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A Comparison of Recovery Times from Exercise and Ischemic Dilations at Constant Pressure and Flow (38953)

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The mechanism of the increase in blood flow that accompanies skeletal muscle exercise (active hyperemia) or that occurs following relief of ischemia (reactive hyperemia) has been extensively studied. Considerable evidence has been presented which suggests that metabolically linked vasoactive chemicals are importantly involved in these hyperemias (1). Other work suggests a significant role for a myogenic mechanism (Bayliss response), at least in reactive hyperemia (2–5).

According to the metabolic hypothesis muscle contraction or ischemia leads to depletion of oxygen and accumulation of vasoactive metabolites, in the former case due to increased metabolism and in the latter to decreased flow. Blood vessel dilation follows. When the exercise or ischemia is terminated, the increased blood flow repletes oxygen and washes out metabolites and as the concentration of these agents return to previous values, so does the vascular resistance. According to the myogenic hypothesis, muscle contraction or arterial occlusion leads to a decrease in vascular transmural pressure, in the former case due to a rise in extraluminal pressure and in the latter due to a fall in intraluminal pressure. This in turn leads to vascular smooth muscle relaxation. On termination of the exercise or ischemia, transmural pressure returns to the previous value and abolishes the vasodilation.

If oxygen and the metabolites are in fact important, the disappearance time of the vasodilation following termination of the exercise or ischemia should be sensitive to the blood flow since the latter would influence the time for recovery of the oxygen and metabolite concentrations. If flow were not allowed to increase, for example, oxygen and metabolite concentrations, and hence vascu-resistance, should be slower in returning to control values. On the other hand, if oxygen and metabolites are not important, one might expect the recovery of resistance following termination of exercise or ischemia to be independent of the rate of blood flow.

The experiments reported here were designed to compare the recovery times from exercise and ischemic dilation in the dog gracilis muscle under conditions of natural flow with those seen when flow is not allowed to increase. The study also allowed us to systematically investigate the influence of duration of ischemia and exercise on recovery time in a given flow mode.

Materials and Methods. Ten mongrel dogs of either sex were anesthetized with sodium pentobarbital (30 mg/kg, iv), anticoagulated with heparin, and mechanically ventilated with room air. The gracilis muscle was surgically isolated from surrounding muscle groups and its origin and insertion tied. Blood entered and left the muscle only through the gracilis artery and vein, respectively. The gracilis nerve was severed. Blood from the femoral artery was directed via polyethylene tubing through a roller pump (Holter RE 161) and into the gracilis artery.

The pump's speed control was modified by connecting it to an electronic controller (Leeds and Northrup model 420 Type P). To study responses at constant flow, the pump was driven at a constant rate. Gracilis perfusion pressure was recorded from the perfusion cannula on an amplifier-recorder. To study responses at constant pressure the amplified output of the perfusion pressure transducer was used as a feedback signal for the controller, which adjusted pump speed so that pressure remained constant.

Ischemic (reactive) dilation was induced by turning the pump off for periods of time ranging between 30 and 300 sec. On restoration of flow, dilation was indicated by a reduced perfusion pressure during constant flow, or by an increased flow at constant pressure. Recovery times were measured as

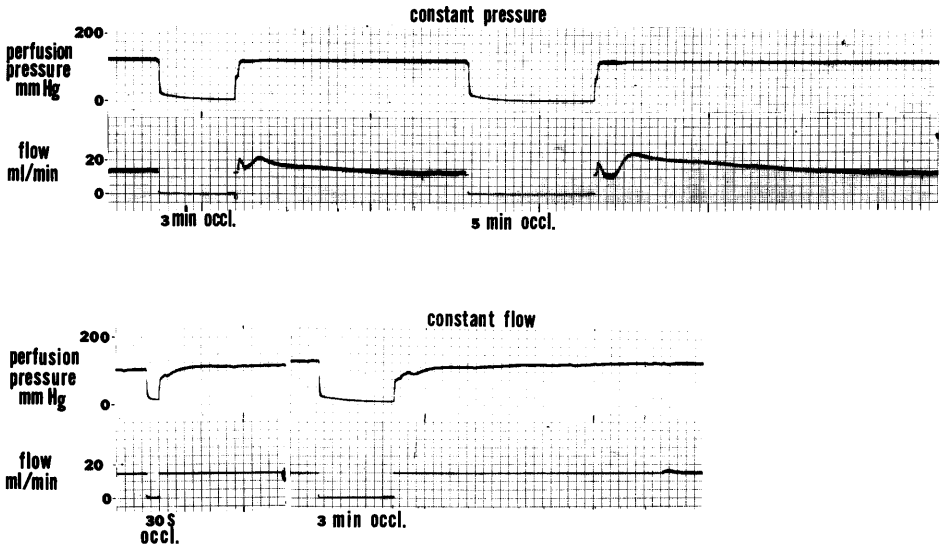

FIG. 1. Effect of ischemia on blood flow at constant pressure (upper panel) and perfusion pressure at constant flow (lower two panels) in one gracilis muscle of the dog.

the time for complete recovery of either pressure or flow to steady state values near baseline.

To study exercise (active) dilation, the distal stump of the severed gracilis nerve was stimulated with square wave pulses of 6 V, 1.6 msec duration at various frequencies and time periods. Recovery times were measured in the same manner as for reactive dilation.

In each experiment, reactive dilation was studied first both at constant pressure and constant flow; active dilation was then studied under both conditions. The sequence of the constant flow and constant pressure conditions were randomized. Recovery times at constant flow were statistically analyzed against those at constant pressure by Student's *t* test for paired replicates.

Average muscle weight was 79 g. The experiments lasted 5–7 hr. Flow averaged 11.2 ml/min for an average pressure of 124 mmHg at the beginning of the experiments, and 11.4 ml/min and 125 mmHg at the end of the experiments. Thus, the resting resistance was normal and remained stable with time.

Results. The general patterns of the responses to complete ischemia in the constant pressure and constant flow modes (Fig. 1) were those reported many times previously (see refs. 6 and 7 regarding the constant flow mode). In the constant pressure mode (natural flow), blood flow exceeded the control value on relief of ischemia and then gradually returned to the control level. In the constant flow mode, pressure was below the control level when flow was restored and then gradually rose to the control level.

In 8 of 10 experiments, in both the constant pressure and constant flow modes, the reactive dilation seen on relief of ischemia was, within 12 sec, sometimes interrupted by transient vasoconstriction lasting 10–43 sec. This constriction can be seen in Fig. 1 where it is particularly prominent in the constant pressure mode. This response has been observed previously (6–8) in forelimb and kidney (see fourth panel in Fig. 6 of ref. 6 and tenth panel of Fig. 5 in ref. 7) and may well result from the sudden increase in transmural pressure (Bayliss response).

Table I shows that the recovery time from ischemic (reactive) dilation was significantly longer at constant flow for all occlusion times studied. It is also apparent that the difference progressed with the length of occlusion, being 1.0 min for the 30-sec occlusion and 5.6 min for the 300-sec occlusion. In addition, the table shows that the absolute recovery time progressed with the duration of occlusion both at constant pressure (natural flow) and constant flow. This was

particularly true at constant flow where recovery time increased from 2.8 to 13.4 min as ischemia increased from 30 to 300 sec.

The general patterns of the responses to exercise were also those reported many times previously, namely a rise in flow in the constant pressure mode (natural flow) followed by a gradual return to the control level and a fall in pressure in the constant flow mode followed by a gradual return to the control level. Transient vasoconstriction was not observed on stopping exercise.

Table II shows that the recovery times from exercise (active) dilation were also longer at constant flow, although the differences were not statistically significant for the 60 sec, 0.2 Hertz, and 2 sec, 3.0 Hertz stimulations. The differences tended to progress both with frequency (exercise duration constant at 60 sec) and exercise duration (frequency constant at 3 Hertz). It is also apparent that absolute recovery time progressed with the frequency and duration of exercise at both natural and constant flow. For example, in the constant flow mode recovery time increased from 1.7 to 21.8 min as exercise duration increased from 2 to 180 sec (frequency constant at 3.0 Hertz).

TABLE I. RECOVERY TIMES FROM ISCHEMIC (REACTIVE) DILATION AT NATURAL AND CONSTANT FLOW

Duration of ischemia	n	Natural flow	Constant flow	Difference	P
(sec)		(min)	(min)	(min)	
30	9	1.8	2.8	1.0	.02
60	10	2.2	3.6	1.4	.02
180	10	4.5	7.4	2.9	.05
300	10	7.8	13.4	5.6	.02

TABLE II. RECOVERY TIMES FROM EXERCISE (ACTIVE) DILATION AT NATURAL AND CONSTANT FLOW

Duration of exercise	Frequency[a]	n	Natural flow	Constant flow	Difference	P
(sec)	(Hertz)		(min)	(min)	(min)	
60	0.2	9	1.9	2.5	0.6	.10
60	0.8	9	2.7	6.1	3.4	.005
60	1.6	8	5.2	14.5	9.3	.01
2	3.0	8	1.1	1.7	0.6	.30
60	3.0	7	7.9	15.0	7.1	.005
180	3.0	7	13.4	21.8	8.4	.005

[a] Voltage and duration of the pulse were 6 V and 1.6 msec, respectively, in all cases.

Discussion. Previous studies make the metabolic hypothesis for regulation of blood flow in skeletal muscle appealing. It has been frequently shown that reactive hyperemic peak and excess flow progress with the duration of arterial occlusion. During reactive and exercise hyperemia, the venous blood has enhanced vasodilator properties (9). This study provides further evidence in support of the hypothesis. Recovery from exercise and ischemic dilation was prolonged when flow was not allowed to increase. This observation is similar to that of Blair *et al.* (10) in the human forearm and is compatible with the proposal that recovery time is related to the rate of restoration of oxygen and metabolite concentrations to normal, and that this, in turn, is a function of the rate of blood flow.

Restoration of oxygen and metabolite concentrations should also be a function of the degree to which they are altered and within certain limits, this should progress with the duration of ischemia, the frequency of muscular contraction (duration of exercise constant) and duration of exercise (frequency of contraction constant). Thus, the increase in recovery time as a function of ischemia duration, contraction frequency, and exercise duration at both natural and constant flow is also compatible with the metabolic hypothesis. The fact that the increase as a function of the parameters was more pronounced at constant flow simply reflects the simultaneous influence of both flow and degree of alteration in oxygen and metabolite concentration.

Intraluminal pressure and hence transmural pressure fall to the same level during ischemia in the natural and constant flow modes. However, pressure does not immediately rise to the control level on relief of ischemia in the constant flow mode and consequently the arteries are subjected to less stretching during the recovery period at constant flow. Thus, it might be argued that there is less of a stimulus for a myogenic response under this condition and that this

accounts for the prolongation of the dilation. Similar reasoning might be applied to exercise dilation since here too the arteries are subjected to less stretch during the recovery period at constant flow. On the other hand, recovery time progressed with the duration of ischemia in a given flow mode and this cannot be explained by differences in transmural pressure. The same is true for the progression of recovery time with the duration of exercise at constant frequency.

These findings do not detract from the myogenic hypothesis. Vasodilation due to a fall in transmural pressure probably contributes to the hyperemia, especially in the case of short periods of occlusion or exercise where the changes in the oxygen and metabolite concentrations are minimal. There is in fact evidence for a Bayliss response in gracilis muscle. Honig and Frierson (11) report vasodilation in response to passive stretch of the gracilis muscle at a frequency of 2/sec for 10 sec. In the present study, the vasodilation seen following relief of ischemia was sometimes interrupted by a transient vasoconstriction. This could represent vascular smooth muscle contraction subsequent to stretch as reperfusion raises intraluminal pressure. Unlike in the kidney (7), the response cannot be due to static or traumatized blood since such blood causes vasodilation rather than constriction in skin and skeletal muscle (6). Assuming the vasoconstriction does result from a Bayliss response, the subsequent vasodilation and recovery from vasodilation is most compatible with the metabolic hypothesis. Although static blood could influence the magnitude of this vasodilation, it could not account for the prolongation of recovery time by constant flow or the increase in recovery time as a function of ischemia duration since the amount of static blood is a constant.

Summary. Recovery times from exercise and ischemic dilation in gracilis muscle were compared during constant pressure (natural flow) and constant flow perfusion. Recovery times were longer at constant flow. This finding provides additional support for the metabolic hypothesis for the regulation of blood flow in skeletal muscle.

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