume. Using plethysmographic recordings of total volume and a scintigraphic procedure to determine the intravascular volume, Schnizer et al. (1978) could show that the vascular filling is almost completed at the end of rapid volume changes and that a further slow increase in volume is to be attributed to an increase in extravascular volume. Sejrson et al. (1981) have emphasized the validity of this assessment.

Based on these findings, it seems cogent to consider the volume changes observed in both test series predominantly as changes in interstitial fluid volume. The results of the second test series, in which the changes in calf volume were measured after 9 h and then after 24 h both when the capacity vessels were empty and filled show a close correlation, which conclusively supports the above assumption.

The rise in calf volume recorded during relaxed standing in test series 1 represents increased transcapillary filtration, as well as reduced re-absorption of interstitial fluid due to local increases in transmural pressure. Both processes are due to a disturbance of the Starling equilibrium in the exchange vessels caused by the blood column, which has a hydrostatic effect.

The pressure reducing effect of the musculo-venous pump in the leg veins in orthostasis has often been demonstrated (Kriessmann 1975). Arnoldi's (1965) studies can be cited as evidence of the efficiency of the muscle pump. He based his studies on a relatively low rate of contractions, and showed that, on average, the pressure in the posterior tibial vein dropped to 34 mm Hg after a single contraction of the calf muscles, and that the level of resting conditions was, on the average, not reestablished until after 15 s. Since the form of contraction chosen by Arnoldi (1965) (plantar flexion of the foot against resistances) is very similar to standing on the toes, a marked decrease in mean venous pressure in the region of the calf is to be expected, considering the experimental sequence of the first test series. It cannot be assumed, however, that this contraction-induced reduction in pressure in the exchange vessels necessarily results in a Starling equilibrium followed by a constant volume in the calf. The decrease in venous pressure should, however, at least result in a significant reduction in the rate of volume increase during muscular contractions when compared to that of relaxed and motionless standing. The stimulation of lymphatic flow, also caused by muscular contractions, is expected to support this tendency (White et al. 1933; Taylor et al. 1973; Olszewski et al. 1977). This edema-protective effect of the muscle pump was evident in 50% of the subjects. However, the observation that in other subjects the calf volume increases more rapidly and strongly during light muscular exercise than during relaxed standing seems to indicate processes which counteract the effects of venous pressure reductions and increases in lymphatic flow during muscular exercise.

Here, the blood circulation of the muscles during orthostasis and muscular exercise should be of major significance. In orthostasis, the reduced blood supply in the muscles (Höjensgard and Stürup 1953; Hildebrandt 1960; Reeves et al. 1961; Henriksen and Sejrsen 1977; Sejrsen et al. 1981) affects the transcapillary fluid exchange in various ways. Precapillary vasoconstriction acts in two ways. It reduces the area of capillary filtration and increases the ratio of pre- to postcapillary resistance. Both processes lower the rate of filtration (Stick 1981). Furthermore, filtration is also slowed down since the local colloid osmotic pressure rises in the perfused capillaries to a lesser extent. This is supported by measurements by Nicolaysen et al. (1980) which show that the colloid osmotic pressure of the blood in the vein on the dorsum of the foot increases during standing.

During exercise, by contrast, these mechanisms by which outward filtration is reduced are restricted or neutralized: the precapillary resistance is reduced and the number of perfused capillaries is higher (Barcroft and Dornhorst 1949; Folkow et al. 1971), while, at the same time, the local colloid osmotic pressure is lowered by a washing-out of proteins from the more strongly perfused capillaries. Hence, additional circulation with its positive effect on filtration during muscular exercise counteracts the drop in venous pressure which has an edema-protective effect. The results of the first test series reported here suggest that even though the dominance of the edema conducive and edema protective mechanisms varied from subject to subject, on average these opposing mechanisms were in balance under the particular experimental conditions.

Since differing patterns of exercise were chosen, changes in extravascular volume reported in this study cannot be compared with the results of other authors, who found a marked increase in extravascular fluid after brief and heavy exercise (Lundvall et al. 1972; Schnitzer et al. 1979).

According to the results of test series 1 and the processes discussed above, one has to assume that an equilibrium of Starling forces in the calf could not be reached in the interval between measurements in the morning and the evening recorded for the subjects of the second series. During the interval between measurements, the subjects' body posture was mainly upright: they walked and stood on average 30% and 13% of the time respectively, and sat for 55% of the time. Only 3 subjects were supine for about 1 h during this interval. In view of the mainly upright posture, the average volume increase of the calf during 9 h, namely 1.7%, is remarkably low compared with the average volume increase of 1.1% after 20 min of orthostasis.

Furthermore, comparison of the individual volume increases with the records of the subjects' daily activities shows that similar increases in extravascular volume occurred regardless of the subject's activity pattern. However, the activities superimpose changes in leg volume during the course of the day on those reported by Rieck and Hildebrandt (1974), who measured volume changes in supine resting subjects. Since the factors contributing to the regulation of extravascular volume are highly complex, it remains to be seen which mechanism has an edema-protective effect in the human lower extremity during the day. The measurements of single or several of so-called Starling forces undertaken on animals, and

frequently described in the literature (Aukland 1973; Fadnes et al. 1978; Taylor 1981), are only of limited value when applied to the upright human body posture, especially since the animal vessels physiologically are not exposed to the high hydrostatic pressures which occur in man's lower extremities.

The findings presented here and those described in the literature seem best to fit the following hypothesis: in the vertical position, both in relaxed standing and during muscular exercise, the increase in transcapillary filtration is more or less marked. The increased lymphatic flow has an edema-protective function (Engeset et al. 1977; Olszewski et al. 1977), a flow which only sets in at a certain increase in interstitial volume or a specific filling of the lymphatic vessels (Entrup et al. 1966). Also, the muscle pump active in lymphatic drainage, only reaches maximum effectiveness when a certain volume is exceeded. This hypothesis accounts for the low increase in extravascular volume observed during the day when compared with 20 min of orthostasis.

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