Pre- and postcapillary resistance in skeletal muscle

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Methods

Thirty-two dogs weighing 10–25 kg were anesthetized by intravenous injection of sodium pentobarbital (30 mg/kg body wt). Additional doses of sodium pentobarbital were given when needed.

The preparation consisted of the skinned muscles of the lower leg with their attachment to the distal part of the femur and tibia-fibula preserved. The muscles of the preparation consisted of the gastrocnemius-plantaris and the remaining foot and toe flexors and extensors. The foot was exarticulated at the ankle joint and the femur amputated above the knee. Bleeding from the bone marrow was prevented with bone wax. The popliteal artery and vein were isolated for cannulation and all other vessels tied. Heparin was given at an initial dose of 6 mg/kg followed by one-half this amount every 30 min thereafter. The femoral artery of the ipsilateral limb was cannulated with polyethylene tubing through which blood was supplied to the hindlimb preparation for autoperfusion. The isolated limb was placed on a platform suspended from a recording beam balance, the movements of which were sensed by a linear differential transformer (Atcotran, type 6208). The sensitivity of this balance was adjusted to give a galvanometer deflection of 25–30 mm for a weight change of 1 g.

The venous outflow passed into a plastic reservoir and was returned to the animal by way of the jugular vein. Side branches close to the preparation allowed measurements of arterial perfusion pressure and venous outflow pressure. Arterial pressure could be lowered by a screw clamp on the arterial tubing and the venous outflow pressure was adjustable by altering the height of an orifice draining into the reservoir. Arterial inflow was continuously monitored using a Medicon K-2000, 400 cycles/sec sine-wave electromagnetic flowmeter with a cannulating-type flow probe. In addition to these determinations venous outflow was frequently measured directly at the venous outflow orifice using a
graduated cylinder and stop watch. Arterial and venous pressures, blood flow, and weight were continuously recorded on an Offner type R Dynograph.

The experimental design used here was similar to that used in previous studies on the isolated intestine (5) and the whole hindlimb (3). The principle for mean capillary pressure determination is a modification of Pappenheimer and Soto-Rivera's original method (7). In short, this implies that the preparation is brought to an isogravimetric state during which no weight changes occur. Arterial inflow and venous outflow are occluded simultaneously and a side branch in the venous and arterial circuit connected to a saline-filled reservoir is opened. The level of this reservoir is then adjusted to give a hydrostatic pressure which again makes the preparation isogravimetric at zero flow. The pressure at which the preparation becomes isogravimetric is taken as the mean capillary pressure which existed before flow was occluded.

Muscular contractions were elicited by electrical stimulation of the muscle branches of the sciatic nerve utilizing bipolar platinum electrodes connected with a square-wave generator (Grass, model S 4). Stimulation was performed with frequencies of 1 to 2 impulses/sec at a stimulation strength of 1 v and duration of 1 msec.

RESULTS

Arterial pressure was reduced stepwise from the initial level of 100 or 110 mm Hg to 30 mm Hg by adjusting a screw clamp on the arterial tubing and at the same time the venous pressure was elevated in order to prevent slow weight changes which would indicate a reduction in capillary pressure. In this way the capillary pressure was maintained at a constant level. Using the value for mean capillary pressure obtained with the zero flow-isogravimetric technique, the total vascular resistance during each isogravimetric period can be separated into arterial and venous components. In Fig. 1 the pattern of arterial resistance with stepwise reduction of arterial pressure is shown. Similar to the findings of Hanson and Johnson (3) in the whole hindlimb of the dog, we also could distinguish three different types of resistance responses. In type I preparations arterial resistance declined with each reduction of arterial pressure over the full range of pressures. A gradual fall in resistance occurred at the range of higher pressures followed by a sharp drop as the pressure was decreased below 70 mm Hg. This type of response was observed in 8 of 32 experiments (25%). In type II preparations there was an initial slight rise in arterial resistance as the pressure was decreased over its higher range followed by a pronounced fall as the arterial pressure was reduced below 60-70 mm Hg. In some experiments included in this group arterial resistance remained practically unaltered until arterial perfusion pressure had been reduced to 60 mm Hg at which time the resistance fell. In 16 experiments the type II resistance response was observed (50%). In type III preparations there was a progressive increase of arterial resistance over the whole range of pressure reduction. This type of response was observed in the remaining eight experiments (25%). Figure 1 shows the pooled data from 10 experiments of types I and II. As seen from the graph depicting arterial resistance there is a progressive reduction of this variable below 70 mm Hg indicating arterial dilatation, which can be called an autoregulatory response. The same pattern is also seen during muscular exercise, although here autoregulation is present over the whole pressure range.

The pattern of venous resistance is particularly interesting since there is a considerable increase in post-capillary resistance with decreasing arterial pressure (increase to 360% of the initial value when arterial pressure is reduced to 30 mm Hg). With muscular exer-
cise this response of the venous vasculature is totally abolished, as is evident from Figs. 1 and 3. It is apparent from Fig. 3 that the isogravimetric venous pressure which obtains at zero flow is not out of line with the pressures which obtain at low flows. The consistency of this data lends credulity to the calculated values of postcapillary resistance.

In order to investigate the nature of the venous resistance response a sympathetic blocking agent was infused. For this purpose phenoxybenzamine (Dibenzyline hydrochloride, Smith, Kline and French) was administered in doses of 2-10 mg in a solution containing 0.2-0.5 mg/ml by intra-arterial infusion into the arterial tubing supplying the muscle preparation 90 min before the experiment. The result of five experiments is shown in Fig. 2A. In all experiments phenoxybenzamine brought about some reduction of the venous resistance over the whole pressure range but the curvilinear resistance response was still present. The effect of chronic denervation on the venous resistance was also studied in nine experiments 14 days following surgery. Denervation was accomplished by cutting the sciatic nerve. As seen from the data in Fig. 1 this procedure did not have any significant effect on the resistance pattern. Finally, infusion of low molecular weight dextran (Rheomacrodex, Pharmacia, mean molecular weight: 40,000) was used in a dosage of 500 ml of a 10 % solution in physiological saline. The dextran solution was administered intravenously after removal of 400 ml of blood. Following the dextran infusion the hematocrit declined from a mean value of 47 to 28 %. Low molecular weight dextran significantly changed the venous resistance response in five experiments, as evident from Fig. 2B. Dextran given in conjunction with an initial dose of Dibenzyline practically abolished the rise in venous resistance with stepwise reduction of arterial pressure seen in the control experiments.

**DISCUSSION**

The relationship of isogravimetric venous pressure to flow with reduction of arterial pressure is shown in Figs. 3 and 4. These graphs show a distinct curvilinear relationship between pressure and flow in resting muscle. This evidently indicates a progressive increase in venous resistance concomitant with the reduction of arterial pressure and the compensatory elevation of venous outflow pressure. The relationship of venous pressure vs. flow in the whole hindlimb as reported by Pappenheimer and Soto-Rivera (7) and Hanson and Johnson (3), however, followed a straight line (as shown by the broken line in Fig. 4A). This made possible extrapolation to zero flow and the corresponding isogravimetric pressure. The results of the present series of experiments on resting muscle are quite similar to previous observations by Johnson and Hanson (5) in the intestine but quite evidently contrary to those obtained in the whole hindlimb (3, 7). The disagreement between the results of the present series of experiments utilizing a skinned muscle preparation without the paw and the results of experiments in the whole hindlimb may be that there is a passive dilatation of the veins in the skin of the whole hindlimb which masks a simultaneous increase in venous resistance in the muscle. This may be a factor of importance since the whole hindlimb contains an appreciable portion of skin which amounts to 15 % by weight. This problem is the subject of the accompanying paper (6).

An important question that arises from the above results concerns the nature of venous vascular response on reduction of arterial pressure. In a previous study on the dog intestine it was concluded that the response was mediated through a local sympathetic axon reflex (4) since it was abolished by sympathetic blocking agents and chronic denervation. The present investigation does
not support this since chronic denervation was not followed by any significant attenuation of the venous resistance response. In this connection it may be questioned whether the denervation approach employed here was an effective means of blocking the total sympathetic innervation of the hindlimb vasculature. There is, however, some experimental evidence that practically all vasomotor fibers to the peripheral vasculature reach their effector organs within the mixed somatic nerves (1). The experiments with sympathetic blocking agents did show a slight reduction of the venous resistance but the curvilinear response pattern was still present. Low molecular weight dextran as such seemed to lower venous resistance, whereas the combination of both Dibenzyline and dextran was still more effective (cf. Fig. 2B).

The ability of dextran to alter the venous resistance response may be linked to either of two possible mechanisms. In the first place, it may be associated with hemodilution because there was a 40% reduction of the hematocrit after infusion of dextran. Second, it has been reported that low molecular weight dextran possesses specific deaggregating properties (2). Under the present experimental conditions after traumatic surgery and with progressively slowed blood flow the possibility cannot be ruled out that some degree of corpuscular aggregation may have been present, especially in the postcapillary section of the terminal circulation.

The pronounced ability of muscular exercise to abolish the venous resistance response may be connected with the powerful vasodilator activity which overrules local vasoconstrictor impulses connected with sympathetic axon reflexes or similar mechanisms. Moreover, postcapillary corpuscular aggregation should theoretically be counteracted by the mechanical shaking activity associated with rhythmic muscular contractions.

In accordance with previous studies (3) autoregulation was present in most experiments and it was also observed during muscular exercise, which is in agreement with the studies of Stainsby (8).

REFERENCES