Hemodynamics of Collateral Vasodilatation following Femoral Artery Occlusion in Anesthetized Dogs

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ABSTRACT

Dilatation of collateral blood vessels was studied following occlusion of the femoral artery in anesthetized dogs. This was achieved by measuring pressure and flow in the anterior tibial artery distal to the occlusion and pressure in the femoral artery proximal to the occlusion. Dilatation of the collateral vessels to the anterior tibial artery was estimated by the increase in the conductance of the collaterals from the minimum value measured 8 to 10 seconds following onset of the occlusion. Conductance rose 277 ± 67 (SEM)% during the first 70 seconds following occlusion and an additional 178 ± 66% during the ensuing hour. When the femoral artery was reopened after a 2-minute period of occlusion, the collaterals reconstricted to their preocclusion size in 12 to 14 minutes. Elimination of circulatory reflexes by total spinal anesthesia did not alter the course of collateral vasodilatation. However, when systemic arterial pressure was lowered to approximately 45 mm Hg for 8 minutes prior to occlusion, the collaterals dilated almost completely even before the occlusion was instituted, indicating that tissue ischemia is in some way related to collateral vasodilatation.

ADDITIONAL KEY WORDS

collateral circulation, collateral conductance, dog hind limb, hypotension, tissue ischemia, vasoconstriction, spinal anesthesia

Although our knowledge of the peripheral circulation has advanced rapidly in recent years, the hemodynamic changes in the collateral vessels which follow within a few minutes after occlusion of a major artery to a limb have not been thoroughly characterized. Therefore, the goal of this study has been a clear characterization of these changes as well as an attempt to identify some of the factors responsible for the initial onset of collateral vascular dilatation.

A few attempts to study hemodynamics of the collateral circulation in the limb have been reported. Winblad et al. (1) studied arterial blood pressure, tissue Po2, and angiograms following occlusion of the femoral artery in the dog. They noted an immediate drop in anterior tibial pressure to between 35 and 60 mm Hg and a return to about 80 mm Hg in 2 to 8 minutes. The pressure then remained constant for 4 months of observation. John and Warren (2) observed similar changes in pressure distal to a femoral occlusion in the dog. These authors noted that pressure fell from between 100 and 150 mm Hg to between 20 and 60 mm Hg, then began to rise within 3 seconds, and in about 3 minutes reached 30 to 50% of the preocclusion level. Using a venous-occlusion plethysmograph to estimate blood flow, they recorded a fall in flow to zero for the first 5 minutes after occlusion, then flow returned at a slow rate to 25 to 33% of the preocclusion level in 30 minutes. Flow recovered to preocclusion values in 3 to 9 days. Thulesius (3) recorded venous flow following occlusion of the femoral artery in the cat. He observed that flow dropped to 20 to 30% of control.
initially and rose to 50% of control in 2 to 3 minutes. In the present study, we have investigated changes in the collateral circulation during the first few minutes and up to an hour following occlusion. Pressure and flow were simultaneously measured in the anterior tibial artery following occlusion of the femoral artery in the dog. A rapid but partial recovery of flow as well as pressure was recorded after occlusion. We have also searched for possible causes of the dilatation of the collateral circulation. The evidence presented fails to support a nervous reflex mechanism for initiation of collateral circulation development but instead supports peripheral ischemia as one of the responsible factors.

**Methods**

Experiments were performed on 52 mongrel dogs weighing 16 to 29 kg. The animals were lightly anesthetized with pentobarbital sodium, 25 mg/kg iv, and anticoagulated with heparin, 5 mg/kg iv. The femoral artery was occluded with a bulldog clamp in the femoral triangle distal to the profunda femoris artery. To record pressure, 23-gauge needles on the ends of polyvinyl catheters, 48 cm long and 0.056 cm internal diameter, were inserted respectively into the femoral artery 3 cm proximal to the occlusion site and into the anterior tibial artery midway between the knee and the ankle. The catheters were connected to Statham strain-gauge pressure transducers, Model P23AC, and the pressures were recorded on a Grass polygraph, Model P7. The frequency response of the needle-catheter transducer-recorder system was uniform (±5%) to 5 cps as determined by the Hansen calibration technique (4). An electromagnetic flow transducer, lumen diameter 1.5 or 2 mm, was fitted over the anterior tibial artery 3 cm proximal to the pressure needle. All arterial branches between the flow transducer and pressure needle were ligated. The flow transducer was connected to a Medicon gated sinewave electromagnetic flowmeter, Model K-2004. The zero flow baseline was established while the vessel was occluded immediately distal to the flow transducer. No data was accepted during the course of an experiment in which negative pen deflections or electrical instability were recorded. The small flow transducer caused an approximate 40% constriction in area of the anterior tibial artery resulting in an average pressure drop of 20 mm Hg across the transducer. This degree of constriction, however, has been shown not to reduce blood flow significantly (5). Furthermore, we recorded identical post-occlusion anterior tibial pressure responses with and without flow transducers on the artery, indicating that the constriction did not affect the collateral response.

Eighteen dogs were rendered areflexic by injecting absolute alcohol (10 ml) intraspinally at L4 and forcing this all the way up the spinal canal while the dogs lay in a 3° head-up position. Five of the dogs were also placed in a 3° head-down position while an additional 5 ml of alcohol was forced caudally. The spinal anesthesia caused a rapid fall in blood pressure and a total cessation of respiration. Blood pressure was returned to control level by continuous intravenous infusion of norepinephrine and respiration was artificially maintained. Dogs anesthetized in this fashion have been shown in many studies to be areflexic (6). The absence of reflexes was verified by the failure to elicit a carotid sinus reflex in all dogs and the failure to elicit reflex changes in brachial artery flow when, in 4 dogs, the hindpaw was immersed in ice water and water at 50°C.

The following formulas were used to calculate collateral conductance (Cc) and peripheral conductance (Pc) during occlusions:

\[
Cc = \frac{F_{at}}{P_{at} - P_{nt}},
\]

\[
Pc = \frac{F_{at}}{P_{at}},
\]

where \(P_{at}\) is femoral artery pressure, \(P_{nt}\) is anterior tibial artery pressure and \(F_{at}\) is anterior tibial artery flow. By these definitions, collateral conductance is the conductance of blood around the femoral artery occlusion to the anterior tibial artery, and peripheral conductance is the conductance of blood from the anterior tibial artery to the veins (assuming venous pressure of zero). These definitions can be justified because Quiring (7) has shown that all major collateral vessels bridging a femoral arterial occlusion enter proximal to the anterior tibial artery, and because all arterial branches between flow transducer and pressure needle were ligated.

**Results**

**COLLATERAL VASODILATATION FOLLOWING FEMORAL ARTERY OCCLUSION**

Blood pressures in the femoral and anterior tibial arteries and blood flow in the latter were recorded simultaneously in 93 experiments on 21 dogs. A bulldog clamp was applied to the femoral artery for 2 minutes to 1 hour. To make repeated studies in the same animal, the clamp was often removed following 2 to 3 minutes of occlusion and...
then was reapplied after a 12-minute recovery period. This period of recovery was sufficient for maximum collateral vasoconstriction as is discussed in the next section.

The average preocclusion levels of the different measured parameters in all the experiments were as follows: mean anterior tibial artery blood flow, 17 ml/min; mean femoral artery pressure, 127 mm Hg; mean anterior tibial artery pressure, 105 mm Hg. The pressure difference of 22 mm Hg from femoral to anterior tibial artery is attributable to pressure drops of 20 mm Hg across the flow transducer and 2 mm Hg along the arterial segment. After occlusion of the femoral artery, the tibial artery flow and pressure dropped to minimum values in about 8 seconds, reaching respectively 21 ± 4(SEM)% and 28 ± 4% of the preocclusion levels. The values subsequently began to rise, and in 70 seconds flow reached 58 ± 4% of control and pressure reached 53 ± 3% of control. Flow and pressure each rose an additional average of 12% during the following hour in 8 dogs observed for this period of time.

To illustrate the changes in the monitored parameters, a polygraph record from an experiment is shown in Figure 1. Immediately upon occlusion, blood flow through the obstructed segment of the femoral artery ceased and anterior tibial artery flow and pressure dropped as the arteries emptied. Within 20 seconds, however, the peripheral runoff of blood from the arteries was exceeded by inflow from the collateral circulation, and tibial artery flow and pressure rose rapidly. The values leveled off in 1 minute and rose at a slow rate during the remainder of the occlusion period. Upon release of the occlusion clamp, reactive hyperemia occurred, with flow first overshooting and then returning to control level in about 2 minutes. Femoral artery pressure remained essentially constant over the entire period.

Collateral vasodilatation was estimated by calculating changes in the conductance of blood in the collaterals supplying the anterior tibial artery at different times following occlusion of the femoral artery. Figure 2 shows the collateral conductance changes measured during the first 3 minutes following occlusion in 21 dogs and during the remainder of the hour in 8 of the dogs. Following occlusion, collateral conductance fell to a minimum in 8 to 10 seconds, then rose 277 ± 67% from minimum in 70 seconds; it continued to increase an additional 178 ± 66% in one hour in the 8 dogs observed for this time period. This indicated an appreciable collateral vasodilatation within 70 seconds following occlusion, and vasodilatation continued at a slower rate for at least 1 hour.

Changes in the caliber of peripheral resistance vessels were evaluated by calculating
changes in peripheral conductance. Prior to occlusion, peripheral conductance was $0.16 \pm 0.03 \text{ (ml/min)/mm Hg}$ in 21 dogs. It fell to $0.12 \pm 0.01 \text{ (ml/min)/mm Hg}$ 10 seconds following occlusion, at the same time that anterior tibial artery pressure decreased by 98 mm Hg. Conductance then rose to $0.17 \pm 0.09 \text{ (ml/min)/mm Hg}$ in 1 minute and remained almost constant for the remainder of the hour. These calculations show that the peripheral vessels constricted slightly following occlusion presumably due to a tremendous fall in intravascular pressure and then dilated back to a constant level within 1 minute.

**COLLATERAL VASOCONSTRICTION FOLLOWING REMOVAL OF THE FEMORAL ARTERY OCCLUSION**

The collateral vessels began to reconstrict after the occlusion clamp on the femoral artery was removed. The time course of this vasoconstriction was appraised by calculating collateral conductance during successive occlusions. If the interval of time between two successive occlusions was adequate for maximum collateral reconstriction to occur, collateral conductance immediately following the second occlusion fell to the same minimum value and increased by the same amount as during the first occlusion. However, when the collaterals had not had time to constrict, the conductance immediately following the second occlusion was near the maximum level reached during the first occlusion and did not increase much further. The collateral conductance level immediately following occlusion therefore reflected the degree to which the collaterals had constricted prior to that occlusion.

Figure 3 shows the changes in collateral conductance in 4 dogs during the application of an occlusion clamp for 2 minutes and following its removal. The collaterals dilated rapidly during occlusion, indicated by a rapid rise in conductance from $0.02 \text{ (ml/min)/mm Hg}$
mm Hg to above 0.1 (ml/min)/mm Hg. Additional 2-minute occlusions were applied and removed at various time intervals. The minimum conductances during each occlusion were calculated and are shown in Figure 3. The minimum conductance during the second occlusion applied 1 minute after removing the first occlusion was about 0.1 (ml/min)/mm Hg, and the conductance did not increase significantly above this value during the 2-minute occlusion period. This showed that the collaterals had not constricted during the minute between occlusions. Collateral conductance remained at high levels during occlusions applied after recovery periods of 2, 3 and 4 minutes. At intervals longer than 4 minutes, the minimum collateral conductance gradually diminished and conductance gradually increased from minimum, showing that the collaterals had constricted when recovery periods were sufficiently long. Finally, after a 12- to 14-minute period of recovery, the minimum conductance fell again to 0.02 (ml/min)/mm Hg. This was, therefore, the time interval necessary for complete reconstriction of previously dilated collateral vessels. These results were confirmed in essentially all experiments, since collateral conductance reached minimum only following a 12-minute recovery period.

COLLATERAL VASODILATATION IN AREFLEXIC DOGS

Total spinal anesthesia was administered, as described in Methods, to 18 dogs to eliminate reflexes mediated through the central nervous system. The collateral response to acute femoral artery occlusion was then recorded. As a control, the response was recorded from 14 dogs with intact nervous systems, verified by eliciting the carotid sinus reflex. The preocclusion blood pressures of these dogs were at the same levels as those in the spinal anesthetized dogs.

The distal pressure and flow response patterns in the areflexic dogs showed the typical fall and recovery. Neither the magnitude nor time sequence of events in these response patterns appeared to be altered by interruption of nervous conduction. Table 1 shows the changes in collateral conductance during the first 2 minutes following femoral artery occlusion. The differences in the collateral conductance increases in control and spinal-anesthetized dogs were not significant (P > 0.2).

The blood pressure in 5 dogs was lowered by hemorrhage and then increased back to normal by infusion of blood. The dogs were bled again, and the pressure raised to normal using a norepinephrine drip. The collateral response at a given pressure level was identical during both blood and norepinephrine infusion.

PENTOBARBITAL EFFECTS ON COLLATERAL VASODILATATION

Since sodium pentobarbital was administered to all animals, the precise effect of the anesthetic itself upon nervous control and collateral vasodilatation cannot be assessed in these experiments. However, occlusion of the carotid arteries, in 14 dogs, resulted in a rise in femoral artery pressure of between 35 and 50 mm Hg, indicating that the carotid sinus reflex was still active during anesthesia. Also, an additional 5 mg/kg sodium pentobarbital was administered to 4 dogs, and the anterior tibial pressure and flow re-

| TABLE 1 |

Collateral Conductance in Control and Spinal-Anesthetized Dogs

<table>
<thead>
<tr>
<th></th>
<th>No. of dogs</th>
<th>Preocclusion anterior tibial pressure (mm Hg)</th>
<th>Preocclusion anterior tibial flow (ml/min)</th>
<th>Minimum collateral conductance after occlusion (ml/min)/mm Hg</th>
<th>Subsequent collateral conductance increase in 2 minutes (ml/min)/mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>14</td>
<td>110 ± 9</td>
<td>11.1 ± 5</td>
<td>0.04 ± .01</td>
<td>0.12 ± .03</td>
</tr>
<tr>
<td>Spinal anesthesia</td>
<td>18</td>
<td>112 ± 10</td>
<td>13.2 ± 3</td>
<td>0.03 ± .02</td>
<td>0.11 ± .02</td>
</tr>
</tbody>
</table>

Values are means ± sem.

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responses to femoral artery occlusion were recorded. Then another 20 mg/kg sodium pentobarbital was given, and the responses to occlusion were again recorded. At all levels of anesthesia the parameters fell and rose to a plateau in the typical fashion, indicating that 25 mg/kg to 50 mg/kg pentobarbital caused little or no alteration of the collateral vasodilatation response.

EFFECT OF SYSTEMIC HYPOTENSION ON COLLATERAL VASODILATION

The effect of preliminary systemic hypotension on collateral vasodilatation was investigated by observing the response to femoral artery occlusion following hemorrhage. The animals were bled into a reservoir, and pressure was held at selected levels for at least 8 minutes; then the femoral artery was occluded. Figure 4 shows the distal pressure response during the 2 minutes following occlusion in a typical experiment. At an initial, preocclusion, anterior tibial pressure of 115 mm Hg, the fall and recovery immediately following occlusion were distinct, but after a decrease in the preocclusion pressure to 80 mm Hg, the fall and recovery became less marked. This trend continued until at a preocclusion pressure of 45 mm Hg the fall and recovery were no longer evident, and pressure immediately reached the plateau level. The simultaneously measured flow patterns, shown in Figure 5, show a normal response when the preocclusion flow was 19 ml/min. However, there was a progressive elimination of the fall and recovery phase as the preocclusion flow was decreased to 2.5 ml/min.

The collateral conductance changes which occurred during the first two minutes after occlusion in 5 dogs are summarized in Table 2. At normal perfusion pressure and flow, collateral conductance rose 287% from minimum after the femoral artery was occluded. At a lower perfusion pressure and flow, collateral conductance was high at the initial level and it increased little above this level.
DILATATION OF COLLATERAL VESSELS

TABLE 2

<table>
<thead>
<tr>
<th>Preocclusion anterior tibial artery pressure (mm Hg)</th>
<th>Preocclusion anterior tibial artery flow (ml/min)</th>
<th>Minimum collateral conductance after occlusion (ml/min)/mm Hg</th>
<th>Subsequent collateral conductance increase in 2 minutes (ml/min)/mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Above 100</td>
<td>16.0 ± 2.2*</td>
<td>0.05 ± .01</td>
<td>0.13 ± 0.07</td>
</tr>
<tr>
<td>60-100</td>
<td>8.8 ± 1.1</td>
<td>0.08 ± .01</td>
<td>0.12 ± 0.04</td>
</tr>
<tr>
<td>30-59</td>
<td>4.5 ± 1.0</td>
<td>0.15 ± .01</td>
<td>0.09 ± 0.03</td>
</tr>
</tbody>
</table>

*Mean ± SEM.

This showed that the collateral vessels were already dilated when the femoral artery was occluded. After blood was reinfused into the animals to raise pressure and flow back to normal, the collateral vessels returned to their normally constricted state in 10 to 15 minutes.

Discussion

These experiments show the magnitude of fall in both blood pressure and flow in the anterior tibial artery following occlusion of the femoral artery and also characterize the subsequent partial recovery of these parameters during the first hour. Since the blood flowing into the anterior tibial artery must have been supplied by collateral vessels bridging the site of occlusion, the measurement of the flow and pressure in the distal artery is an index of the hemodynamics in these collateral vessels.

The mechanism or mechanisms responsible for acute opening of collateral vessels has remained unknown partly because only an incomplete description of all the changes involved has been available in the literature. Among those few investigators who have attempted to measure hind limb collateral blood flow changes are John and Warren (2) who measured blood flow using a venous occlusion plethysmograph, and Theis (8) and Eckstein et al. (9) who used a cannula one end of which was open to atmosphere and the other was inserted into the peripheral stump of a cut femoral artery. Both these techniques of flow measurement severely alter the arterial-venous pressure gradient and therefore are of questionable reliability. Thulesius (3) monitored femoral vein flow in the cat with a photoelectric drop counter. Although he was successful in measuring flow during the initial phase of occlusion, the device used could not follow rapid changes in arterial flow. In the present experiment we measured pressure and flow simultaneously, flow being measured with an electromagnetic flowmeter, and so we were able to record instantaneously with minimal disturbance to the circulation.

Collateral vasodilatation following occlusion was estimated by the increase in collateral conductance from the minimum conductance value recorded immediately following femoral artery occlusion. Due to slow emptying of the distal arterial tree, the minimum collateral conductance value could not be measured until 8 to 10 seconds after occlusion, so that the total change was probably underestimated. Nevertheless, collateral conductance increased to at least 277 ± 67% above minimum within 70 seconds (Fig. 2), indicating a rapid initial collateral vasodilatation. Thus, the changes during the first 70 seconds are very large, and survival of the limb may depend on the mechanism responsible for this initial dilatation. Attention, therefore, was focused primarily on factors operating during this initial 2-minute occlusion period.

Thulesius (3) observed in the cat that collateral resistance fell only 20 to 40% 1 to 2 minutes after femoral artery occlusion, and he suggested that collateral vasodilatation was very slight and delayed in development. These results contrast with a rapid 70 to 80% fall in collateral resistance (277% increase in conductance) in our experiments. The fact that Thulesius was recording flow from the veins rather than the distal arteries un-
doubtedly caused him to miss the rapid changes in blood flow that occur in the distal arteries during the first few seconds after femoral artery occlusion. Due to this limitation he probably underestimated collateral vasodilatation. He suggested that dilatation of peripheral resistance vessels preceded dilatation of collateral vessels, an effect that also occurred in our experiments. However, in almost all of our experiments anterior tibial flow and pressure rose in phase. This showed that collateral vasodilatation was the major factor increasing anterior tibial blood flow, since peripheral vasodilatation should cause a fall in tibial pressure along with a rise in flow.

Contradictory conclusions are also reported in the literature from experiments designed to determine whether or not nervous factors are involved in the initiation of collateral vasodilatation. Longland (10) and Mulvihill and Harvey (11) reported that sympathectomy increased the rate at which collaterals dilate. Shepherd (12) found that interruption of vasomotor tone with tetraethylammonium also resulted in a more rapid collateral vasodilatation. On the other hand, Flasher et al. (13) observed that sympathectomy had no effect on the collaterals. However, none of these authors tested their preparations for sympathetic activity, and one cannot be certain that the circulatory reflexes were entirely absent. In the present study we abolished sympathetic tone with total spinal anesthesia, as verified by a precipitous fall in blood pressure, the absence of the carotid sinus reflex, and the absence of reflex changes in flow with heating and cooling. We found that collateral vasodilatation following femoral artery occlusion was not significantly different in anesthetized dogs with and without reflexes. This showed that reflex inhibition of vasoconstrictor tone is probably not a significant mechanism initiating collateral vasodilatation.

These studies were all performed on animals anesthetized with pentobarbital which could have altered the results somewhat. It is possible that pentobarbital could release sympathetic tone to some extent, and this would lead to a dilatation of the collateral vessels before an occlusion was applied if a nervous reflex mechanism were involved in collateral development. However, the collaterals dilate rapidly and markedly following occlusion, indicating that the collaterals were constricted prior to the occlusion. If they had been more constricted without anesthesia, there might have been an even more pronounced vasodilatation response.

When blood pressure and flow to the hind limb were decreased by hemorrhage prior to occlusion, the fall and partial recovery in the distal pressure and flow response to occlusion became progressively smaller (Figs. 4 and 5, and Table 2). This occurred, presumably, because at low perfusion pressure and flow the collateral vessels had dilated even before the occlusion was instituted; and this might be expected if chemical stimuli associated with tissue ischemia caused changes in the caliber of collateral vessels.

The factors which might have caused collateral vasodilatation could have been simply lack of oxygen, presence of vasodilator substances, or both. Carrier et al. (14) have shown that perfusion of isolated minute arteries with blood of low oxygen content results in vasodilation. Since collateral vessels have little initial flow, they could be very sensitive to oxygen lack. Also, it is possible that metabolites may accumulate in the tissue as a result of ischemia and cause vasodilatation (15). The studies of Hilton (16) suggest that a vasodilator substance can affect collateral vessels some distance away by retrograde conduction of a signal through the smooth muscle of the arterial wall.

Other mechanisms which affect vascular caliber could be responsible for early collateral development. Several investigators have postulated that vascular caliber is controlled by the velocity of blood flow, i.e., increased velocity causes vasodilatation (2). However, no one has been able to suggest a satisfactory means by which the vessel wall could sense the velocity. Another mechanism, suggested by Bayliss (17), is the myogenic
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Tone theory whereby vasodilatation results from a decrease in vascular distension. But here again theoretical objections to this theory make it improbable, for such a response in a large segment of the circulation could lead to instability of the entire circulation (18). Still a third possible mechanism is that turbulence, resulting from high velocity of blood flow, might cause vasodilatation. Further research is necessary to judge these and other theories.

This report concerns itself with dilatation and constriction of pre-existing collateral vessels which supply blood to the anterior tibial artery following closing and opening of the femoral artery. The complete characterization of long-term vasodilatation, and distribution of blood flow following occlusion have not as yet been studied. An excellent review of recent pertinent literature on this subject has been written by Liebow (19).

The importance of the development of collateral circulation is emphasized by the serious consequences of vascular occlusion in adult clinical cases. An acute, uncorrected obstruction of the iliac arteries results in all cases in loss of the extremity, while obstruction of the femoral artery is followed by gangrene in 50% of the cases (20).

Development and regression of collateral circulation represents a form of autoregulation in the sense that collateral blood flow varies in proportion to tissue need (21). The mechanism responsible for collateral development may be the same one responsible for other forms of autoregulation such as reactive hyperemia and autoregulation in response to arterial pressure changes.

References


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