Influence of Experimental Edema on Metabolically Determined Blood Flow

By Robert Zelis, Garrett Lee, and Dean T. Mason

ABSTRACT

To evaluate the effects of edema and elevated tissue pressure on metabolically determined blood flow, forelimb vascular resistance was determined by two techniques. Peak reactive hyperemic blood flow after release of a 5-minute arterial occlusion was bilaterally measured in the brachial arteries of 11 dogs before and after venous congestion of one limb for 4 hours at 70 mm Hg and after infusion of 1,000 ml of 6% Dextran 70. Before determining peak reactive hyperemic blood flow, congestion was released; venous pressure was then similar in both limbs. Congestion reduced peak reactive hyperemic blood flow from 23.9 ± 5.7 (SE) to 16.0 ± 3.6 ml/min 100 g⁻¹ (P < 0.05). Peak reactive hyperemic blood flow was unchanged in the uncongested control limb (21.2 ± 5.2 to 20.4 ± 4.5 ml/min 100 g⁻¹, P > 0.5) at the time when it was reduced in the congested limb. Total tissue pressure measured with a needle was greater in the congested limb (9.1 ± 1.7 mm Hg) than it was in the uncongested limb (2.5 ± 1.5 mm Hg, P < 0.01). Likewise, pressure in a chronically implanted perforated capsule was −2.1 ± 2.0 mm Hg in the control limb but was +7.2 ± 1.5 mm Hg (P < 0.01) in the contralateral limb following congestion. Dextran 70 was infused after venous congestion; this procedure produced peak reactive hyperemic blood flows and tissue pressures which were similar in both limbs. Similarly, minimum vascular resistance following an ischemic stimulus in an isolated, denervated constant-perfused forelimb was increased from 17.7 ± 2.2 to 23.9 ± 1.8 mm Hg/ml min⁻¹ 100 g⁻¹ (P < 0.01) following congestion in five dogs. Brachial arterial sodium content was unchanged in four dogs following 4 hours of congestion. These data suggest that, in the presence of edema, metabolic arteriolar dilation may be impaired.

KEY WORDS tissue pressure reactive hyperemia Dextran 70 congestive heart failure limb congestion forelimb vascular resistance

Systemic vascular resistance is increased in congestive heart failure, but the etiology of this increase has not been completely explained (1-5). Although exaggerated sympathoadrenal discharge has been observed during exercise in heart failure (2, 3, 6-9), the contribution of the sympathetic nervous system, circulating catecholamines, and local catecholamine stores to increased limb vascular resistance at rest remains controversial (10-14). Local factors seem to be important in limiting metabolically induced muscle vasodilation in patients with congestive heart failure (3, 4). Such patients have been shown to have an attenuated blood flow response after release of arterial occlusion, i.e., their reactive hyperemic response is decreased. Likewise, subjects with symptomatic heart disease exhibit a reduced local dilator response to steady-state rhythmic forearm exercise (15) and respond poorly to dilator drugs and local heating (4). The inhibited dilator responses seem to be partially independent of sympathetic activity, since they are not restored by alpha-receptor or nerve blockade (4, 15). Although recent studies have suggested that this abnormality is partially due to an increase in vascular sodium content, which could alter the mechanical properties of the arterioles (16, 17), another possibility is that elevated tissue pressure limits maximum metabolic blood flow at the capillary level. Some investigators think that tissue pressure has an important autoregulatory role, and there are good data derived from models to support this theory (18-21). It is uncertain whether increased tissue pressure in edematous patients with congestive heart failure is capable of limiting muscle blood flow during exercise. Therefore, the present study examined the effect of altering tissue pressure on metabolically determined blood flow in normal dogs.

Methods

Studies were performed on 20 normal healthy mongrel dogs (17–34 kg) anesthetized with sodium pentobarbital and supported by a Harvard model 613...
respiration pump. Arterial blood pressure was measured with a Statham P23Db pressure transducer through a catheter inserted in the abdominal aorta. Body temperature was recorded with a thermister (Yellow Springs Instrument Company) inserted in the femoral artery, and body temperature was regulated by a heating pad. All drugs were given via a catheter in the femoral vein. Limb vascular resistance was measured by two independent techniques. Likewise, tissue pressure was also measured by two different methods.

MEASUREMENT OF VASCULAR RESISTANCE

In 11 dogs, electromagnetic flow transducers (Biotronex Laboratory model BL 610) of comparable sensitivities were placed snugly around each brachial artery, and an inflatable cuff was wrapped around each forelimb just distal to the transducer (Fig. 1). The flow transducers were calibrated by blood infusion through arterial segments in situ, and zero flow was obtained in the experimental dogs by slow arterial occlusion distal to the flowmeter. Forelimb venous pressure was monitored bilaterally through a catheter in the cephalic vein of each limb distal to the inflatable cuffs. The reactive hyperemic response was determined as the peak blood flow after release of arterial occlusion to the forelimb made temporarily ischemic by inflating the cuff to 300 mm Hg. The peak flow after release of a 5-minute arterial occlusion was not significantly different from that obtained by prolonging arterial occlusion to 10 minutes (22, 23). Although longer occlusions, especially if they are accompanied by exercise, can lead to some further reduction in vascular resistance, it has been demonstrated that arterial occlusion reduces tissue pressure (24, 25). Since the study was designed to evaluate the effects of elevated tissue pressure on reactive hyperemic blood flow, the shortest possible period of arterial occlusion consistent with near maximum blood flows was chosen. Therefore, the 5-minute reactive hyperemic response was used as the metabolic stress and is referred to as the peak reactive hyperemic blood flow. After the initial determination of a reactive hyperemic response, simultaneous 5-minute reactive hyperemic blood flow responses were determined bilaterally in duplicate and averaged during the control period at the start of the experiment and after 4 hours of venous congestion at 70 mm Hg of one forelimb. The work of Guyton et al. (24-27) and some preliminary experiments performed in our laboratory have suggested that lower venous pressures held for shorter durations would not be sufficient to produce limb edema comparable to the clinical situation. Following release of congestion and return of venous pressure to control levels, the limb was allowed to stabilize for 5 minutes; then tissue pressure was measured (see the following section) and the reactive hyperemic response was determined in duplicate. Next, 1,000 ml of 6% Dextran 70 (Cutter Laboratories) was infused and the measurements were repeated. The Dextran 70 infusion is a complex intervention; it induces an increase in capillary pressure as well as the desired increase in serum oncotic pressure. Minimum forelimb vascular resistance was calculated by dividing mean arterial blood pressure by peak blood flow.

In addition, five dogs were investigated using a constant-flow technique. Blood was taken from the femoral artery via a heat exchanger and perfused with a model RL 175 Holter pump (Extracorporeal Medical Specialists) at a constant rate into the brachial artery in an isolated, denervated forelimb connected to the torso by the brachial vein, the cephalic vein, and the humerus. The reactive hyperemic response was determined by discontinuing perfusion for 5 minutes and observing the initial plateau in perfusion pressure after restoration of flow. Minimum forelimb vascular resistance was calculated by dividing this perfusion pressure by flow. Minimum resistance thus obtained was determined in duplicate during a control period and after 4 hours of venous congestion of the forelimb at 70 mm Hg. Next, 1,000 ml of Dextran 70 was infused and the measurements were repeated. In all instances, limbs were excised at the termination of the study and weighed so that flow could be expressed in terms of ml/min 100 g⁻¹ tissue.

MEASUREMENT OF TISSUE PRESSURE

An index of tissue pressure was measured in the initial 11 dogs studied by the flowmeter technique; in both forelimbs pressure was directly equilibrated through a 27-gauge needle in the muscle (28-30) with an MSS microdisplacement pressure transducer (Electrometric Incorporated). A second index was obtained by the Guyton technique, utilizing perforated capsules implanted subcutaneously in each forelimb 4-6 weeks before the actual study (24-27). After the congestion period, a 27-gauge needle was inserted through the skin into the cavity of the capsule through one of the perforations. The pressure in the fluid center of the endothelialized capsule was measured as an index of in-

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![FIGURE 1](http://circres.ahajournals.org/)

Schematic illustration of the preparation used to evaluate the reactive hyperemic response which was measured simultaneously in both forelimbs by flow transducers on the brachial arteries. An index of tissue pressure was obtained by measuring pressure through a 27-gauge needle (1) in the muscle at equilibration or (2) within a capsule implanted previously in the subcutaneous tissue.
terstitial pressure, whereas the pressure measured by the needle reflected total tissue pressure. It is assumed that when edema was produced, both indexes measured total tissue pressure, i.e., interstitial fluid pressure plus solid tissue pressure.

MEASUREMENT OF TEMPERATURE LOSS DURING CONGESTION

In three dogs, subcutaneous and muscle temperature were measured by a needle thermistor placed bilaterally in the mid-forelimb before and after 4 hours of venous congestion of one limb at 70 mm Hg.

DETERMINATION OF VASCULAR SODIUM CONTENT

In four additional dogs, one of the forelimbs was subjected to 4 hours of venous congestion at 70 mm Hg, and the contralateral forelimb served as the control. Following congestion, similar segments of the brachial artery were removed bilaterally and dried to constant weight in a vacuum at room temperature. The samples were then extracted with 0.1N HNO₃ at room temperature for 1 week, and their sodium content was determined by flame photometry (16, 31, 32).

Results

VASULAR DILATOR RESPONSE

In the 11 dogs studied by the bilateral flowmeter technique, resting blood flow was similar in both limbs prior to venous congestion of one limb (control limb 2.0 ml/min 100 g⁻¹, experimental limb 2.4 ml/min 100 g⁻¹). Following venous congestion of the experimental limb, basal blood flow was significantly decreased to 1.6 ml/min 100 g⁻¹ (P< 0.01); basal blood flow simultaneously measured in the uncongested control limb increased to 4.0 ml/min 100 g⁻¹ (P<0.05). Likewise, the peak reactive hyperemic blood flow after release of the 5-minute arterial occlusion and the calculated minimum vascular resistance were similar in both limbs prior to venous congestion (Figs. 2 and 3). After the period of venous congestion, peak reactive hyperemic blood flow was significantly reduced from 23.9 ± 5.7 (SE) ml/min 100 g⁻¹ to 16.0 ± 3.6 ml/min 100 g⁻¹ in the congested limb (P<0.05) and minimum vascular resistance was significantly increased from 8.1 ± 1.5 mm Hg/ml min⁻¹ 100 g⁻¹ to 12.8 ± 2.6 mm Hg/ml min⁻¹ 100 g⁻¹ (P< 0.01) (Fig. 3B). However, in the control uncongested limb there was no significant change during this interval in either peak reactive hyperemic blood flow (21.2 ± 5.2 to 20.4 ± 4.5 ml/min 100 g⁻¹, P>0.5) (Fig. 2A) or minimum vascular resistance (8.2 ± 1.6 to 8.2 ± 1.6 mm Hg/ml min⁻¹ 100 g⁻¹, P> 0.5) (Fig. 3A). Dextran 70, infused after the period of venous congestion, increased peak reactive hyperemic blood flow significantly and reduced minimum vascular resistance significantly in both limbs (P<0.01) (Figs. 2 and 3). At the same time mean blood pressure was elevated 32%. There was no significant difference between the two limbs in peak reactive hyperemic blood flow or minimum vascular resistance following Dextran 70 infusion. Venous pressure just prior to release of arterial occlusion was similar in both limbs in all instances.

Using the constant-flow technique, the initial
plateau of arterial perfusion pressure seen after restoration of flow following the 5-minute arterial occlusion was used to calculate minimum vascular resistance (Fig. 4). Mean minimum forelimb vascular resistance of the five dogs increased from 17.7 ± 2.2 to 23.9 ± 1.8 mm Hg/ml min⁻¹ 100 g⁻¹ following 4 hours of venous congestion (Figs. 4 and 5). Dextran 70 infusion performed in two of the five dogs after congestion reduced vascular resistance to a mean of 12.4 mm Hg/ml min⁻¹ 100 g⁻¹ (Fig. 4C).

**CHANGES IN TISSUE PRESSURE**

In the dogs studied with the flowmeter technique, tissue pressure in muscle measured by the needle method following venous congestion was significantly greater in the congested limb (9.1 ± 1.7 mm Hg) than it was in the control uncongested limb (2.5 ± 1.5 mm Hg, P < 0.01) (Fig. 6A). Pressure within the implanted capsules in the muscle was increased significantly by venous congestion (Fig. 6B, C). Dextran 70 infusion reduced the mean pressure to 6.6 and 4.9 mm Hg in the control and congested limbs, respectively (Fig. 6D).

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**FIGURE 4**

Tracings of arterial perfusion pressure of the isolated limb just prior to and during restoration of flow after 5 minutes of ischemia before (A) and after venous congestion (B) and after intravenous Dextran (C). The initial plateau of pressure 3-6 seconds after restoration of flow was considered to represent minimum vascular resistance.

**FIGURE 5**

Mean minimum forelimb vascular resistance ± se determined by the constant-flow technique (see text) before (control) and after venous congestion.

**FIGURE 6**

Interstitial pressure measured directly from a needle in the muscle (A, C) and within chronically implanted perforated capsules in the subcutaneous tissue (B, D) in both control and congested limbs after release of congestion (A, B) and after intravenous Dextran 70 infusion (C, D).
congested limb was $+7.2 \pm 1.5 \text{ mm Hg}$, whereas it was $-2.1 \pm 2.0 \text{ mm Hg}$ ($P < 0.01$) in the uncongested limb (Fig. 6B). When Dextran was infused following venous congestion, the needle pressure and the capsule pressure fell in the previously congested limb; however, they were unaltered in the control limb (Fig. 6C, D). In two dogs studied by the constant-flow technique, venous congestion elevated capsule pressure from $-1.7$ to 9.8 mm Hg.

**Changes in Tissue Temperature with Congestion**

Following 4 hours of venous congestion, forelimb muscle temperature fell 2.32°C and subcutaneous temperature fell 3.00°C (Table 1). To control for systemic heat loss, the temperature in the congested limb was compared with that simultaneously measured in the contralateral control limb. When the differences between limbs was evaluated, the true temperature differential was 1.10°C for muscle temperature and 1.81°C for subcutaneous temperature.

**Vascular Sodium Content**

In four dogs, the sodium content of the brachial artery in the uncongested limb was $40.9 \pm 2.2 \text{ mEq/100 g}$ and was not significantly different from that measured in samples taken at the same time from the contralateral congested limb ($39.0 \pm 1.2 \text{ mEq/100 g}$, $P > 0.4$).

**Discussion**

The most important finding of this study was that chronic venous congestion can significantly alter the magnitude of the blood flow response to a metabolic stimulus. Thus, using two different preparations for the evaluation of the reactive hyperemic response, it was observed that peak reactive hyperemic blood flow was significantly decreased and calculated minimum vascular resistance was significantly increased following a period of prolonged venous congestion (Figs. 2 and 3). Moreover, vasodilator capacity remained unchanged in the contralateral uncongested limbs studied at similar times. Although sympathetic alpha-adrenergic activity is an important regulator of regional blood flow and can partially attenuate submaximal arteriolar dilation, it is unlikely that such activity is a major factor contributing to the decreased peak reactive hyperemic blood flow observed after limb congestion (15, 33, 34). Since blood flows were always measured simultaneously in control and experimental limbs, systemic changes in sympathetic tone, circulating catecholamines, or other humoral factors should have influenced both limbs to a similar extent. Vasodilator capacity was also reduced following venous congestion by the technique in which the forelimb was isolated and completely denervated (Figs. 4 and 5). On the other hand, when Dextran 70 was infused following venous congestion, there was marked bilateral accentuation of the peak reactive hyperemic blood flow which was similar in both limbs (Figs. 2 and 3). Part of this response could be explained by the concomitant rise in arterial blood pressure.

It is important to evaluate a number of local factors that may have contributed to the observed differences in maximum blood flow between edematous and nonedematous limbs. It has been noted that temporary venous congestion maintained up to the moment of arteriolar occlusion can attenuate the reactive hyperemic response by the Bayliss effect (35–37). The maintenance of an elevated transmural arteriolar pressure due to the high venous pressure allows the vascular wall to maintain a significant degree of myogenic tone. In this study we were careful to ensure that venous pressure was allowed to return to normal prior to arterial occlusion. No significant changes in venous

**Table 1**

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Data are averages for three dogs.
pressure were observed between the two limbs just prior to the release of the 5-minute arterial occlusion before or after congestion. Although it is possible that venous congestion may have induced arterial spasm, it is unlikely that this phenomenon persisted during the postcongestion ischemic tests. With arterial spasm, it takes longer for the arterial blood pressure to fall distal to the site of arterial occlusion (38); however, arterial and venous pressures equilibrated at a low level within 5 minutes. Therefore, it appears that the Bayliss effect was not a major factor limiting flow in this study. It has been suggested that packing the limb with blood by venous congestion prior to arterial occlusion can attenuate the reactive hyperemic response by increasing the amount of oxygen trapped in the limb (39). Although it is possible that this phenomenon may play a role in acute venous congestion, it is unlikely that it is an important factor with chronic congestion, especially after venous pressure has returned to normal. Indeed, the converse is more likely, i.e., metabolites may have accumulated in the edematous tissue and may have even augmented the peak reactive hyperemic blood flow instead of attenuating it.

An important point to consider is whether the basal metabolism of the edematous limb was reduced over the 4 hours of venous congestion. Since congested limbs lose heat, it is possible that in a cooler limb the accumulation of metabolites is less and the reactive hyperemic response attenuated (40, 41). A reduction in arm muscle temperature from 34°C to 19.5°C has been shown to result in a 50% reduction in peak reactive hyperemic flow (41). Importantly, the temperature difference between the congested and the control limbs in the present experiments was less than 2°C (Table 1). Although this difference could have accounted for some reduction in the reactive hyperemic response, it could not have explained the dramatic reduction seen in this investigation.

Since vascular sodium content has been correlated with metabolic dilator capacity, it was important to show that congestion did not cause significant local ionic shifts (16, 17). Both in heart failure and hypertension, arterial sodium is increased and metabolic dilator capacity is reduced. The demonstration that brachial arterial sodium content was not altered by venous congestion eliminated this phenomenon as a significant factor in limiting maximum blood flow.

Having reasonably ruled out the preceding mechanisms as possible factors explaining the observed limited dilator capacity after congestion, the elevated tissue pressure which was noted in the chronically congested limb emerges as a possible explanation for the changes in metabolic blood flow and minimum vascular resistance (Fig. 6). Therefore, it is postulated that the increased transudation of fluid into the surrounding tissue during partial venous occlusion results in an elevated tissue pressure, which leads to compression of the distal end of capillaries, and thus serves as a mechanism by which the reactive hyperemic response is reduced. It has previously been postulated by Rodbard et al. (19, 20) and Beer (21) that much of the local regulation of blood flow occurs at the capillary level. They used a permeable collapsible vessel enclosed in a compliant capsule, the “capillaron,” to demonstrate this principle. Although changes in tissue pressure have also been shown to result in alterations in basal blood flow in animals (21), the current studies are the first to demonstrate that such a mechanism can be operative in regulating metabolically augmented blood flow in vivo. The studies reported in the present paper demonstrated that the maximum blood flow induced by a standard metabolic stress varied inversely with tissue pressure. When tissue pressure was significantly different between two limbs, the maximum blood flows were also different. Likewise, following Dextran 70 infusion when tissue pressure was not significantly different between the autoperfused limbs, neither was blood flow. Similar correlations were noted when vascular resistance was evaluated. In the two dogs studied by the constant-flow technique in which tissue pressure was measured, venous congestion elevated tissue pressure to positive values and inhibited the postischemic vasodilatation. It should be emphasized that the major site of arterial resistance may change during maximum metabolic arteriolar dilation. In atherosclerotic peripheral vascular disease, the vessels contributing most significantly to limb vascular resistance under such conditions are most likely the large atherosclerotic arteries or the collateral vessels around occluded channels (22, 42–45). It is suggested that, when tissue pressure is elevated above atmospheric levels, it may play a role in regulating capillary resistance under conditions of severe metabolic stress such as ischemia or exercise.

The method of measuring interstitial pressure and the concept of negative tissue pressure are still debated; this study does not claim to have resolved this much discussed issue (19, 20, 24, 27, 46–52).
The goal of this investigation was not to determine the true value of tissue pressure but rather to investigate directional changes in flow as a function of directional changes in two indexes of tissue pressure. The measurement of total tissue pressure by a subcutaneous needle in the control limb indicated a positive pressure of a few millimeters of mercury; this finding is consistent with that of other investigators who have used this method (52). The interstitial fluid pressure measured in chronically implanted capsules in normal nonedematous tissue was quite similar to the negative pressure demonstrated by Guyton et al. (24-27) and others (48) who have utilized this technique. Most important, in the edematous limbs, tissue pressure was consistently positive and significantly greater than that in the contralateral nonedematous limb. The finding that the needle pressure and the pressure within the capsule were similar in the edematous limb is in accordance with the findings of Guyton and suggests that, in this circumstance, capsule pressure reflects total tissue pressure, i.e., solid tissue pressure plus interstitial fluid pressure. It is probably total tissue pressure which is important in reducing metabolic blood flow following venous congestion. When Dextran 70 was infused following venous congestion, tissue pressure (by capsule and needle) was reduced but still positive, yet metabolic blood flow had returned to above control values. Although the Dextran 70 infusion is a complex intervention which may induce changes in viscosity or capillary surface area as well as elevations in blood pressure, these data suggest that total tissue pressure must be significantly positive before metabolically determined blood flow is altered.

One question left unanswered by this study is whether edema alters metabolic blood flow through a structural as well as a functional mechanism. The magnitude of the measured change in tissue pressure was quite small; simple hydraulic considerations would predict a reduction in peak reactive hyperemic flow of only 10% instead of the 33% seen in the present study. Such a quantitative relationship has been demonstrated between the reactive hyperemic response and the magnitude of limb external compression (53). It is possible that interstitial pressure was actually significantly higher in muscle surrounded by fascia than it was in relatively compliant subcutaneous tissue. On the other hand, actual structural changes in vessels, such as capillary endothelial or basement membrane swelling, could lead to increased resistance measured in the total vascular bed. In chronic congestive heart failure, increased basement membrane thickness has been described (54).

This study was not designed to determine whether muscle blood flow under normal conditions is predominantly under myogenic, metabolic, or tissue pressure control (18). Since edematous subcutaneous tissue becomes considerably more compliant as tissue pressure becomes positive (25, 26, 55), perhaps capillary compression as a means of altering augmented blood flow is a more important mechanism in muscle which is surrounded by a noncompliant fascia. It is possible that this mechanism is an important factor limiting blood flow in exercising extremities in edematous states such as congestive heart failure, especially when systemic venous pressure is chronically elevated. On the other hand, the edema of congestive heart failure may be different from that produced in this model by limb congestion at very high venous pressures for 4 hours. Further studies need to be done to determine the magnitude of tissue pressure elevation in heart failure with edema. However, it is intriguing to speculate that increased tissue pressure may occur in skeletal muscle and be an important contributor to the increased vascular resistance seen in heart failure. Perhaps the term "vascular stiffness" which has been applied to patients in congestive heart failure to reflect their diminished arteriolar dilator capacity is a misnomer, since this study has demonstrated that it is possible that some of the increase in resistance may also be perivascular.

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References


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41. COLES, D.R., AND COOPER, K.E.: Hyperemia following ar-
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