VI. Neural Control of Microcirculation

Neural Modulation of Transcapillary Exchange of Fluid and Solutes in Whole-Organ Preparations

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Activation of sympathetic adrenergic postganglionic fibers that release norepinephrine at the neuromuscular junction can influence resistance, capacitance, and exchange functions in the microcirculation. Although the predominant response is an increase in precapillary resistance that reduces blood flow through the tissue (at constant pressure perfusion), there are two distinct components that can be separated into an initial (1-2-minute) and late (2-15-minute) response. The initial (1-2-minute) response is a decrease in venous and capillary pressures in passive response to decreased flow promoted by an increase in precapillary resistance. Venous pressures are reduced even though postcapillary resistance is increased. The decrease in capillary pressure promotes absorption of fluid from tissue to plasma. Venous constriction results in a translocation of fluid out of the terminal venous system into the larger venous conduits toward the heart. Total blood volume in an isolated organ system decreases and is manifested as a decrease in volume (plethysmographic) or weight (gravimetric). The decrease in volume is a result of three interrelated factors: 1) decrease in flow through the organ, 2) active venoconstriction and a translocation of blood out of the organ, and 3) absorption of fluid from tissue to plasma, which flows out of the organ with venous drainage. With prolonged sympathetic nervous system stimulation, the late response (3-15 minutes) is a gradual decrease in precapillary resistance that increases blood flow through the organ. Venous and capillary pressures passively increase in association with increases in flow. The mechanism of the decrease in precapillary resistance, which has been labeled sympathetic or autoregulatory "escape," has never been clearly identified but has been attributed to the accumulation of vasodilator metabolites. Precapillary resistance decreases and approaches control in skeletal muscle and skin, returns to control rapidly in the intestine, and appears to be reasonably well maintained in adipose tissue. As measured by filtration coefficients, capillary surface area appears to be unaffected or increased in skeletal muscle and skin, remains decreased in the intestine, and may be increased in adipose tissue. This demonstrates that precapillary sphincters (or terminal arterioles) controlling flow to the capillary exchange surface area respond to a sympathetic neural stimulus different than other precapillary resistance vessels. In every organ, except adipose tissue, in which measurements have been made, the transcapillary exchange of solutes is decreased during sympathetic neural stimulation. This results from a decrease in flow and a decrease in delivery of solute to the exchange surface area. Decreased exchange may also result from a decrease in surface area available for exchange by mechanisms that alter the distribution of flow to those tissue elements where exchange does not readily occur. The exact mechanisms relating to this complex response have not been clearly defined. In adipose tissue only, it appears that sympathetic neural stimulation may alter capillary membrane structure to cause an increase in capillary permeability to solutes. (Circulation Research 1987;61[suppl II]:II-12-II-19)
Materials and Methods

For this report, the circulatory changes occurring with sympathetic nerve stimulation in the isolated dog hind limb will be used as an example to describe the general response. A review of the literature supports the notion that this is a representative example of the response observed in skin, skeletal muscle, and intestine, although there are qualitative and quantitative differences among these organs. There is insufficient information in the literature to be able to determine if the response in lung, heart, bone, liver, kidney, and brain would be similar. However, the response in adipose tissue is very different.

The isolated dog hind limb preparation used in this laboratory has been described in detail in many publications. Briefly, the hind limb was isolated with the aid of a cautery, and the weight of the limb was continuously monitored. Constant pressure perfusion of oxygenated blood at 37°C was accomplished by using a column of blood maintained at such height as to exert a constant pressure head of 100 mm Hg at the femoral artery over wide variations in resistance to flow through the hind limb. Pressures were measured in the femoral artery and vein, saphenous vein, and a small muscle and digital vein using a branch cannulation technique with conventional polyethylene catheters and pressure transducers. Flow was measured with a Biotronix electromagnetic flowmeter calibrated using a stopwatch and graduated cylinder. Sympathetic stimulation was performed using both the femoral and sciatic nerve after neuromuscular blockade with 4 mg/kg gallamine triethiodide (Flaxedil), which was supplemented every 20 minutes with 1 mg/kg to maintain muscle paralysis. Atropine sulfate (0.8 mg/kg) was administered to eliminate the possible involvement of cholinergic fibers. The stimulation frequency for the response shown in Figure 1 was 40 impulse/sec of 5-msec duration and supramaximal amplitude and was made using a Grass stimulator.

Determination of mean capillary hydrostatic pressure (Pc) during the hemodynamic response was made using the following relation:

\[ Pc = Rv \cdot Q + Pv \]

where \( Rv \) (postcapillary resistance) was determined using the isogravimetric procedure, but \( Q \) (blood flow) and \( Pv \) (femoral venous pressure) were measured parameters obtained in the experimental state. Postcapillary resistance was determined in the control state and at 10 minutes (4 preparations) and 20 minutes (14 preparations) during stimulation. There was no significant difference in the experimental values of venous resistance determined at 10 and 20 minutes, which is consistent with a prolonged and sustained increase in postcapillary resistance during sympathetic nerve stimulation observed by others.

Precapillary resistance (\( Ra \)) and \( Rv \) were determined by the relations \( Ra = Pa - Pc - Q \) and \( Rv = Pc - Pv + Q \) where \( Pa \) is femoral artery pressure and \( Q \) is femoral blood flow.

Results

The hemodynamic response to activation of the sympathetic nervous system in the isolated dog hind limb preparation is presented in Figure 1. Description of the response will be divided into three categories reflecting the three major segments of the vasculature, i.e., the precapillary segment, which under the specific conditions of these experiments represents all components of the arterial vascular tree from the effective midpoint of the capillaries to the point in the femoral artery where pressure was measured; the postcapillary segment, which represents all components of the venous vascular tree from the effective midpoint of the capillaries to the point in the femoral vein where pressure was measured; and the capillary segment. The latter refers to those anatomical areas (including small venules) where exchange of fluid and solutes can occur.
between blood and tissue. Additionally, the response can be separated into two phases: an initial phase corresponding to the effect observed between 0–2 minutes and a late phase corresponding to the response observed from 2–16 minutes (Figure 1).

Precapillary Segment

Activation of the sympathetic nervous system results in contraction of vascular smooth muscle of small arteries and arterioles and a subsequent increase in precapillary vascular resistance. Since upstream arterial pressure does not increase appreciably, the predominant initial (1–2-minute) effect is a decrease in blood flow through the organ. Figure 1 shows the precipitous decrease in flow (venous outflow); the small (negligible) increase in femoral arterial pressure, which was transient; and the calculated increase in precapillary resistance, which occurred on beginning stimulation.

Following the initial (1–2 minute) vasoconstrictor response is a slow relaxation of arteriolar vascular smooth muscle, even though sympathetic stimulation is continued. This relaxation is shown most clearly in Figure 1 by the calculated decrease in precapillary resistance and increase in flow (venous outflow), which in this particular experiment begins at approximately 2 minutes after beginning stimulation and continues for the entire late phase (2–16 minutes). Decreasing precapillary resistance during continued stimulation has been designated as the "sympathetic escape" phenomenon and occurs in most tissues that have been studied.

Following the initial increase, the precapillary resistance decrease in the late phase of the response was persistent over the time course of stimulation but was extremely variable from preparation to preparation. In 6 experiments, precapillary resistance returned to prestimulation control values by 6–12 minutes. In the remaining 8 experiments, precapillary resistance, although continually decreasing, remained below prestimulation control values for the entire period of stimulation (16–20 minutes).

Postcapillary Segment

On beginning stimulation, venous pressures in all segments of the hind limb immediately decreased in association with the decrease in flow (Figure 1). The passive collapse of venous vessels in response to the decrease in flow (and transmural pressure) presumably contributes to an increase in postcapillary resistance. Superimposed on this passive mechanical component of increased postcapillary resistance is an active component of venous constriction. Evidence of active venous constriction includes: 1) Venous pressure in the small digital veins increased above control values in association with a decrease in flow through the preparation. 2) Postcapillary resistance increased almost threefold as determined using the isogravimetric procedure (from 0.10 ± 0.024 to 0.301 ± 0.032, mean ± SEM for 14 experiments) independent of whether the measurement was made between 6–10 minutes after beginning stimulation or at 25–30 minutes after flow had returned to control values (Figure 2). (Measurements made at 6–10 minutes were always slightly higher than those made at 25–30 minutes, presumably reflecting the passive "collapse" component.) 3) When arterial and venous pressures are held constant during sympathetic neural stimulation, an increase in venous resistance can be calculated. These data demonstrate in the present study, as in a number of other studies, that unlike the precapillary segment response, the postcapillary resistance increase (and thus venous smooth muscle contraction) appears to be sustained for much longer periods of time during the stimulus.

Constriction of veins leads to an increased pressure difference between the small collecting veins and/or venules and the large venous conduits going to the heart, which, in turn, leads to a translocation of blood out of the collecting veins and venules toward the heart. Thus, when the sympathetic nerves to an organ are stimulated, a decrease in capacitance of the veins is clearly manifested as a decrease in volume (plethysmographic) or weight (gravimetric) of the organ. This is clearly shown in Figure 1 as a decrease in limb weight during the initial phase (0–2 minutes) of the response. A quantitative evaluation of the capacitance response (volume loss through venoconstriction) is difficult to assess under the experiment conditions of constant pressure perfusion because of the contribution of decreased flow (and thus, reduced intravascular volume) that occurs with the increase in precapillary resistance. When the sympathetic nerves are stimulated or norepinephrine is infused under conditions of constant flow perfusion, the capacitance change with sympathetic stimulation is clearly demonstrated because venous outflow exceeds the constant arterial inflow in association with the loss in weight and/or volume.

![Figure 2](https://example.com/figure2.png)
**Capillary Exchange Segment**

Activation of the sympathetic nervous system can influence the transcapillary exchange of fluid and solutes. In experiments on the whole hind limb (Figure 3), filtration coefficients ($K_f$) were measured at various times during the period of stimulation. Our results are consistent with many previous studies on skeletal muscle and/or skin that show an initial decrease in $K_f$ (determined from 1 to 3 minutes after beginning stimulation) and either no change or an increase in $K_f$ when measurements are made 5 minutes or more after starting adrenergic stimulation.

$m$ values of 0.012 ± 0.002 (mean ± SEM for 8 experiments). The increase in $K_f$ was not statistically significant in our studies but, as noted above, significant increases in this parameter during sympathetic stimulation in skeletal muscle have been reported by others.

The movement of fluid and convective transport of solutes across the exchange surface membrane depends on the prevailing balance of forces as described by the well-established Starling relation. Stimulation of the sympathetic nerves directly affects capillary hydrostatic pressure. Capillary hydrostatic pressure depends on arterial pressure, venous pressure, and the ratio of postcapillary to precapillary resistance ($R_v: R_a$).

In Figure 1, $P_a$ changed little, both $R_v$ and $R_a$ increased, and $P_v$ decreased. The ratio $R_v: R_a$ decreased because the resistance increase was greater in $R_a$ than in $R_v$. The net result of these changes was to lower capillary hydrostatic pressure, which promotes absorption of fluid from tissue to plasma. The calculated changes in capillary hydrostatic pressure are also shown in Figure 1. Initially (1–2 minutes), capillary pressure decreased by approximately 7 mm Hg below the level (15 mm Hg) required to maintain an isogravimetric state (no net fluid filtration or absorption). Following this initial decrease, capillary pressure began to increase in association with autoregulatory escape of the precapillary resistance vessels and the attendant increase in flow. This portion of the response, which is directly related to the escape phenomenon, was highly variable. In some preparations, capillary pressure rapidly increased and exceeded control values at 5–8 minutes after beginning stimulation, and in others, it slowly approached control values as shown in Figure 1. This variability probably relates to the physiologic state of the preparation and specifically to the vascular smooth muscle responsiveness. It would be anticipated that there was continual absorption of fluid from tissue to plasma in the experiment shown in Figure 1 because capillary pressure approached but did not exceed the control value of 15 mm Hg (the equilibrium pressure [isogravimetric capillary hydrostatic pressure] where the Starling forces are balanced and there is no net fluid movement).

**Discussion**

The activation of sympathetic nerves causes vascular effects that may differ both quantitatively and qualitatively among animals, organs, tissues, and specific vessels. The predominant response, however, is vasoconstriction promoted by the release of norepinephrine at the neuroeffectector junction, which causes constriction of vascular smooth muscle. Constriction of precapillary vessels by sympathetic nerve stimulation has been demonstrated in the vascular beds of heart, lungs, brain, adipose tissue, intestine, kidney, bone, and skin and skeletal muscle. The constrictor response is graded with an increasing number of impulses causing greater vasoconstriction. The maximum vasoconstriction, in most tissues, appears to be obtained with a stimulus of 8–10 impulse/sec.

With continued stimulation of the nerves, autoregulatory "escape" occurs in the precapillary segment. In the present study, this escape is demonstrated by the observed decrease in precapillary resistance. Such escape has been attributed to the accumulation of vasodilator metabolites that increase in the organ extravascu-

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**Figure 3.** Capillary filtration coefficients for isolated dog hind limb during sympathetic neural stimulation (Panel A). For control and sympathetic stimulation at 15–20 minutes, a three-point filtration measurement was made. For sympathetic neural stimulation at 1–3 minutes, only one point was obtained in 4 experiments because of time limitations. Point plotted is mean value for 4 experiments. Panel B: Graphic representation of changes in blood flow and filtration coefficients ($K_f$) in isolated hind limb. Note that $K_f$ during stimulation (15–20 minutes) exceeds control value, even though sympathetic stimulation is maintained (see Cobbold et al).
lar space (from cellular metabolism concomitant with decreased flow and reduced O2 delivery) and diffuse to arteriolar smooth muscle to cause arteriolar smooth muscle relaxation. The direct accumulation of vasodilator metabolites in vascular smooth muscle presumably would be additive and enhance the relaxation. Vasodilator metabolites override the direct vasoconstrictor response related to norepinephrine release. A second mechanism that may be a component in the escape phenomenon is neural “fatigue,” where there may be a decreasing concentration of neurotransmitter released with continued stimulation. Whatever the mechanism, during decreasing precapillary resistance, blood flow through the organ increasingly washes vasodilator metabolites from the tissue and simultaneously provides oxygen and nutrient delivery to all tissue segments.

Autoregulatory escape in precapillary vessels has been demonstrated in skeletal muscle, skin, kidney, and intestine (see review by Renkin\textsuperscript{46}) but, at this time, has not been studied adequately in heart, lung, brain, adipose tissue, and bone to provide any reasonable comment on the magnitude or time course of the response.

Whole-organ studies of the kind reported here cannot distinguish whether different segments of the arterial vasculature respond differently to the same stimulus. Although such studies are few, it is clear from the limited data available that smaller arterioles, such as third- and fourth-order arterioles, are more responsive and constrict more vigorously than the larger first- and second-order arterioles.\textsuperscript{31,44,47,48} It would be of interest to determine if autoregulatory escape was also different in the various arteriolar segments.

Postcapillary Segment

Sympathetic neural stimulation results in contraction of venous vascular smooth muscle, as shown in skin, intestine, brain, liver, and skeletal muscle, leading to vasoconstriction and an increase in postcapillary resistance.\textsuperscript{5,7,40-55} Unlike precapillary vessels, the postcapillary segment does not exhibit autoregulatory escape. The reason that arteriolar and venous smooth muscle respond differently to similar stimuli has never been clearly identified but is related in some unknown manner to differences in the excitation-contraction coupling process of the specific vascular tissue. The venous constrictor response is graded with an increasing number of impulses causing greater vеноconstriction. The maximum response appears to be obtained with 8–10 impulse/sec, but maximum vеноconstriction has been shown to occur at frequencies as low as 4–6 impulse/sec. In addition to the resistance increase, the contraction of venous smooth muscle also results in a whole-organ capacitance response.

The functional significance of active vеноconstriction has long been recognized and appreciated. Translocation of blood from the smaller veins, where it has been stored by virtue of the pressure-volume characteristics of the venous system, helps to restore an effective circulating blood volume in pathophysiologic states such as hypovolemic shock. Although this concept has been used as a fundamental principle in explaining circulatory homeostasis in pathophysiologic states, the absolute mechanism of the response has been, and is still being, questioned. Much of the controversy revolves around the fact that in a variety of tissues, either few or no adrenergic fibers can be demonstrated in venules and veins using standard histochemical techniques.\textsuperscript{32,47,54,57} An alternative hypothesis has been advanced that norepinephrine released from precapillary vascular nerve terminals is washed downstream and promotes venoconstriction. Samples of venous effluent blood taken during neural stimulation have been shown to contain appreciable amounts of norepinephrine.\textsuperscript{58,59}

Although active venous constriction and a translocation of blood have been shown in skin, skeletal muscle, intestine, liver (see Rothe\textsuperscript{55} for review), and lungs,\textsuperscript{60} such a phenomenon has not, as yet, been demonstrated in adipose tissue, brain, heart, bone, or kidney.

Capillary Exchange Segment

Activation of the sympathetic nervous system can influence the transcapillary exchange of fluid and solutes. The mechanisms for this are reasonably straightforward and are an alteration of capillary hydrostatic pressure by changing precapillary and postcapillary resistance, regulation of the number of capillaries open for flow, and direct effect on the characteristics of the capillary membrane as a barrier to fluid and solute movement.

Capillary Hydrostatic Pressure

There are few studies that directly address the changes in capillary hydrostatic pressure that result when the sympathetic nerves are stimulated. In skeletal muscle, skin, and intestine, indirect assessments have been made.\textsuperscript{3,8,29,40-52} and although there are quantitative differences, the results presented in this report are generally representative of the reported response. Capillary hydrostatic pressure initially decreases and then promotes absorption of fluid from tissue to plasma. The late response indicates that capillary pressure increases in association with decreased precapillary resistance and increased capillary inflow. Data are not available to assess capillary pressure changes in brain, heart, lungs, and bone during sympathetic stimulation. In those organs where measurements have been made, the initial fall in capillary pressure appears to be graded with an increased number of impulses, which results in greater decreases in capillary pressure and the maximum fall being obtained at stimulus frequencies of 8–10 impulse/sec. Since these data derive from indirect indexes, it will be very informative when direct measurements of capillary hydrostatic pressure are made in the microcirculation during sympathetic neural stimulation and to correlate these with whole organ results; the methods are now available to do this.

Interestingly, the decrease in capillary hydrostatic pressure and, thus, absorption of fluid in the overall
response in the isolated dog hind limb is attenuated by several factors; namely, a decreasing precapillary resistance that increases inflow to the capillary (tending to increase pressure), a sustained increase in postcapillary resistance that attenuates outflow from the capillary (tending to increase pressure), and a dilution of capillary intraluminal and a concentration of extraluminal proteins, both of which tend to inhibit the loss of fluid from the extravascular compartment.

**Exchange Surface Area**

The factors and forces that regulate or modulate the surface area available for exchange are poorly understood, and little unambiguous quantitative information is available on this variable in any organ system. The data in this study point out the now well-established fact that the vasoconstrictor influence on those vascular elements controlling precapillary resistance and on those vascular elements controlling capillary surface area are different when sympathetic nerves are stimulated or norepinephrine is administered. This difference is shown by the fact that the capillary-filtration coefficient tended to increase above control despite a sustained increase in precapillary resistance.

Explanations for increases in precapillary vascular resistance that are associated with an increased surface area available for transcapillary exchange of fluid during the late phase (2-10 minutes) of the response include: 1) A local increase in vasodilator metabolites that accumulate at precapillary sphincters, thus increasing capillary surface area. This may be related to local hypoxia and metabolically linked to an increase in inorganic phosphate and AMP concentrations. 2) A myogenic response, that is, precapillary sphincter relaxation promoted by a decrease in transmural pressure. 3) Alterations in intracellular and extracellular potassium and hyperosmolality. The observed response is most likely related to a multifactorial mechanism.

In the intestine, the surface area for exchange remains decreased during continued sympathetic neural stimulation. There is little information in the literature related to this response for heart, lung, brain, kidney, or bone.

During continuous sympathetic neural stimulation in skeletal muscle and intestine, the transport of solutes between blood and tissue is reduced. Studies related to this aspect of capillary exchange are relatively few and have been reviewed in some detail. The apparent inconsistency in results (i.e., an increased surface area for exchange as determined by Ks and decreased surface area as determined by solute exchange measurements) has several possible explanations. Clearly, the reduction in blood flow to the exchange surface that accompanies the increase in arteriolar resistance limits the amount of solute that can be delivered to and thus make contact with the exchange membrane for transport between blood and tissue. However, there appear to be other mechanisms, independent of blood flow, augmenting the response. One mechanism is a redistribution of flow to microvascular channels where exchange of solutes does not readily occur. It has been proposed that these functional shunts may be very short capillaries where the velocity of flow is high and there is insufficient time for solutes to exchange.

**Exchange Surface Permeability**

Sympathetic nervous system activation may directly influence the exchange surface membrane to increase or decrease permeability. In the present study, isogravimetric capillary pressures (Pci) were measured during sympathetic stimulation. Measurements of Pci for 14 experiments were 12.2 ± 1.0 mm Hg in the control state and 12.8 ± 0.8 mm Hg during sympathetic stimulation (mean ± SEM). This parameter is a measure of the proportion of the protein osmotic pressure across the capillary wall. No change in this variable indicates there was no change in capillary permeability to proteins. In adipose tissue, the results clearly indicate that the permeability to plasma proteins and smaller solutes is increased during stimulation of the sympathetic nerves. It has also been suggested that stimulation of sympathetic nerves in brain tissue may increase the permeability of capillaries to water. The studies of brain are inconclusive primarily because microvascular hemodynamics have not been assessed and capillary surface area changes have not been singularly quantified during the response. To our knowledge, no other reports have presented quantitative evidence suggesting that activation of the sympathetic nervous system directly alters exchange surface membrane permeability to fluid or solutes in other organs or tissues. A review of the literature indicates that quantitative differentiation of changes in many essential microvascular variables (i.e., surface area, membrane ultrastructure, and capillary hydrostatic pressure) during activation of the sympathetic nervous system is lacking in many organs and tissues, including kidney, liver, heart, lungs, brain, and bone.

The challenge for the future appears to be directed at those scientists involved in the direct measurement of microvascular variables. Measurements need to be made to define and quantitate vascular smooth muscle and endothelial cell responses to sympathetic neural stimulation in the various discrete microvascular segments of the circulatory tree. Such studies should enhance our understanding of the basic mechanisms that are responsible for whole-organ alterations in resistance, capacitance, and exchange functions.

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Editorial constraints have permitted only a partial listing of the references. A complete set of references is available on request.

**Key Words** • sympathetic neural stimulation • precapillary and postcapillary resistance • transcapillary exchange • venous capacitance
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Circ Res. 1987;61:II-12-II-19
doi: 10.1161/01.RES.61.5_suppl.II-12
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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