Myogenic hyperemia following brief tetanus of canine skeletal muscle

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MOHRMAN, David E., and Harvey V. Sparks. Myogenic hyperemia following brief tetanus of canine skeletal muscle. Am. J. Physiol. 227(3): 531-535. We have tested the hypothesis that a portion of the vasodilatory response to brief (1 s) tetanus could be initiated by the rapid alterations in extravascular pressure and in vascular transmural pressure associated with muscle contraction. Dogs were anesthetized with pentobarbital and the calf muscles were isolated so that vascular responses could be studied under conditions of constant flow or constant pressure. An inflatable cuff was placed around the calf to provide a means of increasing extravascular pressure in the absence of muscle contraction. Intramuscular pressure was estimated with a small, fluid-filled balloon placed deep within the muscles and connected to a low-displacement pressure transducer. Intramuscular balloon pressure increased linearly with increased gastrocnemius tension development caused by increased stimulation frequency (16-64 impulses/s). Elevation of intramuscular balloon pressure to the same level caused by tetanic stimulation resulted in a vasodilatory response which was approximately one-half as large as that following tetanic contraction when flow was constant and approximately one-third as large when pressure was constant. We conclude that a portion, but not all, of the vasodilation following brief tetanus of skeletal muscle may be a response to alterations in vascular transmural pressure associated with tetanic contraction.

exercise hyperemia; vascular resistance

THE ACTIVE RESPONSE of resistance vessels to alterations in transmural pressure is viewed as an important component involved in the autoregulation of blood flow when perfusion pressure is changed (3). There is, however, little evidence concerning the possibility that alterations in transmural pressure of resistance vessels during exercise could elicit a myogenic decrease in resistance to flow and thus participate in the control of exercise hyperemia. During tetanic contraction of skeletal muscle, extravascular pressure increases so that the pressure across the vascular wall is decreased or reversed and the vessels tend to collapse. Although it is likely that shearing forces as well as compressional forces play a role in the increased resistance to flow during tetanic stimulation (5, 6), there is no doubt that the increase in extravascular pressure occurs (6, 7).

According to the Bayliss mechanism (1), we might expect the sudden increase in extravascular pressure, and, therefore, the decrease in transmural pressure, to stimulate relaxation of the resistance vessels and thus participate in the hyperemia response in the period following brief tetanic contraction. We have recently described a resistance response to brief tetanus which has a time course that is apparently too rapid to be controlled by changes in oxidative metabolism (9). The current study was undertaken to determine whether the vascular response to brief tetanus can be explained wholly or in part by vascular reactions to alterations in transmural pressure.

METHODS

Five male mongrel dogs, weighing 20-25 kg, were anesthetized with sodium pentobarbital (35 mg/kg, supplemented as required). The calf muscles were isolated in a manner similar to that reported by Kjellmer (8). All structures in the popliteal region except the femoral artery and vein and the femur were transected. The calf was skinned and the paw was removed. The femoral vein was cannulated just proximal to the popliteal junction and the effluent was returned to a reservoir connected to the contralateral femoral vein. A portion of the venous effluent was drawn from a side tap in the venous cannula at a constant flow (2.3 ml/min) through a cuvette densitometer (Gilford 103 IR) for continuous monitoring of the venous hemoglobin saturation. Venous pressure was kept constant at the height of the outflow tubing. Flow was supplied from the contralateral femoral artery. In constant-pressure experiments, flow through the calf-muscle preparation was monitored with a Parks Doppler ultrasonic flowmeter with the probe placed around either the Silastic outflow tubing coming from the venous cannula or the inflow tubing. In some later experiments, two flow probes were used so that both inflow and outflow could be recorded simultaneously. Flowmeters were calibrated by timed collection of venous outflow at the beginning of each experiment. The zero base line was established and checked periodically throughout the experiment by completely stopping the flow with arterial occlusion. In constant-flow experiments blood from the contralateral femoral artery flowed through a finger pump and into the cannulated popliteal artery. Perfusion pressure was measured between the pump and the muscle bed. In both types of experiment, vascular conductance was calculated as the ratio of flow in milliliters per 100 g per minute to perfusion pressure in millimeters Hg.

The muscle was stimulated by exciting the distal end of the sectioned sciatic nerve using supermaximal square voltage pulses (2-10 V, 0.1 ms). One-second trains of stimuli at frequencies between 16 and 64 impulses/s were
used to produce brief tetanic contractions of graded intensities. Isometric tension development of the gastrocnemius muscle was recorded by connecting the isolated tip of the calcaneus, to which the achilles tendon attaches, to a force transducer. The muscle was held at in vivo length.

A polyethylene catheter (PE-100) with a small embolotomy balloon on its end was filled with saline. The balloon was cylindrical in shape and approximately 1.5 mm in diameter by 5 mm in length. The balloon was placed in the belly of the gastrocnemius muscle along a pathway previously opened by insertion of a blunt 1.5-mm-diam rod. This catheter was then connected to a small displacement force transducer (Beckman) to form a closed-fluid system with which changes in intramuscular balloon pressure would be recorded. The bladder from a standard blood pressure cuff was placed around the calf and was loosely but completely wrapped with adhesive tape to prevent outward expansion during inflation. The pressure cuff was connected to a manual slide valve. In one valve position, the cuff was inflated by a pressure-regulated gas supply. In the opposite valve position, the cuff was rapidly deflated by venting to the atmosphere.

Electrical stimulation of the sciatic nerve for 1 s at frequencies between 16 and 64 impulses/s caused graded increases in intramuscular balloon pressure. These intramuscular balloon-pressure pulses were then duplicated without muscular contraction by use of the pressure-cuff system and the resulting vascular responses were compared to those following tetanus.

RESULTS

Figure 1 shows curvilinear, strip-chart recorder tracings taken from experiments in which the effects of brief tetanus and brief increases in extramuscular pressure were compared during constant-pressure perfusion. Figure 1A shows the venous flow response to electrical stimulation of the sciatic nerve at a rate of 16/s for 1 s. The rapid upswing in flow observed at the time of the contraction represents a propulsion of blood from the muscle by the increased extravascular pressure. Venous outflow then reaches a minimum during which time the veins of the muscle preparation refilled with blood. Then venous outflow increases from a control value of 20 to 56 ml/100 g per min about 4 s after the end of the stimulation. Accompanying the stimulation of the sciatic nerve is an increase in gastrocnemius tension development and an increase in intramuscular balloon pressure of 80 mmHg. A few minutes later the cuff around the muscle preparation was inflated to a pressure of 80 mmHg for a period of 1 s. This resulted in an increase in venous outflow reflecting the emptying of the veins, then a fall while the veins refilled following the cessation of increased cuff pressure, and then an increase in venous outflow from the control value of 20 to a peak of 32 ml/100 g per min. Since the arterial pressure was unchanged during the flow response and the venous pressure was fixed at the height of the orifice of the outflow tubing, this increase in flow must represent an increase in vascular conductance.

Figure 1B shows the results of a constant-pressure experiment in another preparation in which arterial inflow was measured. When the sciatic nerve was stimulated at 32 impulses/s for 1 s, gastrocnemius tension increased to 80% of maximum, intramuscular balloon pressure increased to 65 mmHg, and arterial inflow slowed because of extravascular compression. Within 5 s after the end of contraction, arterial inflow reached 38 ml/100 g per min and then gradually declined to a control value of 14 ml/100 g per min. When the external cuff was inflated to raise the intramuscular balloon pressure to 65 mmHg for 1 s, flow also decreased briefly because of extravascular compression, but it then increased shortly after cuff deflation to a peak value of 22 ml/100 g per min.

Figure 2 shows simultaneous tracings of intramuscular balloon pressure, gastrocnemius tension development, perfusion pressure, arterial inflow and venous outflow, and venous oxygen saturation during constant-flow perfusion. First the muscles of the calf were caused to contract by stimulating the sciatic nerve at a frequency of 32 impulses/s for 1 s. This resulted in a rise in intramuscular balloon pressure as well as an increase in tension production by the gastrocnemius muscle. Perfusion pressure rises abruptly with the onset of contraction reflecting the heightened vascular resistance associated with contraction. Perfusion pressure then falls rapidly after cessation of the contraction to a minimum value which occurs approximately 4 s after the end of the stimulation. During these changes in perfusion pressure, arterial inflow was relatively constant. On the other hand, venous outflow showed an increase associated with the contraction and a decrease representing...
MYOGENIC HYPEREMIA AFTER TETANUS

FIG. 2. Curvilinear strip-chart records of events associated with 1-s tetanus (32 impulses/s) and elevated cuff pressure for 1 s with constant flow.

refilling of veins and then a continued steady venous outflow. Seconds after the contraction, venous oxygen saturation decreased and then slowly returned to the control value. A short time later, the cuff around the calf muscles was inflated to mimic the increase in intramuscular balloon pressure which occurred during muscle contraction. This resulted in changes in perfusion pressure which are similar to the changes occurring in response to muscle contraction, except that the perfusion pressure did not fall as much as after muscle contraction. Inflow showed no significant changes and venous outflow again showed the transients associated with emptying and refilling of capacitance vessels. There was no change in venous oxygen saturation following cuff inflation. In all cases there are small increases in gastrocnemius tension associated with the increase in cuff pressure. This apparently results from distortion of the calf muscles caused by inflation of the cuff, as will be discussed below.

Relationship between tension development and intramuscular balloon pressure. Figure 3 shows the relationship between gastrocnemius tension development and intramuscular balloon pressure during 1-s contractions caused by stimulating the sciatic nerve at rates between 16 and 64 impulses/s. The gastrocnemius tension axis was normalized by expressing each tension response as a fraction of the average tension response to 64 impulses/s within each muscle preparation. This was necessary because of the wide range of maximum tensions produced from one animal to another in spite of the relatively consistent responses obtained within any one animal. The complex geometrical relationship of fibers within the gastrocnemius muscle and the amount of stretch applied to the muscle may be two of the factors that contribute to the variability observed among dogs. Intramuscular balloon pressure also varied from preparation to preparation. A stimulation rate of 64 impulses/s caused increases in balloon pressure ranging from 135 mmHg for one animal to 400 mmHg for another animal. For this reason we also normalized the intramuscular balloon pressure data in terms of the mean response to 64 impulses/s within each dog. Figure 3 demonstrates that there is a fairly linear increase in intramuscular balloon pressure with increasing tension development. Figure 3 also shows that both tension and intramuscular balloon pressure increase with increasing stimulation frequency.

Relationship between increased intramuscular balloon pressure and increased conductance. Figure 4 contains plots of active changes in conductance after elevations in intramuscular balloon pressure caused by muscular contraction and inflation of the cuff around the muscle preparation. As shown in Figs. 1 and 2, these peak conductance changes occur approximately 4-5 s after either intervention. Section A shows the conductance response observed under free-flow conditions and section B shows the conductance changes observed under constant-flow conditions. Individual observations of increased intramuscular balloon pressure were normalized as outlined above. The peak change in conductance for each observation was normalized within each animal by dividing it by the mean of the peak conductance changes that occur after stimulation of the sciatic nerve at 64 impulses/s for 1 s. We then assigned the data to a set depending upon the value for the increase in intramuscular balloon pressure. There were four sets containing relative values of intramuscular balloon pressure ranging from .1 to .33, .34 to .67, .68 to 1.0, and greater than 1.0. The average and standard error of the mean for each of these sets of data were calculated and appear in Fig. 4. It is evident that under conditions of both constant flow and free flow, conductance is increased more by muscular contraction than by a simple elevation in intramuscular balloon pressure. On the other hand, in both situations a significant fraction of

FIG. 3. Relationship between gastrocnemius tension development and intramuscular balloon pressure. Both variables are normalized against mean response to 64 impulses/s for each dog.
We do not believe cuff inflation caused skeletal muscle to contract since it does not result in increased muscle oxygen consumption since the venous oxygen saturation does not change after cuff inflation under conditions of constant flow. In addition, the vascular responses following cuff inflation during constant flow are much larger than those following an actual contraction with equivalent tension development. Thus we believe that the vascular response observed following cuff inflation is initiated by changes in extravascular pressure and that the small recorded tension changes are artifacts due to the conical shape of the muscle preparation which causes physical displacement away from the force transducer when the cuff is inflated.

Although there are other possible explanations for the vasodilator response following brief cuff inflation, for example, selective mechanical stimulation of vasodilator nerves, the most probable cause appears to be the well-documented effect of changes in transmural pressure on the blood vessel wall itself. There is little doubt that muscle contraction increases intramuscular pressure. Gray and Staub (6) observed increases in wedged venous pressure of 27–200 mmHg during muscle stimulation at 30–40 impulses/s after they occluded the venous outflow and, seconds later, the arterial inflow. Khayutin (7) found that muscle stimulation at a frequency of 32 impulses/s caused pressure to increase to 400 mmHg inside an arterial segment passed transversely through the muscle. This value is considerably higher than the intramuscular balloon pressures we observed during similar contractions, but the recorded values of intramuscular pressure depend heavily on the method used to measure it. Thus we have used intramuscular balloon pressure as an estimate of the forces tending to compress blood vessels. The measurement appears to be consistent within animals but not useful in comparing absolute values from animal to animal.

Vasoconstriction of resistance vessels in response to increased intravascular pressure, first described by Bayliss (1), has served as a basis for development of the proposed myogenic mechanism for autoregulation of blood flow (3). Several investigators have demonstrated that increased transmural pressure results in increased vascular smooth muscle tone and vasoconstriction, whereas decreased transmural pressure results in decreased vascular smooth muscle tone and vasodilation (2, 4). This phenomenon could be invoked to explain the results of the present experiments since the elevation in extravascular pressure should result in decreased transmural pressure and relaxation of vascular smooth muscle with vasodilation. One important difference between the technique presented here and that presented in most reports is the use of a brief impulse alteration in transmural pressure rather than a sustained step response. Smieško (10), however, has provided evidence that transients in perfusion pressure lasting 1 s cause vasodilation of the vascular bed of dog gracilis muscle. He also demonstrated that the direction of the square-wave transient did not significantly influence the magnitude of the time course of the vasodilator response. Instead, the response is apparently sensitive to the ascending component of the perfusion-pressure square wave. Since there is a rapid increase in transmural pressure occurring as extravascular compression is removed, in our studies, it is possible that the vasodilator response we have observed is the result of the same mechanism as the one described by Smieško. This possibility is supported by the similarity of the dynamics of the vascular

### DISCUSSION

The results of the experiments recorded above indicate that extravascular compressional forces accompanying muscular contraction may play a role in causing exercise hyperemia. During both free and constant flow, elevation of intramuscular pressure by external cuff inflation is followed by an increase in vascular conductance. For the same increase in intramuscular balloon pressure a second cuff inflation elicits a peak conductance increase which is approximately one-third of that following a 1-s tetanus under conditions of free flow. During constant flow, the conductance increase following brief cuff inflation is roughly one-half the magnitude of that following brief tetanus.

Since most tracings show a small muscle-tension response during cuff inflation, we considered the possibility that cuff inflation caused a contraction which in turn could have produced the vascular response through a metabolic vasodilator mechanism. However, several considerations lead us to the conclusion that increased vascular conductance following brief cuff inflation is due to increased extravascular pressure. We do not believe cuff inflation caused skeletal muscle to contract since it does not result in increased muscle oxygen consumption since the venous oxygen saturation does not change after cuff inflation under conditions...
response in each of the two studies. In both cases the peak change in conductance occurs between 3 and 4 s and the response is largely over within 30 s.

Regardless of the precise nature of the stimulus, it appears that extravascular compression can be responsible for a significant fraction of the vascular response following brief tetanus. During serial twitch contractions of the type often used in studies of exercise hyperemia, tension development is considerably lower than during the tetanic contractions. On the basis of the relationship between tension and intramuscular pressure plotted in Fig. 4, one might conclude that changes in intramuscular pressures may be too small during twitch exercise to be of significance in determining the vascular response. However, in situations in which repeated short bursts of tetanus are used as a model of muscular activity, it seems probable that a portion of the accompanying hyperemia could be the result of a vascular response to rapid, large alterations in transmural pressure.

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REFERENCES


