The effect of passive tilting on microvascular parameters in the human calf: a strain gauge plethysmography study

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1. Cumulative small steps in venous congestion pressure were used to study the effect of passive tilt on vascular parameters in dependent tissues. Using this protocol we have non-invasively assessed venous pressure ($P_{v,est}$), isovolumetric cuff pressure ($P_{v,i}$), which is the congestion cuff pressure (P_{cuff}) that has to be exceeded to induce fluid filtration. We have also assessed microvascular filtration capacity (K_f), which is the linear relationship between filtration rate (J_v) and P_{cuff}, when $P_{cuff} > P_{v,i}$, and is the product of the available exchange vessel surface area and wall conductance.

2. Subjects were passively tilted to increase the venous pressure at the level of the calf by $47{\cdot}4 \pm 2{\cdot}4$ mmHg (mean ± S.E.M.). The value of $P_{v,i}$ increased from $20{\cdot}6 \pm 1{\cdot}8$ to $48{\cdot}5 \pm 3{\cdot}8$ mmHg after the imposition of the tilt. This change may reflect the increased colloid osmotic pressure at the microvascular interface that is known to occur in response to this manoeuvre.

3. The pre-tilt value of K_f did not change after the imposition of the passive tilt, the values being $3{\cdot}2 \pm 0{\cdot}4 \times 10^{-3}$ and $3{\cdot}6 \pm 0{\cdot}4 \times 10^{-3}$ ml min^{-1} (100 ml^{-1}) mmHg^{-1}, respectively, ($n = 13$).

4. These results support the notion that passive postural change alters the pre-capillary resistance, thereby altering the pressure and flow characteristics within the exchange vessels, but does not alter the surface area available for fluid exchange in the calf, contrary to previous findings in the dependent human foot using a single-step venous occlusion protocol.

Mellander, Öberg & Odelram (1964) reported that the capillary filtration coefficient (microvascular filtration capacity, K_f) in the tissues of the foot fell from $7{\cdot}7 \times 10^{-3}$ to $1{\cdot}7 \times 10^{-3}$ ml min^{-1} (100 ml^{-1}) mmHg^{-1}, on lowering the foot in an 80 deg tilt. It was proposed that posturally induced alterations in pre-capillary vascular smooth muscle tone would attenuate the transmission of the increased arterial pressure to the microvessels and also decrease the surface area available for exchange. (The value of K_f depends on the product of surface area and the hydraulic conductance per unit surface area of wall.) Both the observations and the reasoning are cited in contemporary reviews (Aukland, 1994), despite the observations of Levick & Michel (1978) who found no evidence of a decrease in the number of perfused capillaries in the toe following a move from the supine to the upright posture and those of Sejrsen, Henriksen & Paaske (1981) and Michel & Moyses (1985, 1986) who found no evidence to support a change in capillary filtration capacity in orthostasis.

A number of reports (e.g. Noddeland, Aukland & Nicolaysen, 1981; Rayman, Williams, Gamble & Tooke, 1994) have confirmed earlier observations that, following a passive head up tilt, the colloid osmotic pressure (COP) of venous blood draining from a dependent limb increased markedly (Youmans, Wells, Donley, Miller & Frank, 1934). The postural increase in local venous COP, is presumably brought about by an enhanced fluid extraction in the microvasculature, secondary to mechanisms causing pre-capillary constriction, e.g. activation of the veno-arteriolar reflex (Henriksen & Sjersen, 1977) or a myogenic response. Other explanations for the observations of Mellander *et al.* (1964) therefore seemed possible, namely enhanced fluid extraction across the endothelial walls enabled by a reduced flow rate and increased hydrostatic pressure. Such a combination would sustain nutritive blood flow whilst providing compensatory intravascular colloid osmotic buffering.

Our preliminary observations (Gamble, Figgis, Christ & Gartside, 1991; Gamble, Gartside, Morrell & Christ, 1994). were in keeping with those of Sejrsen *et al.* (1981) and Michel & Moyses (1985, 1986), in that they did not show a change in K_f following the imposition of a passive tilt. The present studies take these observations further and question whether the reported reduction in J_v could be attributed to the differences in methodology as well as to variations in

other parameters acting at the microvascular surface, e.g. the increased local intravascular COP pressure, which is known to occur following the imposition of a passive tilt (Noddeland *et al.* 1981).

METHODS

Assessments of fluid filtration and other microvascular parameters were made using a mercury in Silastic® silicone rubber strain gauge system, described in detail elsewhere (Gamble, Gartside & Christ, 1993). Using the protocol described in this paper, it was found that, provided small, cumulative steps in congestion cuff pressure (P_{cuff}) were used, no fluid filtration was observed until the congestion pressure exceeded a specific value, termed the isovolumetric cuff pressure ($P_{v,i}$), which was always greater than the ambient venous pressure ($P_{v,est}$) in the limb under study. In the present study we have used this protocol before and after the imposition of a passive tilt. We have used the term microvascular filtration capacity (K_f), in preference to 'capillary filtration capacity' or 'capillary filtration coefficient', because the events measured reflect filtration at the whole microvascular interface and not just at the capillaries.

Briefly, thirteen healthy subjects, comprising research associates and students (7 females; mean age, 32 ± 4 years), were studied in the afternoon, following normal daily activity. They were questioned and examined to confirm the absence of metabolic and vascular disease, including varicose veins. They had been asked to refrain from smoking, or drinking caffeine- or alcohol-containing beverages for a minimum of 4 h before the study.

The subjects rested supine on a tiltable bed fitted with an evacuable mattress (Innovention Products Ltd, Watford, Herts, UK). The bed was adjusted so that the mid-point of the studied calf was at the level of the right atrium (the 'reference point' taken was one-third of the distance down from the sternal angle to the posterior surface in the supine subjects) for a period in excess of 15 min prior to the start of the study. The support for the left leg was arranged so that, on tilting, it would not bear any load; the calf was also left free for attachment of the strain gauge. The subject was aligned so that, on tilting, the body weight was taken by the contralateral limb. After these adjustments, the air in the mattress was evacuated, to provide rigid support for the body on tilting. Arterial blood pressure was measured non-invasively on the contralateral calf of each subject, using a Criticon Dynamap Vital Signs Monitor (type 8100, Criticon, Tampa, FL, USA). Triplicate measurements of blood pressure were made before and after imposing the postural change and the mean values of systolic, diastolic, mean arterial pressure and heart rate, obtained in each posture, were calculated. The strain gauge was fixed around the calf at a site of known circumference and then stretched to a standard tension, so that any increases or decreases in circumference would be encompassed within the linear part of the strain gauge's range. A congestion cuff, with six inlet ports for rapid inflation, was placed around the ipsilateral thigh and a rigid corset placed around the outside of the cuff to minimize filling volume and thus filling time. The cuff was inflated via a pump and servonull pressure control system; the controlling pressure being measured by a transducer connected to the congestion cuff. The required pressure was signalled from the computer keyboard. The maximum cuff pressure used was no greater than the mean arterial diastolic blood pressure, measured in the subject in each posture. The strain gauge was calibrated at the start of each study, using a standardized protocol so that the relationship between the change in strain gauge signal in response to known stretches could be determined (Gamble *et al.* 1993). Skin surface temperature was measured at a site close to the strain gauge, using a thermocouple (type K) and a Keithley 871 Digital Thermometer (Keithley, Cleveland, OH, USA); the temperature was noted at each pressure step (mean value, 31·7 °C; range, 33·4–29·9 °C). Room temperature, which was also recorded, was kept constant within the range of 22–24 °C by a temperature control unit.

The strain gauge and cuff pressure signals were amplified and sampled by an analog-to-digital converter card in an IBM PC-compatible computer and saved for off-line analysis.

Tilt protocol

Stage 1. This stage used the protocol previously described for assessing K_f and $P_{v,i}$ (Gamble *et al.* 1993). After 3 min of strain gauge recording, P_{cuff} was raised in a series of small steps (size, 9·6 ± 3·5 mmHg, mean ± S.E.M.); each step was sustained for 5 min. Pressure steps were continued until at least three increased values of fluid filtration had been obtained. After sufficient information for the determination of K_f, $P_{v,i}$ and non-invasive venous pressure ($P_{v,est}$) had been gained, the congestion cuff was deflated and the resulting change in limb circumference recorded. After a 15 min interval the next stage of the study was initiated.

Stage 2. The subject was passively tilted (foot down) through 40–60 deg. The vertical height between the right atrium, taken as one-third of the distance down from the sternal angle to the posterior surface, and (i) the calf at the position of the strain gauge and (ii) the middle of the congestion cuff, was measured using a tape measure and a 900 mm spirit level, so that the hydrostatic load resulting from the tilt could be determined The strain gauge signal was recorded for 40 ± 10 min to establish that steady-state filtration was sustained without decrement, before initiating stage 3 of the protocol.

Stage 3. In stage 3, the protocol for stage 1 was repeated whilst the subject remained in the tilted position. The tilt imposed an increase in hydrostatic pressure at the levels of both calf and congestion cuff and it was found that higher values of P_{cuff} were required before increases in fluid filtration were observed. Once again the maximum P_{cuff} values used never exceeded the diastolic pressure, measured on the contralateral calf after the imposition of the tilt (see Table 1). Two subsidiary studies were also performed.

i. *Long-term intra-individual variation.* The cumulative small pressure step protocol was repeated five times on seven male student subjects (mean age, 21 ± 0·8 years). The subjects were studied at weekly intervals to determine the intra-individual coefficient of variation for K_f.

ii. *Short-term intra-individual variation.* In these studies, two cumulative pressure step protocols, separated by an interval of 15 min, were performed on fourteen student volunteers (9 male; mean age, 21 ± 0·8 years). The main objective of this study was to demonstrate that, in the absence of a change of posture, the first procedure did not influence the results obtained in the second.

Strain gauge record analysis

The rationale for the recording and analysis techniques have been discussed in detail elsewhere (Gamble *et al.* 1993), so a brief explanation will suffice. A typical strain gauge response to the imposition of a pressure increment is shown in Fig. 1*A*. It comprises an initial rapid volume change attributable to both vascular distension (ΔV) and fluid filtration, followed by a slow change due to fluid filtration only. We have previously shown that, providing small congestion pressure steps are used, 90 s is adequate for the completion of the ΔV component (Gamble *et al.* 1993). The

computer analysis can separate the distension and filtration components by calculating the linear relation of the volume change between cursors placed at '*a*' and '*b*'. This linear component was attributable to fluid filtration only, provided '*a*' was placed at least 90 s after the imposition of the congestion pressure step. The interval '*a* − *b*' was never less than 1·5 min. The calculated slope, reflecting the rate of volume change between '*a*' and '*b*', was stripped from the whole strain gauge response to the pressure increment, leaving a curve reflecting the time course of vascular distension. These data were then subjected to an exponential fitting routine and the difference between the fitted curve and the original data, the 'residual data', displayed (Gamble *et al.* 1993). Examination of the residual data would reveal evidence of slow compliance increment or decrement, sometimes termed 'creep'; however, such events were not observed in these studies.

Figure 1*B* shows the relationship between the values of fluid filtration rate (J_v), estimated from the slope of the curve between *a* and *b* in Fig. 1*A*, and the corresponding values for P_{cuff} that were obtained in a typical study from one subject. This figure demonstrates the principles used in the determination of K_f (Gamble *et al.* 1993). The linear regression determination is based on the pressure and J_v co-ordinates obtained at pressures above those at which J_v increased with the application of pressure. The slope of this relationship represents K_f, which is equivalent to

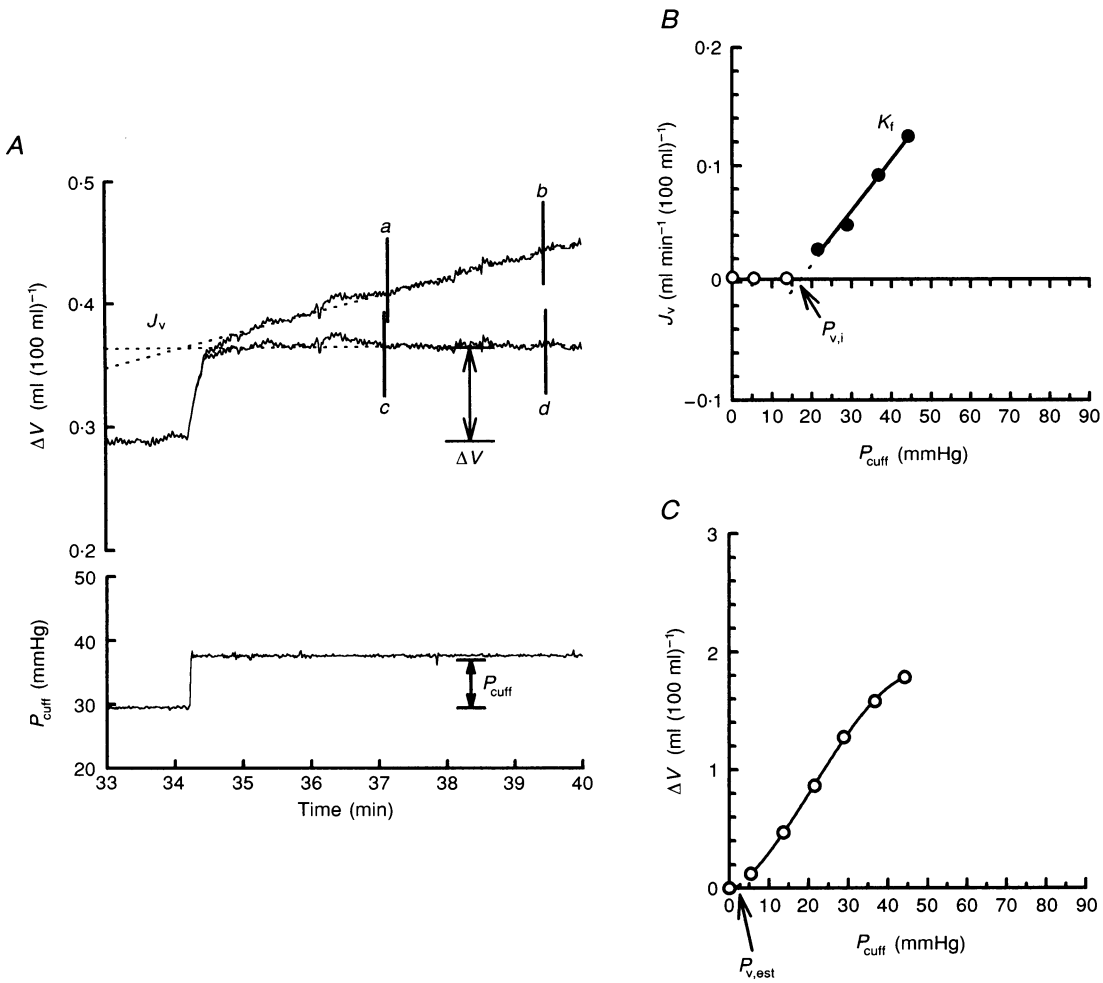

Figure 1

A, original data from one study showing the volume response following the imposition of a single, small (8·0 mmHg) congestion pressure step. It depicts the stages of analysis used for assessing the results during each study. Cursors placed at *a* and *b* enable the calculation of the fluid flux (J_v) by least-squares regression based on the data between these points. The line on which cursors *c* and *d* are placed represents the maximum venous filling volume (ΔV) obtained after the value J_v has been subtracted from the original trace. Each step analysis yields the values of step size (P_{cuff}), ΔV and J_v obtained in response to the pressure step. *B* shows the J_v responses to congestion pressure steps in one study on a supine subject. Microvascular filtration capacity is calculated by least-squares regression using the co-ordinates at pressures greater than those required to induce fluid filtration (●). $P_{v,i}$ is determined by extrapolation of the slope (K_f) to the pressure intercept where $J_v = 0$. *C* shows the relationship between ΔV, which is the venous filling volume obtained in response to each congestion pressure step (P_{cuff}) in the same subject (*B*). The results are fitted by a curvilinear fitting routine and venous pressure ($P_{v,est}$) is estimated by extrapolation (dashed line). The estimated venous pressure is taken to be the congestion cuff pressure which has to be exceeded to induce a volume change.

$\Sigma(L_pA)$, where L_p is the hydraulic conductance per unit surface area and A the total surface area available for filtration. The intercept of the line on the abscissa ($J_v = 0$), obtained by extrapolation, represents $P_{v,i}$. This is the cuff pressure which has to be exceeded in order to induce net fluid filtration at the level of the strain gauge. There is considerable existing evidence to show that this intercept is not at zero cuff pressure (e.g. Krogh, Landis & Turner, 1932; Landis & Gibbon, 1933; Pappenheimer & Soto-Rivera, 1948; Gamble *et al.* 1993). Since, in the present studies, the venous pressure was not routinely monitored invasively, we have termed the intercept the isovolumetric cuff pressure ($P_{v,i}$). The isovolumetric cuff pressure will be less than the isovolumetric pressure at the microvascular interface, the difference depending upon the values of post-capillary resistance and blood flow.

Values of P_{cuff}, when plotted with respect to the corresponding values of ΔV (Fig. 1*C*), gave a relationship that was a function of the vascular and surrounding tissue compliance. The intercept on the P_{cuff} axis, where $\Delta V = 0$, was obtained by extrapolation of the relationship between the data points above the pressure at which the first discernible response was obtained using a curvilinear fitting routine (SigmaPlot, Jandel Scientific GmbH, Erkrath, Germany). The intercept on the P_{cuff} axis, at $\Delta V = 0$, gives an estimate of the venous pressure at the level of the strain gauge (Gamble *et al.* 1993); we therefore call this the estimated venous pressure ($P_{v,est}$).

The results in Fig. 2 were taken from an independent study on a series of young males. It shows the relationship between P_{cuff} and venous pressure (P_v), measured invasively in the saphenous vein of a supine subject whose mid-calf was at the same level as the right atrium. The full data, which have been reported to the Physiological Society (Christ, Gartside & Gamble, 1996) show that local P_v equals P_{cuff} once the latter has been raised above the ambient venous pressure ($P_{v,est}$). Moreover, the relationship between P_{cuff} and P_v is given by the equation $P_v = P_{cuff} \times 0{\cdot}98 + 2{\cdot}35$, where the pressures are measured in millimetres of mercury. Thus $P_{v,est}$ determined from the intercept on the absicca in Fig. 1*C* is a very close approximation to the local P_v.

During stage 3, the value P_{cuff} underestimated the pressure imposed at the level of the strain gauge because it did not allow for the column of blood between the congestion cuff and the level of the gauge. In all thirteen studies the difference in venous pressure between (i) the right atrium and the congestion cuff and (ii) the right atrium and the calf at the level of the strain gauge, was calculated from the differences in the vertical height in centimetres between these points. The values of vertical height were multiplied by the factor 0·776 (to correct for the gravitational constant and the specific gravity of blood, which was assumed to be 1·055). Using these calculations, venous pressure at the level of the gauge was 16·4 ± 1·5 mmHg higher than the venous pressure at the level of the cuff, or than P_{cuff} itself, under conditions where P_{cuff} had been raised above local P_v.

Statistical analysis

The means and standard errors of the mean were calculated and compared using either Student's t test for paired or unpaired data or the Wilcoxon ranked sign test, depending upon whether the data were normally distributed or not. Multiple comparisons were made using the appropriate analysis of variance and Dunnett's multiple comparisons test or the Kruskal–Wallace one-way ANOVA for non-parametric data. Significance was assumed at a level of $P < 0{\cdot}05$.

Ethical approval

The study was approved by the Ethical Subcommittee of Charing Cross and Westminster Hospital. All subjects gave verbal informed consent.

RESULTS

Values of $P_{v,i}$, K_f and $P_{v,est}$ in the supine calf

The values for J_v and ΔV that were obtained in response to P_{cuff} steps in a typical example are shown in Fig. 1*B* and *C*, respectively.

The mean pre-tilt values for $P_{v,i}$, K_f and $P_{v,est}$ were 20·6 ± 1·8 mmHg, 3·2 ± 0·4 × 10^{-3} ml min^{-1} (100 ml^{-1}) $mmHg^{-1}$ and 6·7 ± 1·0 mmHg, respectively.

Long- and short-term intra-individual variation in K_f

The thirty-nine measurements of K_f, made at weekly intervals on seven subjects, gave a coefficient of variation (S.D./mean × 100%) of 10·6 ± 0·1% (range, 12·9–6·0%). In the short-term intra-individual variation study, where two cumulative congestion pressure step protocols were followed, with an intervening rest period of 15 min, the difference between the values of K_f obtained from the studies, expressed as a percentage of the initial value (i.e. $(K_{f2} - K_{f1})/K_{f1} \times 100\%$) was 6·3 ± 4·3%. The difference in $P_{v,i}$ was also small (−6·9 ± 8·1%). The results obtained from

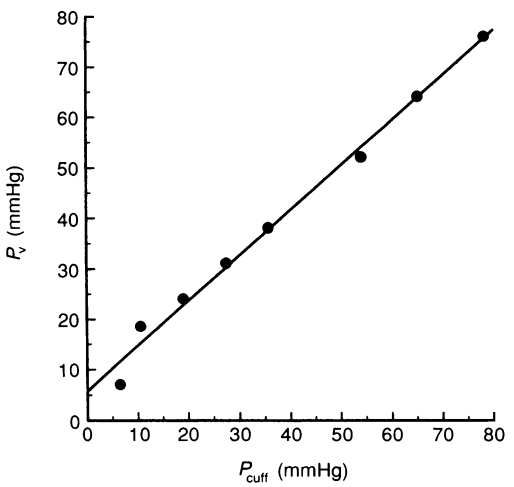

Figure 2

The results from one study in which venous pressure was invasively monitored via a catheter inserted into the medial saphenous vein in a young, healthy supine subject. The figure shows the relationship between the imposed congestion pressure and the invasively monitored venous pressure.

these consecutive studies were not significantly different from one another.

Effect of tilting

Immediately prior to the imposition of the tilt, modest steady-state fluid filtration was observed in all but four of the subjects. Despite this, the mean value of J_v was negative ($-1{\cdot}97 \pm 5{\cdot}0 \times 10^{-3}$ ml min^{-1} (100 ml)$^{-1}$, mean ± S.D.); which reflected the weighting imparted by the ranges of the four showing steady-state volume loss relative to the nine showing very small levels of filtration (ranges, $-1{\cdot}4$ to $-5{\cdot}06 \times 10^{-2}$ relative to $9{\cdot}0 \times 10^{-3}$ to $5{\cdot}5 \times 10^{-4}$, respectively). The tilt caused an increase in vertical height of blood between the right heart atrium and the calf. The mean increase in hydrostatic pressure, estimated from the product of vertical height, gravitational constant and specific gravity of blood was $47{\cdot}4 \pm 2{\cdot}4$ mmHg. On imposing the tilt, all subjects showed an initial rapid increase in calf volume. This initial rapid volume response was followed, in all but three subjects, by a slow sustained volume increase, which was assumed to represent fluid filtration. In three of the thirteen subjects, tilting caused a small, but sustained, reduction in limb volume. Fluid filtration was measured again at 10 and 20 min intervals after imposing the tilt. The J_v was estimated by least-squares regression over a period of 3–4 min, e.g. 8–12 min after the imposition of the tilt. Figure 3 depicts the mean values of J_v obtained at these times and shows that the mean value of J_v increased from the pre-tilt value of $-1{\cdot}97 \pm 5{\cdot}0 \times 10^{-3}$ to $3{\cdot}12 \pm 1{\cdot}33 \times 10^{-2}$ ml min^{-1} (100 ml)$^{-1}$ (mean ± S.D.; range, $-4{\cdot}40 \times 10^{-2}$ to $8{\cdot}31 \times 10^{-2}$ ml min^{-1} (100 ml)$^{-1}$) measured after 10 min of tilt ($P < 0{\cdot}001$, Wilcoxon ranked sign test). At 20 min the value of J_v ($3{\cdot}14 \pm 0{\cdot}1 \times 10^{-2}$ ml^{-1} min^{-1} (100 ml)$^{-1}$) had not changed significantly from the 10 min value ($P = 0{\cdot}98$, Student's paired t test).

We have shown that large congestion pressure steps require a much longer time, than the small cumulative pressure steps, for the completion of the ΔV component; so that we must wait longer before fluid filtration can be reliably assessed (Gamble *et al.* 1993). Since the tilt imposed an increase in venous pressure of about 50 mmHg, J_v could only be assessed reliably 7–10 min after its imposition. The mean J_v value obtained at these times in response to the tilt ($3{\cdot}12 \pm 1{\cdot}33 \times 10^{-2}$ ml min^{-1} (100 ml)$^{-1}$) was very much less than the J_v value predicted from the supine responses (see Fig. 1*B* for example). Using the linear equation, $J_v = K_f(P_{cuff} - P_{v,i})$, the mean predicted value of J_v would be $7{\cdot}92 \pm 1{\cdot}27 \times 10^{-2}$ ml min^{-1} (100 ml)$^{-1}$. The much lower value obtained in each tilted calf suggested that factors other than the applied pressure were influencing J_v when the subject was tilted. In other words, J_v was hugely 'buffered' by the time of measurement. The question then arises, what caused the buffering? Was it a change in K_f, or was it a change in the forces opposing capillary pressure? It therefore became of great interest to estimate K_f in the dependent calf.

Changes in the values of K_f, $P_{v,i}$ and $P_{v,est}$ in the calf during foot-down tilt

Figure 4*A* and *B* depicts, respectively, the values for J_v and ΔV obtained during a study on one subject. The open symbols represent the values obtained in the supine posture and the filled symbols, those obtained after 35 min of sustained tilt. In Fig. 4*A* we see that, prior to the application of congestion pressures, the value of J_v was barely distinguishable from zero ($3{\cdot}0 \times 10^{-3}$ ml min^{-1} (100 ml)$^{-1}$). In this study the tilt imposed a pressure increase of 54·9 mmHg at the level of the gauge and we can see that 30 min after the imposition of the tilt there was significant filtration ($3{\cdot}77 \times 10^{-2}$ ml min^{-1} (100 ml)$^{-1}$, ▲). However, the value of J_v was far less than the 0·171 ml min^{-1} (100 ml)$^{-1}$ calculated (Fig. 4*A*, △) from the tilt-imposed pressure increase and the pre-tilt value of the slope K_f. Moreover, we can see that, whereas K_f remained unchanged (Fig. 4*A*) the intercepts, representing $P_{v,i}$ (Fig. 4*A*) and $P_{v,est}$ (Fig. 4*B*) increased markedly. Tilting caused a marked alteration in the extrapolated intercepts $P_{v,est}$ and $P_{v,i}$. The closed triangle in Fig. 4*B* represents the volume change that occurred in response to the tilt procedure itself. It can be seen that this change in volume might have been predicted in response to an equivalent P_{cuff} value in the supine posture.

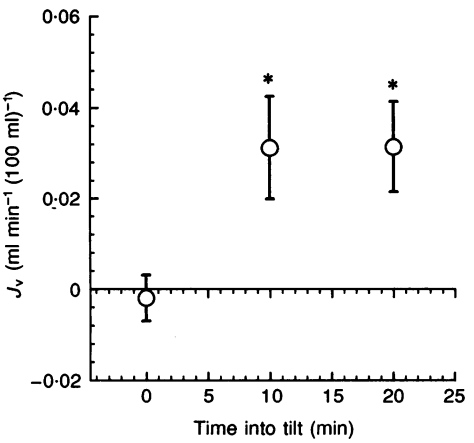

Figure 3

The graph depicts the values (means ± S.D.) for J_v that were obtained in 13 studies before and then at 10 and 20 min following the imposition of passive tilt. Whilst the 10 and 20 min values are significantly different from the pre-tilt value (* $P < 0{\cdot}01$, Dunnett's multiple comparisons test with Bonferroni correction) they are not significantly different from each another, suggesting that the buffering forces at the microvascular interface had achieved a new equilibrium within 10 min of imposing the tilt.

Microvascular filtration capacity (K_f)

In the tilted posture (stage 3) the mean value of K_f, ((3·6 ± 0·4) × 10^{-3} ml min^{-1} (100 ml)$^{-1}$ $mmHg^{-1}$, mean ± S.E.M.) was not different from the mean value measured during stage 1, (3·2 ± 0·4 × 10^{-3} ml min^{-1} (100 ml)$^{-1}$ $mmHg^{-1}$; $P = 0·45$, Student's t test, 13 paired values) see Table 2 and Fig. 5.

Tilt-induced changes in arterial blood pressure in the contralateral calf

The tilt-induced increases in systolic, diastolic and mean arterial blood pressures in the contralateral calf, which were 47·9 ± 4·8, 45·9 ± 4·3 and 50·7 ± 5·2 mmHg, respectively, were not significantly different from one another ($P = 0·72$,

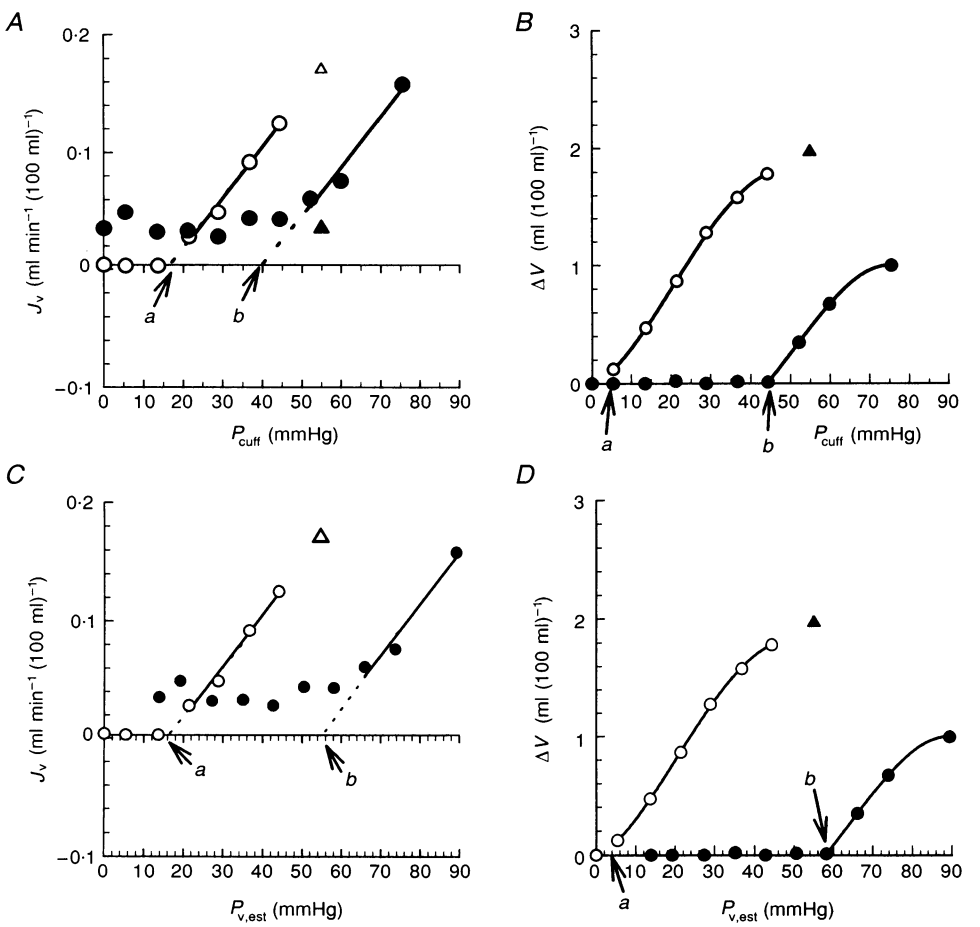

Figure 4

A shows the relationship between the values for P_{cuff} and J_v that were obtained before and after imposing the passive tilt in one subject. ○, pre-tilt data; ●, intra-tilt data. Note that whilst $P_{v,i}$ increases in response to the tilt (intercepts *a* and *b*, where net $J_v = 0$), the slopes represented by the continuous lines do not change. The figure also shows the value J_v predicted on the basis of the pressure imposed by the tilt (△) and the value J_v that was actually obtained at that pressure (▲). *B* shows the relationship between the values for ΔV and P_{cuff} that were obtained in the same study. ○, pre-tilt data; ●, intra-tilt data. It can be seen that the intercept ($\Delta V = 0$, derived by curvilinear extrapolation) increases in response to the tilt procedure (see intercepts *a* and *b*). ▲, the volume response to the passive tilt itself. *C* is an adaptation of *A* showing the relationship between the values for P_{cuff} and J_v that were obtained before and after imposing the passive tilt in one subject. In this figure, the post tilt values have been corrected for the increased vertical height between the congestion cuff and the level of the strain gauge (see text for details). ○, pre-tilt data; ●, intra-tilt data. Note the marked increase in the intercept value ($P_{v,i}$) denoted *a* and *b* compared with those in *A*. As in *A*, △ reflects the value J_v predicted on the basis of the pre-tilt slope K_f and the pressure imposed by the tilt. *D* is an adaptation of *B* showing the relationship between the values for ΔV and P_{cuff} that were obtained in the same study, but after correcting for increased vertical height between the congestion cuff and the level of the strain gauge (see text for details). ○, pre-tilt data; ●, intra-tilt data. It can be seen that there is a marked increase in the post-tilt value $P_{v,est}$ (intercept *b*, $\Delta V = 0$) compared with the value contained in the uncorrected *B*.

Table 1. Values of calf arterial pressure in each posture and change in venous pressure ($\Delta P_{t,est}$) imposed by the tilt

	Systolic arterial pressure (mmHg)	Diastolic arterial pressure (mmHg)	Mean arterial pressure (mmHg)	$\Delta P_{t,est}$ (mmHg)
Pre-tilt	119·1 ± 4·0	53·5 ± 2·8	75·0 ± 3·7	0
Tilt	167·6 ± 7·1	96·9 ± 6·2	125·7 ± 7·1	47·4 ± 2·4
Difference	47·9 ± 4·8	45·9 ± 4·3	50·7 ± 5·2	47·4 ± 2·4
n	10	10	10	13
P relative to $\Delta P_{t,est}$	n.s.	n.s.	n.s.	

$\Delta P_{t,est}$, the theoretical increase in calf venous pressure due to gravity as a result of the tilt. Data are means ± S.E.M. P values obtained using Student's paired t test. n.s., not significantly different from $\Delta P_{t,est}$.

Kruskal–Wallis one-way ANOVA). The mean values of systolic, diastolic and mean arterial blood pressure are summarized in Table 1.

Estimation of venous pressure ($P_{v,est}$)

On tilting, the mean value of venous pressure, estimated from the extrapolated intercept of the ΔV *versus* P_{cuff} plot, rose from 6·7 ± 1·0 mmHg (pre-tilt) to 34·5 ± 2·9 mmHg, the difference was highly significant ($P < 0·001$, Student's paired t test). When these results were corrected for the increase in pressure attributable to the vertical distance between the calf and the cuff, the mean value became 51·0 ± 2·8 mmHg. Figure 4*C* shows the Fig. 4*A* data corrected for the vertical height component. The net increase in $P_{v,est}$ (44·3 ± 2·9 mmHg) did not differ significantly either from the calculated hydrostatic load imposed by the tilt (47·4 ± 2·9 mmHg) or from the measured increases in mean arterial pressure (50·7 ± 5·2, $P = 0·77$, Kruskal–Wallis one-way ANOVA), see Tables 1 and 2.

Isovolumetric cuff pressure ($P_{v,i}$)

The mean intra-tilt value of $P_{v,i}$ (32·1 ± 3·2 mmHg) was greater than the mean pre-tilt value (20 ± 1·8 mmHg). When the intra-tilt data were corrected for the increase in pressure attributable to the vertical distance between the calf and the cuff, the mean value became 48·5 ± 3·8 mmHg, see Fig. 6. The net increase in $P_{v,i}$ (27·9 ± 3·3 mmHg) was significantly less than the hydrostatic load imposed (47·4 ± 2·4 mmHg, $P < 0·001$, Student's paired t test). The effect of this correction is shown in Fig. 4*D*. It is clear that ignoring the significance of the value $P_{v,i}$ may have a substantial effect on the calculation of K_f.

Table 2. Values (means ± S.E.M.) obtained during the tilt studies

	K_f (ml min^{-1} (100 ml)$^{-1}$ mmHg^{-1} × 10^{-3})	$P_{v,i}$ (mmHg)	$P_{v,est}$ (mmHg)	n
Pre-tilt	3·17 ± 0·35	20·6 ± 1·8	6·7 ± 1·0	13
After tilting				
Uncorrected	3·55 ± 0·35	32·1 ± 3·2	34·5 ± 2·9	13
Corrected*	—	48·5 ± 3·8	51·0 ± 2·8	13
Difference	—	27·9 ± 3·3	44·3 ± 2·9	13
P values		< 0·001	n.s.	

$\Delta P_{t,est}$, the theoretical increase in calf venous pressure due to gravity as a result of the tilt. P values obtained using Student's paired t test. n.s., not significantly different from $\Delta P_{t,est}$. * Corrected for calf − cuff vertical height difference, see text. NB the values of diastolic blood pressure measured using the Dynamap system are lower than those that would have been obtained using the Riva–Rocci method (Gorny, 1993). The difference probably reflects the greater sensitivity of this device in detecting pressure oscillations at the lower pressure.

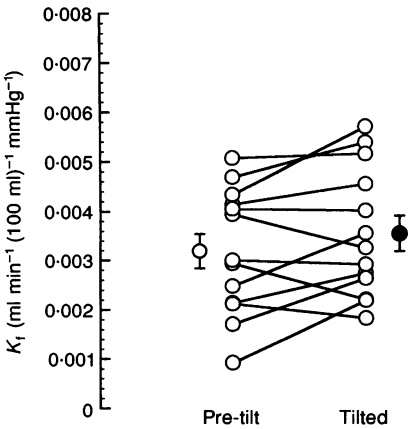

Figure 5

The graph shows the K_f values that were obtained before and after imposing the tilt in each of the 13 studies. It also compares the means ± S.E.M. values that were obtained in these two postures; the values are not significantly different from one another ($P = 0{\cdot}45$, Student's paired t test).

DISCUSSION

The primary objective of the present study was to re-examine the suggestion that there is a reduction in microvascular filtration capacity following a passive change from the supine to the erect posture (Mellander *et al.* 1964). The results obtained from this study, like those presented in preliminary communications (Gamble *et al.* 1991; Gamble *et al.* 1994), together with those of Sejrsen *et al.* (1981) and Michel & Moyses (1985, 1986) provide no evidence of a change in K_f in response to passive postural change. There are differences in the protocol and methods of measurement however, which might account for the discrepancy with the findings of Mellander *et al.* (1964), as discussed next.

In Mellander's work the filtration coefficient was measured in the cat hindlimb and human foot, not the calf. In the studies of Mellander *et al.* (1964), changes in volume were measured using a water-filled plethysmograph at 35 °C. In the human studies, an 80 deg tilt was used, which should impose a greater hydrostatic load than that used in the present study. However, it was noted that the range of venous pressures in the supine subjects was 25–35 mmHg. It was explained that the venous pressure was kept high to overcome the compression effect that the latex stocking and water-filled plethysmograph might have on the veins. The venous pressure rose from 35 to 84 mmHg on the imposition of tilt, an increase of 49 mmHg (Mellander *et al.* 1964), which was comparable to the pressure increase imposed in the present study. Changes in filtration capacity were estimated from the filtration response to a single increase in venous pressure of about 24 mmHg, which was repeated a number of times. Possible sources of error due to the assumptions made with the single-step method of assessment have been discussed previously by Michel & Moyses (1987). In their paper, Mellander *et al.* (1964) assumed that the whole of the venous pressure change observed in response to the cuff congestion was responsible for the measured change in fluid filtration. In addition to the results presented in the present paper, the observation that a finite value of congestion pressure has to be exceeded before an increase in the rate of fluid filtration is observed, has been reported by a number of workers (Krogh *et al.* 1932; Landis & Gibbon, 1933; Pappenheimer & Soto-Rivera, 1948; Gamble *et al.* 1993). In the present paper it was noted that higher P_{cuff} values had to be used to achieve filtration after the imposition of the tilt. The value of $P_{v,i}$ depends on the balance of hydrostatic and osmotic forces at the microvascular interface. Since the colloid osmotic pressure of blood draining from a dependent limb is known to increase during dependency, a change in the value of $P_{v,i}$ may be due to this.

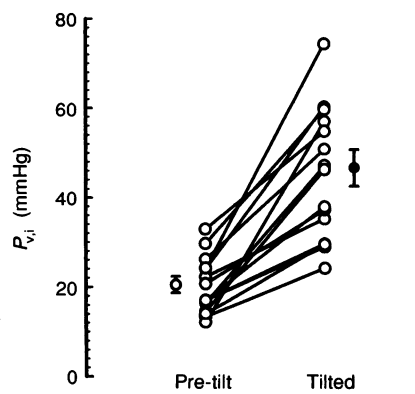

Figure 6

The graph depicts the $P_{v,i}$ values that were obtained before and after the imposition of passive tilt in each of the 13 studies. The figure also shows the mean ± S.E.M. $P_{v,i}$ values that were obtained before (○) and after (●) imposing the tilt. The differences between them are highly significant ($P < 0{\cdot}003$, Student's paired t test).

Although P_v was not routinely invasively measured, our recent data (Christ *et al.* 1996) shows that, provided the subject is appropriately aligned and differences in vertical height between the site of cannulation, the congestion cuff and strain gauge are accurately measured, P_{cuff} gives a very close approximation of P_v, once the former has been raised above the intrinsic venous pressure. These results confirm the observations of others (e.g. Levick & Michel, 1978) but are nevertheless important for the validation of the method, hence the emphasis placed on them here.

Since K_f is calculated as the linear relationship between J_v and changes in P_{cuff}, it is neccessary to make sure that only the J_v values where P_{cuff} exceeds $P_{v,i}$ are admitted for the calculation of the slope. In Fig. 7 we compare the effect of calculating the value K_f from two different procedures. In one, the dotted line (*a*) reflects the change in J_v achieved by the application of a single pressure step, here the initial pressure is taken as the $P_{v,est}$ and the slope K_f (*a*) is $3{\cdot}15 \times 10^{-3}$ ml min^{-1} (100 ml)$^{-1}$ mmHg^{-1}. Using the small cumulative pressure step protocol, the value of K_f obtained, only admitting the J_v values where $P_{cuff} > P_{v,i}$ for the calculation of the slope, was $4{\cdot}29 \times 10^{-3}$ ml min^{-1} (100 ml)$^{-1}$ mmHg^{-1}. We can also see that the value of slope *a* will vary with the size of the single pressure step used. This line of reasoning has been used previously by Michel & Moyses (1987).

Whilst the single large pressure step used by Mellander *et al.* (1964) before the imposition of the tilt may not have activated the veno-arteriolar reflex, the tilt itself will have done so. The resulting increase in local COP (Rayman *et al.* 1994) will have raised the congestion pressure which had to be exceeded to achieve fluid filtration. This change also needs to be taken into account when calculating K_f after tilting. It would seem that the single-step method of assessment might give rise to a considerable underestimate of K_f.

In their paper, Mellander *et al.* (1964) reasoned that the changes in the filtration coefficient observed were attributable to closure of pre-capillary sphincters, causing 'functional shunting of the blood through a smaller number of capillaries'. Such a change would result in a decreased area available for filtration. Mellander *et al.* (1964) cited the observations of Přerovský, Vavrejn & Linhart (1962), who found a lower clearance rate of subcutaneously injected $^{131}I^-$ in the lower limb, which they attributed to a decrease in blood flow. They also reported evidence of lower clearance rates in the distal with respect to the proximal region. Mellander *et al.* (1964) suggested that the differences might be attributed to altered available surface area and to vascular adjustments, which were greatest in the regions where protection against excessive loss of fluid would otherwise be most pronounced. However, studies on the effect of posture on the pressure in the skin capillaries of fingers and toes have shown that the number of patent capillaries remained unchanged (Levick & Michel, 1978). These workers found it hard to equate their observation with the suggested decrease in filtration capacity. Moreover, in later studies using strain gauge plethysmography on the foot, Michel & Moyses (1986) found that there was no evidence of 'a large reduction in capillary filtration capacity in dependent feet during quiet sitting'. They obtained values of K_f that were different neither from the values obtained in the supine subject (Michel & Moyses, 1987), nor from the values reported in the present paper.

We have found a wide inter-individual range of K_f values. However, the $10{\cdot}6 \pm 0{\cdot}9$% coefficient of variation obtained in the parallel studies on long-term intra-individual variation, which was of the same order as that found by Jaap, Shore, Gartside, Gamble & Tooke (1993), suggests that the method is reproducible and that the inter-individual variation observed might reflect either differences in surface area available for exchange, or differences in permeability. The young subjects studied for the present paper differed markedly in their levels of physical fitness. A number of studies have investigated the effects of physical training on the capillary density in skeletal muscle (e.g. Andersen & Kroese, 1978; Kiens *et al.* 1993). Biopsy assessment of exercising and non-exercising muscle in these, and other, studies has shown marked increases in capillary density during the course of training. In 1987, a quantitative study of the exchange microvasculature of muscles from the human foot and hand enabled Clough (1987) to calculate the

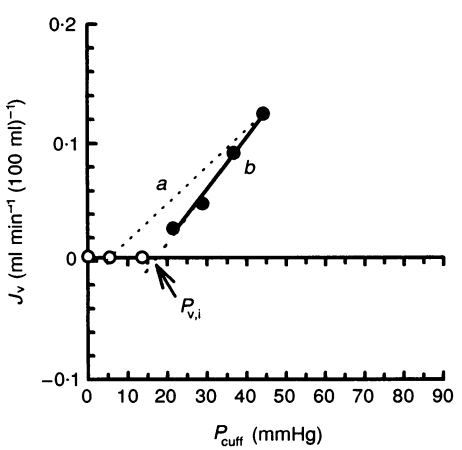

Figure 7

This figure is an adaptation of Fig. 1*B*. The intercept ($J_v = 0$) for slope *a* is the ambient venous pressure and that for *b* is $P_{v,i}$. The differences in the slopes *a* and *b* illustrates the influence that the analysis technique might have on the determination of K_f. This is discussed in the text.

surface area available for exchange per gram of skeletal muscle tissue on the basis of the number of capillaries per millimetre squared. Using these data, and information on the capillary density in the skeletal muscle of athletes and non-athletic control subjects, we can reasonably expect a 3·6-fold difference in the available surface area for exchange in the subjects being studied. Furthermore, in a recent study (Gamble & Gartside, 1994) we showed an intra-individual 2-fold difference in K_f during the menstrual cycle of females on oral contraceptives. Other, as yet unpublished data, shows similar changes in women not taking oral contraceptives (J. Gamble & I. B. Gartside, unpublished observations). In the light of these data, large inter-individual variations in K_f might be expected as the norm, rather than the exception, in the population under study. Moreover, in the present study, two successive observations were made in the same study session. Our parallel studies on intra-individual variation under these circumstances found no significant changes in the measured parameters during the time course of the study.

If, following a passive postural change, neither the surface area available for exchange, nor the permeability per unit surface area have altered, other explanations for the changes in fluid filtration reported by Mellander *et al.* (1964) need to be sought. The major forces governing the movement of fluid across the microvascular interface are the hydrostatic and colloid osmotic pressures (Starling, 1896). The demonstration of posturally induced changes in mean capillary pressure and increase in the pre- to post-capillary resistance ratio (Levick & Michel, 1978), favour an increased extraction of water at the microvascular interface and a resulting local increase in COP. In their studies, Levick & Michel (1987) only studied central venous COP, which remained unchanged. There have been a number of reports of increases in COP and protein concentration in venous blood draining from dependent tissues (e.g. Rowe, 1915; Thompson, Thompson & Dailey, 1927; Krogh *et al.* 1932; Youmans *et al.* 1934; Noddeland *et al.* 1981; Michel & Moyses, 1987; Moyses, Cederholm-Williams & Michel, 1987; Rayman *et al.* 1994); we believe that the tilt-related increase in isovolumetric cuff pressure reflects the increase in COP at the microvascular interface reported by these workers. Moreover, the change in $P_{v,i}$ is not dissimilar to the change in COP reported by Rayman *et al.* (1994) who, in their studies on diabetics and age-matched controls, found a significant correlation between foot swelling rate and skin blood flow and a negative correlation with COP. There are additional possible buffering mechanisms that should be considered, besides the local increase in plasma COP. Extravasation of plasma water may be associated with changes in lymphatic pumping, interstitial hydrostatic pressure and interstitial COP. Olszewski, Engerset, Jaeger, Sokolowski & Theodorson (1977) observed a 50% reduction in lymph flow from the skin and muscle fascia of the foot in response to a 50 mmHg congestion pressure. However, at a later date, some of the same workers (Olszewski & Engerset, 1980) reported a 65% increase in lymphatic flow in lower limbs after changing from the resting horizontal to the resting upright position. A congestion pressure-induced reduction in lymphatic drainage might be expected to cause an increase in interstitial hydrostatic pressure. However, Christ *et al.* (1994) measured subcutaneous interstitial pressure, using the wick in needle technique at the level of the calf, in supine subjects they found that the interstitial pressure did rise during the course of a cumulative congestion pressure step protocol, but only when the congestion pressure exceeded 32·1 mmHg. The increase in pressure was limited to $0{\cdot}67 \pm 0{\cdot}6$ mmHg, provided the congestion pressure remained below diastolic pressure. This change would assist the buffering mechanism, as would the dilution of interstitial protein resulting from the increased level of tissue hydration. Whilst posturally induced increases in lower limb lymphatic flow (Olszewski & Engerset, 1980) might be expected to reduce the interstitial buffering, it could provide an explanation for the paradoxical increases in fluid reabsorption that were observed, after tilting, in three of the thirteen subjects in the present study.

The posturally related changes in COP might be attributed to two mechanisms: (i) the activation of the veno-arteriolar reflex (Henriksen & Sejrsen, 1977) and (ii) the activation of a myogenic response. In the latter case there is little hard evidence to support the maintenance of a sustained non-cyclic myogenic response to a sustained stimulus (Johnson, 1980), whereas following the imposition of the tilt in the present study, a less than expected rate of fluid filtration was sustained for an excess of 30 min, suggesting no attenuation of the buffering mechanism(s). Evidence suggesting that the veno-arteriolar reflex mechanism plays an important part in this sustained pre-capillary constrictor control mechanism is found in a number of publications. Rayman *et al.* (1994) showed that in patients with an impaired veno-arteriolar reflex, due to neuropathy associated with type I diabetes, the oncotic pressure of the venous blood draining from a dependent foot was significantly lower than that found in age-matched non-neuropathic controls. Moreover, this group of patients have also been shown to have a diminished ability to reduce skin blood flow during dependency (Rayman, Hassan & Tooke, 1986) or in response to venous congestion (Tooke, Lins, Ostergren & Fagrell, 1985) and have an elevated venous capillary limb pressure in the dependent posture (Rayman, Williams, Hassan, Gamble & Tooke, 1986). It might, of course, be argued that the changes causing the neuropathy also impaired the stretch-activated mechanism responsible for the myogenic precapillary constrictor component, or that sympathetic activity is a necessary tonic background stimulus for the response.

One of the major findings from the results in the present paper is that $P_{v,i}$ needs to be exceeded before the relationship between pressure, P_v, and J_v is calculated; which reiterates the earlier observations of Krogh *et al.* (1932), Landis & Gibbon (1933) and Pappenheimer & Soto-Rivera (1948).

In summary, the present results do not show a change in K_f in the calf following an increased hydrostatic load, imposed by a passive tilt. The response of J_v to the tilt was substantially less than that predicted on the basis of the pre-tilt value of K_f and the imposed hydrostatic load, revealing the existence of buffering mechanisms. The P_{cuff} was significantly elevated when the subject was in the tilted posture. We attribute this difference, at least in part, to the increase in local oncotic pressure brought about by the activation of a pre-capillary constrictor mechanism, probably the veno-arteriolar reflex. If this mechanism does reduce the surface area available for filtration, then there would have to be a counter-matching rise in permeability to account for these results. There is no evidence in the literature to support such a change in permeability. Thus, it is concluded that a careful study of the responses to a series of cumulative pressure steps is essential for the assessment of K_f and that assessment of K_f, using single congestion steps, may give misleading results.

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