Shock and active vasodilatation in skeletal muscle

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Summary

The vasodilatation which occurs in the skeletal muscle of the cat following the stimulation of some fibres of the sympathetic nerves and that which follows the intravenous injection of small doses of adrenaline takes place in different vessels. It is, therefore, possible to obtain an augmented effect when both the above stimuli are applied simultaneously. Both mechanisms must be blocked to completely abolish active vasodilatation in skeletal muscle.

THE ROLE of metabolic acidosis in haemorrhagic shock has created a good deal of interest in recent years. For some time it has been recognized that the extent of this acidosis is influenced by the degree of sympathetic activity.

In spite of the fact that Cori & Buchwald showed in 1930 that skeletal muscle when perfused with adrenaline produces lactic acid and, furthermore, that vasodilatation in the perfused area increases the amount produced, many have assumed that the changes observed in shock were due to sympathetic vasoconstrictor activity. Recently, Irving *et al.* (1968) have demonstrated that the effective prevention of the lactic acidosis of adrenaline infusion required the combined blockade of both vasoconstrictor and vasodilator receptors.

They go on to point out, however, that even in this state of α - and β -receptor blockade a rise in lactic acid level still occurs in haemorrhagic hypotension although it is markedly curtailed compared with that in non-medicated animals.

Because of these observations the detailed study of skeletal muscle vasodilatation at rest obviously becomes of importance in the consideration of the total prevention of lactic acidosis.

The experiments described here were carried out on the skinned hind-limb of the cat. A pump delivering a constant volume of blood per minute was inserted in the arterial inflow to the calf muscles of the hind-limb and measurements made of the pressure in the nutrient artery and vein.

From the data obtained it was possible to calculate changes in peripheral resistance which were initially unaffected by variations in the viscosity of the blood because changes of shear rate were minimal. The

sympathetic chain on the side of the limb being investigated was exposed and electrodes applied immediately above the lowest lumbar ganglion so that the sympathetic vasodilator fibres to the hind limb could be stimulated. α -Receptors were blocked by giving intravenous dibenzylamine (phenoxybenzamine hydrochloride 0.6 mg/kg) followed by intravenous ergotamine tartrate (0.3 mg/kg).

The stimulus to the sympathetic trunk and the dose of intravenous adrenaline which gave the maximum vasodilatation in each case were then determined. The effect of these two optimum stimuli given separately and together on peripheral resistance was then determined.

It was found that when the stimuli were given together there appeared to be an augmented effect, such that with a resting peripheral resistance of say 39.90 PRU (peripheral resistance units) (mean of forty experiments) the resistance with adrenaline fell to 13.01 PRU, to 13.04 PRU with sympathetic stimulation and to 7.58 PRU when both stimuli were given together.

I would like to suggest that this indicates that there may be two vascular beds in skeletal muscle, one of which is dilated by intravenous adrenaline and the other by sympathetic stimulation. If this were so then it would follow that α -blockade would only prevent the dilatation due to circulating adrenaline but would not affect that due to sympathetic stimulation which is cholinergic and can only be blocked by atropine (Folkow, 1968).

If there are two vascular beds in skeletal muscle separately controlled in so far as their active vasodilatation is concerned, where are they? Applying a direct approach to solve this problem it can be shown (by using a technique which depends on the clearance of radioactive ions) that the vessels of the connective tissue of a skeletal muscle do not react to the intravenous infusion of adrenaline or the stimulation of the appropriate sympathetic fibres, both of which are capable of producing vasodilatation in the muscle fibre areas of skeletal muscle (Barlow & Walder, 1965). It is, therefore, concluded that both the vascular beds which we are searching for must be associated with the muscle fibre areas of the skeletal muscles.

TABLE 1. Peripheral resistance (PRU) of muscle blood vessels in hind-limb of cat (seventeen experiments)

	Experimental data				Theoretical value for (d) according to model		
	(a) Normal	(b) Adrenaline	(c) Stimulation	(d) Adrenaline + stimulation	A	B	C
Mean	41.22	15.05	14.13	8.15	9.12	12.98	12.04
SE	4.722	1.050	0.752	0.801	0.599	0.734	4.719

A neat explanation which could account for two separately controlled vascular beds in the same muscle would be if red slowly contracting fibres had a separately controlled vascular bed from white rapidly contracting fibres. Using the same technique of observing the clearance of radioactive ions and comparing the responses to intravenous infusion of adrenaline and to sympathetic stimulation of two muscles in the cat, one of which is almost entirely composed of slowly contracting fibres (soleus) and the other almost entirely of rapidly contracting fibres (gastrocnemius) it is found that vasodilatation of the vessels supplying the two types of muscle fibres are in fact similarly controlled. So this is not the explanation.

Applying an indirect approach to solve this problem is, however, more helpful. Assuming that the vascular bed supplying the fibres of skeletal muscle consists of a number of parallel pathways then the simplest representation of it would be as two parallel sets of vessels. If this were so, then there would only be a limited number of possibilities for the action of intravenous adrenaline and sympathetic stimulation (Fig. 1).

(A) One set of vessels could be dilated by intravenous adrenaline, the other set by sympathetic stimulation.

(B) Both sets of vessels could be fully dilated by intravenous adrenaline or by sympathetic stimulation.

(C) Both sets of vessels could be partially dilated by intravenous adrenaline and partially dilated by sympathetic stimulation.

If this is accepted then the data obtained from our experiments on the skinned hind-limb of cats can be fitted to each of the three models described above and the goodness of fit determined. When this is done it is found that model A fits the data best (Table 1) and this is statistically significant to the $P < 0.001$ level. That is, there are two types of vessels in the muscle fibre areas of skeletal muscles: one type dilates as a result of the intravenous infusion of adrenaline and the other dilates as a result of sympathetic stimulation.

FIG. 1. Possible patterns of action of intravenous adrenaline and sympathetic stimulation on the dilatable vascular beds of skeletal muscle.

Thus in order to completely stop the development of lactic acidosis in haemorrhagic shock not only must the α - and β -receptors be blocked but perhaps the sympathetic cholinergic vasodilator fibres should also be blocked.

In case you are about to say that my experiments are on cats and man is different let me remind you that Wilkins & Eichna (1941) described two different types of vasodilator response which could occur independently or simultaneously in the skeletal muscle of man and that Barcroft *et al.* (1944), investigating human forearm vasodilatation, published figures for the dilatation resulting from nervous and humoral stimuli which fit in with my concept very well.

References

BARCROFT, H., EDHOLM, O.G., McMICHAEL, J. & SHARPEY-SCHAFER, E.P. (1944) Post haemorrhagic fainting. *Lancet*, i, 489.
BARLOW, T.E. & WALDER, D.N. (1965) Vasodilatation in skeletal muscle. *Clin. Sci.* 29, 277.

- CORI, C.F. & BUCHWALD, K.W. (1930) The action of epinephrine and insulin under anerobic conditions. *J. biol. Chem.* **87**, 38.
- FOLKOW, B. (1968) Discussion. *Circulation in Skeletal Muscle* (Ed. by O. Hudlika), p. 9. Pergamon Press, Oxford.
- IRVING, M.H., VARGA, D., GILLETT, D.J. & HALMAGYI, D.F.J. (1968) The effect of adrenergic blockade upon shock-induced lacticacidosis in sheep. *Brit. J. Surg.* **55**, 780.
- WILKINS, R.W. & EICHNA, L.W. (1941) Blood flow to the forearm and calf. I. Vasomotor reactions: role of the sympathetic nervous system. *Bull. Johns Hopk. Hosp.* **68**, 425.