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THE CONTROL OF THE CIRCULATION IN SKELETAL MUSCLE DURING ARTERIAL HYPOXIA IN THE RABBIT

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SUMMARY

1. The effects of arterial hypoxia on muscle blood flow were examined in normal unanaesthetized rabbits in relation to simultaneously determined changes in cardiac output, arterial pressure and heart rate. Muscle blood flow was estimated from the difference between total limb flow (local thermodilution) and the estimated skin flow (using a calibrated heat conductivity method). The role of the arterial chemoreceptors and baroreceptors in the control of muscle blood flow was examined and the nature of the sympathetic efferent discharge analysed.

2. In mild hypoxia (P_{O_2} > 35 mm Hg) in the rabbit, muscle blood flow did not change, although cardiac output increased. During moderate hypoxia (P_{O_2} 30 – 35 mm Hg) there was initial vasoconstriction in muscle, followed by a return to control values paralleling the changes in cardiac output. In severe arterial hypoxia (P_{O_2} < 30 mm Hg) the initial vasoconstriction was less marked, and during the 'steady state' there was a large vasodilatation and increase in muscle blood flow, at a time when the cardiac output was not elevated.

3. The early vasoconstriction in arterial hypoxia is mediated mainly through sympathetic vasoconstrictor nerves as a result of strong arterial chemoreceptor stimulation.

4. Increased secretion of adrenaline is an important factor in restoring muscle blood flow to control values during moderate arterial hypoxia, and in elevating the muscle blood flow above these values in severe hypoxia. The peripheral dilator (β-) effects of adrenaline oppose the peripheral constrictor (α-) effects resulting from increased activation of sympathetic constrictor nerves during arterial hypoxia.

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INTRODUCTION

Perfusion of the isolated vascular bed of skeletal muscle with hypoxic blood uniformly produces vasodilatation related to the severity of the hypoxia (Crawford, Fairchild & Guyton, 1959; Ross, Fairchild, Weldy & Guyton, 1962; Guyton, 1963). However, in intact animals, where reflex neuro-humoral mechanisms are superimposed on the local effects, a variety of responses has been observed during arterial hypoxia. In man there is a large increase in the blood flow to skeletal muscle (Abramson & Ferris, 1940; Abramson, Landt & Benjamin, 1943; Anderson, Allen Barcroft, Edholm & Manning, 1946; Black & Roddie, 1958). This dilatation has been attributed to the local effects of hypoxia (Abramson *et al.* 1943), and to the hypocapnia associated with hyperventilation (Clarke, 1952; Black & Roddie, 1958). In diving animals, on the other hand, arterial hypoxia produces marked vasoconstriction (Grinnell, Irving & Scholander, 1942; Andersen, 1964; Scholander, 1964). Daly & Scott (1962) have shown in the dog that perfusion of the arterial chemoreceptors with hypoxic blood produces vasoconstriction in skeletal muscle, which is transient in animals breathing spontaneously but is intensified under conditions of controlled ventilation, thus providing a possible explanation of the above species differences. However, a detailed analysis of the nervous and humoral pathways controlling the circulation to skeletal muscle during arterial hypoxia has not been carried out in the intact animal.

Previous experiments in unanaesthetized rabbits have shown that the changes in cardiac output, heart rate and total peripheral resistance during 'mild' arterial hypoxia resemble the findings in man, but that with increasing severity of hypoxia the response has many features in common with that of diving animals as a result of stronger arterial chemoreceptor stimulation (Korner, 1965*a*; Chalmers, Isbister, Korner & Mok, 1965; Korner & White, 1966). The purpose of the present experiments was to examine the effects of different levels of arterial hypoxia on the circulation of skeletal muscle of the rabbit, to relate these to the concomitant changes in cardiac output, and to examine some of the mechanisms underlying the changes observed.

METHODS

Animals. New Zealand White rabbits cross-bred with the New Zealand Giant strain, varying in weight from 2·4 to 3·2 kg (mean weight 2·7 kg) were used in these experiments.

Operative procedures. A preliminary operation was carried out under sodium pentobarbitone anaesthesia (Veterinary Nembutal, Abbott; initial dose 30–40 mg/kg I.V., supplemented as required), 2–3 days before each experiment. A thermistor catheter was inserted into the upper abdominal aorta, and the trachea transposed into a subcutaneous position as described previously (Korner, 1965*b*). A double lumen thermistor catheter (for measuring flow in the common iliac vein) was inserted into the left inferior epigastric vein close to the

point of its junction with the femoral vein, and its tip was advanced about 2·5 cm into the common iliac vein (Fig. 1*A*). A local thermodilution curve (see below) was recorded to confirm that the thermistor remained in the iliac vein even with the leg maximally flexed. The other end of the catheter, with plug and lead wires, was led beneath the skin of the anterior abdominal wall and brought out at the level of the umbilicus. The injection lumen of the catheter (Fig. 1*B*) was filled with concentrated heparin solution (5000 i.u./ml.). The thermistor catheters were protected by sewing a light calico harness to the rabbit's skin.

The carotid sinus and aortic nerves were sectioned in two animals as described previously (Korner, 1965*b*).

In three animals bilateral adrenalectomy was carried out as a one-stage procedure and the animals were maintained on cortisone acetate and deoxycorticosterone acetate as described previously (White, 1966; Korner & White, 1966). Six to eight days after adrenalectomy

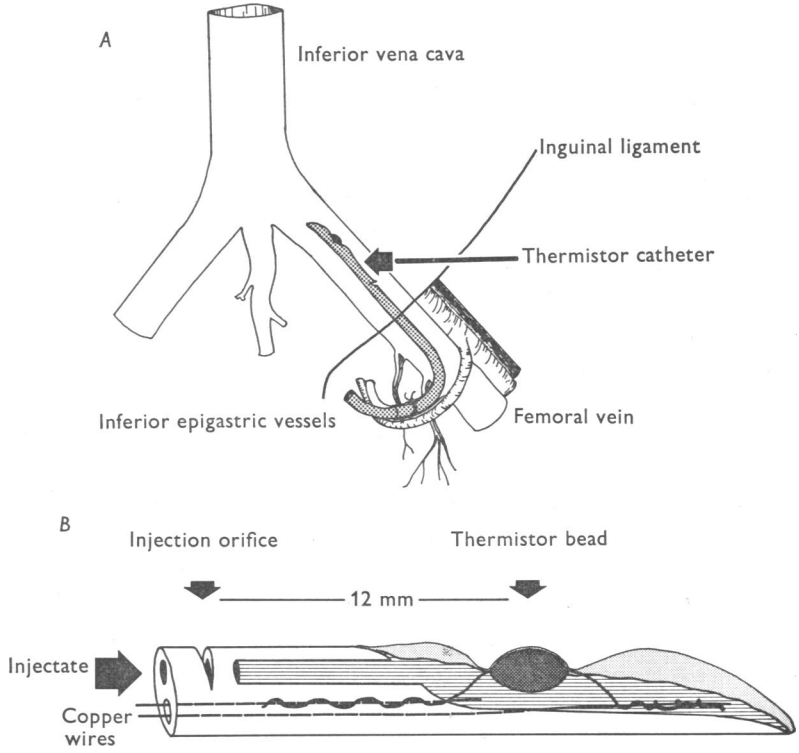


Fig. 1. *A*. Diagram showing insertion of double lumen thermistor catheter into left common iliac vein through the left inferior epigastric vein. Cannulation is carried out through a longitudinal skin incision made over the femoral triangle.

B. Schematic representation of tip of double lumen thermistor catheter. The platinum leads of the thermistor bead (dark hatching) are soldered to double enamelled 37-gauge Cu wires and fixed inside the catheter with epoxyresin (horizontal hatching). The thermistor is insulated from the blood stream by a thin film of silicone rubber (fine stippled hatching) which is built into two small baffles in front and behind the thermistor bead to prevent it from touching the vessel wall. The injection is carried out through a fine slit 12 mm upstream from the thermistor bead.

double lumen thermistor catheters were inserted into each common iliac vein, and an extensive left lumbar sympathectomy was carried out removing the sympathetic chain from just below the level of the renal artery (L 3) to the aortic bifurcation. A left lumbar sympathectomy was also carried out in nine normal rabbits and thermistor catheters implanted bilaterally in their common iliac veins.

On the day of the experiment catheterization of the central ear artery and right atrium, and insertion of a tracheotomy tube were carried out as described previously (Korner, 1965*b*).

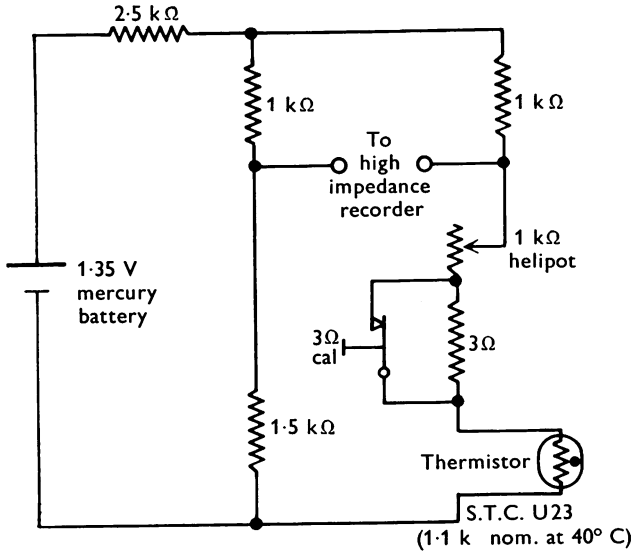
Estimation of muscle blood flow. The blood flow to skeletal muscle in the rabbit's hind limb was estimated from the difference between simultaneous determinations of the total limb (= common iliac vein) flow and limb skin blood flow, making the assumption that the flow to other tissues such as bone and cartilage is a negligible fraction of the total limb flow (Cumming, 1962; Root, 1963). In the rabbit the common iliac vein drains the entire hind-limb region with a small contribution from muscle and skin of the abdominal wall. The venous drainage from the pelvic contents passes mostly to the tail vein (Fig. 1*A*).

The common iliac flow was measured by a local thermodilution technique (Fegler, 1957; Fegler & Hill, 1958; Froňek & Ganz, 1960; Hosie, 1962; Greenfield, Whitney & Mowbray, 1963). A small thermistor (Stantel U 23 UD, Standard Telephones and Cables, Pty, Ltd.) was mounted near the tip of a finely drawn out double lumen polyvinylchloride (PVC) catheter as shown in Fig. 1*B*. The 90 % response time in water to a small temperature change varied from 0·15 to 0·40 sec. A mechanical injector was used to inject fluid rapidly through a fine slit against the direction of blood flow to ensure adequate mixing. The relation between the thermistor resistance and temperature is a logarithmic one (Hosie, 1962), and deviation from linearity becomes particularly important in local thermodilution techniques, where the temperature change at the thermistor may vary from 3 to 8° C. Accordingly the thermistor was incorporated into a special Wheatstone Bridge circuit (Fig. 2*A*) giving an approximately linear voltage output in the temperature range 32–44° C. The bridge current in the thermistor leg was made variable by suitable selection of bridge constants, so that a falling voltage–resistance relation cancelled out the rising resistance–temperature relation in this temperature range. Thermodilution curves were recorded using a Sanborn 350/1100 low level pre-amplifier, and the area of the curve was simultaneously recorded by means of an integrating circuit (Figs. 4, and 9). Limb flow was calculated from the formula

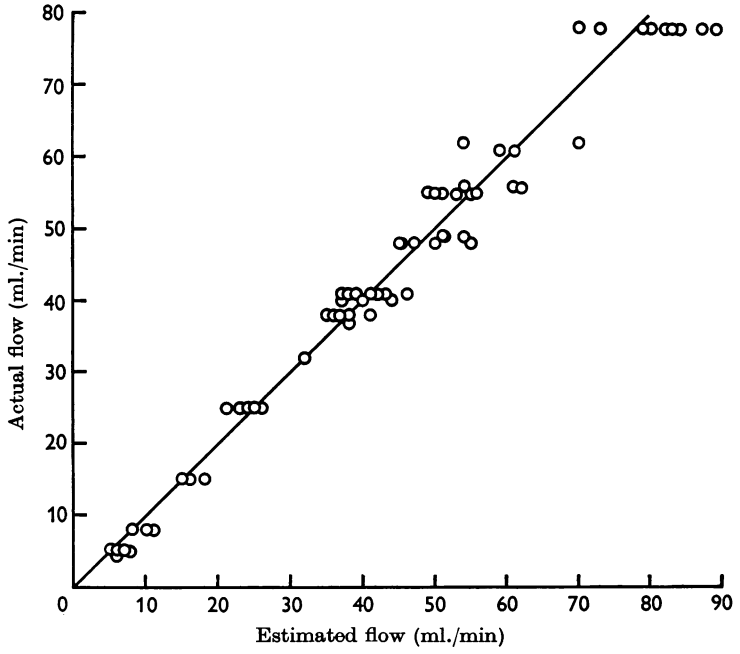
$$Q_b = \frac{60 V_i d_i s_i (T_b - T_i) K}{d_b s_b \int_0^\infty \Delta T_b(t)\,dt},$$

where Q_b is the iliac flow (ml./min), V_i is the volume of injectate, d_i and d_b are the densities of injectate and blood (i.e. 1·018 and 1·045 respectively), s_i and s_b are the specific heats of injectate and blood (i.e. 0·965 and 0·89 respectively (Mendlowitz, 1948), T_i and T_b are the temperature of injectate and iliac vein blood determined just before each curve, T_b is the change in iliac vein blood temperature at times (t) after injection of indicator and K is a correction factor for loss of thermal indicator during injection due to cooling of the catheter wall. The value of K used in the present experiments was 0·94 determined by the method of Goodyear, Huvos, Eckhardt & Ostberg (1959). The injectate used was 0·28 ml. of 6% dextrose in distilled water (calibrated by weighing) at room temperature. The accuracy of flow measurements was checked in model experiments using a 4 mm diameter tube immersed inside an air jacket in a water-bath at 40° C (rabbit's body temperature), through which fluid at this temperature was driven at varying rates using a calibrated motor-driven syringe pump. The results in Fig. 2*B* indicate good agreement between actual flows and estimated flows using the above formula with the present double lumen thermodilution catheter. It was not necessary to use the corrections suggested by Froňek & Ganz (1960).

The blood flow/g of skin was estimated by a thermal conductivity method, using a copper-tellurium heat flow disk (Hatfield, 1950) applied to the skin of the lower hind limb,



A



B

Fig. 2. *A*. Diagram of Wheatstone bridge circuit used for local thermodilution. *B*. Relation between actual flows in model experiments and estimated flows obtained using double lumen thermodilution catheters.

from the relation between heat flow and blood flow determined in perfusion experiments and described in the accompanying paper (Chalmers & Korner, 1966). Under the conditions of the present experiments the heat flow values for the hind limb skin fall into the most sensitive range of the relation between heat flow and blood flow shown in Fig. 2 of Chalmers & Korner)1966). The skin flow values obtained from this region have been assumed to be representative of the skin of the hind limb, since the skin in this region is well removed from the paw and pad regions which contain a greater proportion of arteriovenous anastomoses (cf. Greenfield, 1963). At the end of each experiment the skin of the hind limb was weighed (mean weight 50 g; range 45–60 g), and the 'estimated skin flow' per hind limb calculated.

Measurement of cardiac output, blood pressure and heart rate. The cardiac output was measured from aortic thermodilution curves following injection of 6% dextrose into the right atrium (cf. Korner, 1965*b*). Ear artery pressures and heart rates were determined as described previously (Korner, 1965*b*).

Administration of gas mixtures, and measurement of blood gas tensions and pH. Gas mixtures were freshly prepared from cylinders of air, N_2 and CO_2, and were administered through a respiratory valve as described previously (Edwards, Korner & Thorburn, 1959). Arterial blood was collected anaerobically, and the pH, P_{O_2} and P_{CO_2} determined on 1·5 ml. samples of blood using a blood gas analyser and pH meter (Model 113, Instrumentation Laboratory Inc.) as described elsewhere (Chalmers & Korner, 1966).

Administration of drugs. In a number of experiments systemic β-adrenergic block was induced using propranalol (Inderal; Imperial Chemical Industries). The dosage and method of administration was as described previously (Chalmers *et al.* 1965). Systemic cholinergic block was produced by giving atropine sulphate I.V. at an initial dose of 2 mg, followed by 1 mg at 15 min intervals. Adrenaline tartrate was given by continuous I.A. infusion into the lower abdominal aorta through a fine PVC catheter, using a motor driven syringe pump. The dosage ranged from 0·01 to 0·32 μg/kg/min.

Conduct of experiments. The conduct of the experiments and statistical analysis of the results was similar to that described by Chalmers & Korner (1966).

RESULTS

Resting muscle flow. The mean results of resting muscle flow obtained from twenty-one normal rabbits were $21·5 \pm 3·1$ (S.E. of mean) ml./100 g muscle/min. The skin flow in the rabbit's hind-limb skin was $20·8 \pm 1·1$ (S.E. of mean) ml./100 g skin/min. Both values are considerably above the corresponding values in man (Barcroft, 1963; Greenfield, 1963; Shepherd 1963) but have a similar relation to each other and probably reflect the high rate of resting metabolism of the unanaesthetized rabbit (Korner & Darian-Smith, 1954; Edwards *et al.* 1959).

Effects of arterial hypoxia. The average changes in muscle blood flow observed in the hind limb of twenty-one rabbits during mild, moderate and severe arterial hypoxia are given in Fig. 3 in relation to the simultaneously recorded changes in arterial pressure, heart rate, cardiac output and hind-limb skin flow. The changes in arterial blood gas composition in the three groups of animals are summarized in Table 1.

Mild arterial hypoxia ($P_{O_2} > 35$ mm Hg) was induced in four rabbits by administration of 9–9·5% O_2 in N_2 (9–9·5% O_2). There were no significant changes in muscle blood flow, or in skin blood flow. However, the general

circulatory effects were similar to those observed previously for this degree of hypoxia (Korner, 1965*a*). The cardiac output rose significantly by 11% ($P < 0.01$) during hypoxia, the heart rate returned to control values or above after an initial slight bradycardia, and the arterial pressure was maintained. In the rabbit therefore the circulation in muscle or skin is not the site of increased blood flow with this degree of reduction in arterial P_{O_2}.

TABLE 1. Arterial blood gas tensions and pH in experiments on normal rabbits, and in rabbits studied before and after selective adrenergic block. *C* = control period breathing 21% O_2; *T* = test period breathing low O_2 mixtures as described in text. S.E.Δ = standard error of difference between control and treatment means calculated from within animal comparisons

Group	No.	P_{O_2} (mm Hg)			P_{CO_2} (mm Hg)			pH		
		C	*T*	S.E. Δ	*C*	*T*	S.E. Δ	*C*	*T*	S.E. Δ
		Normal rabbits								
Mild hypoxia	4	98	38	+2·5	32	19	±2·8	7·44	7·59	±0·04
Moderate hypoxia	12	97	32	±1·8	32	18	±1·3	7·48	7·58	±0·03
Severe hypoxia	5	101	26	±3·3	31	20	±1·3	7·47	7·53	±0·06
		Adrenergic block								
Before β-block	7	99	28	±3·7	32	20	±1·8	7·48	7·54	±0·07
After β-block	7	105	29	±2·6	33	19	±2·6	7·46	7·56	±0·04

In twelve rabbits administration of 8% O_2 produced moderate arterial hypoxia (P_{O_2} 30–35 mm Hg). There was significant reduction in muscle blood flow during the early phase of hypoxia, which in view of the rise in arterial pressure must have been the result of vasoconstriction in muscle. In three animals this initial vasoconstriction was maintained during the 25 min period of observation, but in the remainder the muscle blood flow returned to control values or increased above these. The hind-limb skin blood flow increased gradually by a small, but significant amount ($P = 0.01$). The general circulatory findings were in agreement with previous observations (Korner, 1965*a*). The muscle blood flow is thus reduced to about the same degree (to 74% of control) as the cardiac output (to 69% of control) during the early phase of hypoxia, and both parameters return towards their control values in parallel.

Inhalation of 7·5–8% O_2 produced severe arterial hypoxia ($P_{O_2} < 29$ mm Hg) in five animals. There was no consistent change in muscle blood flow during the first 3 min of hypoxia in the group as a whole and vasoconstriction was observed in only two animals (e.g. Fig. 4). In all animals muscle blood flow rose gradually above initial control values as a result of vasodilatation, in some instances reaching values of 200% of control (Fig. 4). With this degree of hypoxia the blood flow in muscle does not

parallel the changes in cardiac output since it is greatly increased at a time when the cardiac output has barely returned to control values.

Effects of section of the carotid sinus and aortic nerves. Two rabbits with indwelling iliac vein catheters were studied one day before, and one day following bilateral section of their carotid sinus and aortic nerves. The response was uniform and the results of one experiment are shown in Fig. 5. With carotid and aortic nerves intact, hypoxia produced the usual initial vasoconstriction in muscle, followed by a brief period of vasodilatation. Administration of 8% O_2+4% CO_2, which intensifies the circulatory

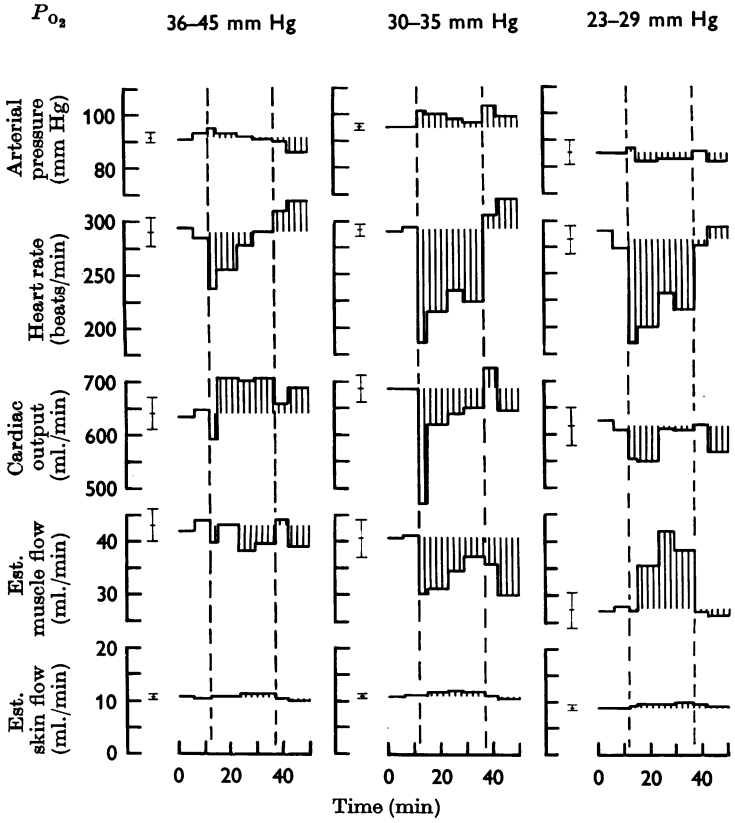


Fig. 3. Mean effects of mild arterial hypoxia in four rabbits (left panel), of moderate hypoxia in twelve rabbits (middle panel) and of severe hypoxia in five rabbits (right panel), on the arterial pressure (mm Hg), heart rate (beats/min), cardiac output (ml./min) estimated muscle blood flow (ml./min) and estimated limb skin blood flow (ml./min). Test mixture breathed between vertical interrupted lines, room air at other times. Hatching denotes deviation of the test and recovery values from initial control values. Symbol on left: mid point is mean initial control value of each parameter and the standard error of a single time interval s the distance above and below this point.

effects of chemoreceptor stimulation in the rabbit (Korner, 1965*a*), increased the magnitude and duration of the vasoconstriction in muscle. Following section of the afferent nerves, there was a marked fall in blood pressure during hypoxia and a small increase in muscle blood flow indicating a much greater degree of vasodilatation in the muscle bed in hypoxia (particularly during the early phase) in the absence of the arterial chemoreceptor and baroreceptor reflexes.

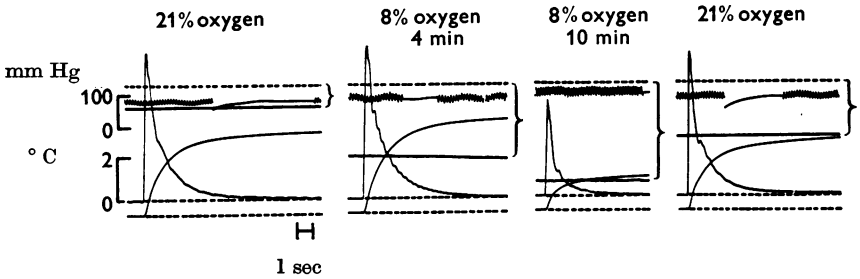


Fig. 4. Recording of (from above down in each record): skin base line ear artery pressure (mmHg), heat flow in hind-limb skin (cal/cm²/min), changes in common iliac vein temperature (° C) immediately after injection of room temperature injectate (local thermodilution curve), and integrated time–temperature curve. The bracket at the right of each record indicates the deflexion produced by the heart flow disk relative to the base line (interrupted line = zero heat flow). The records shown were obtained in an experiment on one rabbit, during the control period breathing 21 % O_2, 4 and 10 min after commencing inhalation of 8 % O_2 (middle two records), and during the recovery period breathing 21 % O_2.

Note initial cutaneous dilatation and slight total limb constriction during hypoxia, followed by further slight skin dilatation and large total limb dilatation.

Role of sympathetic nerves and humoral factors. The circulation of skeletal muscle is influenced by a greater variety of sympatho-adrenal effectors than other peripheral beds (Folkow, 1955; Uvnäs, 1954; Barcroft, 1963). In common with most regions it is controlled by α-adrenergic effectors (Ahlquist, 1958) which include the effects of the sympathetic vasoconstrictor nerves, and the constrictor action of circulating noradrenaline and large doses of adrenaline. However, in contrast with other peripheral beds the circulation of muscle is also influenced by the peripheral β-adrenergic vasodilator effects of small doses of adrenaline (e.g. Celander, 1954) and is also controlled by the cholinergic sympathetic vasodilator nerves (Uvnäs, 1954). The present analysis examined the contribution of these different factors to the extrinsic control of the circulation of muscle during hypoxia.

The sympathetic vasodilator nerves did not appear to play a part in the 'steady-state' vasodilatation of severe arterial hypoxia, since in three rabbits administration of atropine during severe hypoxia did not produce significant changes in muscle blood flow.

The participation of both neural and humoral adrenergic factors in the control of the circulation of muscle during hypoxia was seen in experiments in nine rabbits with a left lumbar sympathectomy in which the effects of brief periods of arterial hypoxia were studied in the two hind limbs. In some animals the blood flow in muscle decreased on the innervated limb and increased slightly on the denervated side, suggestive of a preponderance of increased sympathetic constrictor nerve activity during

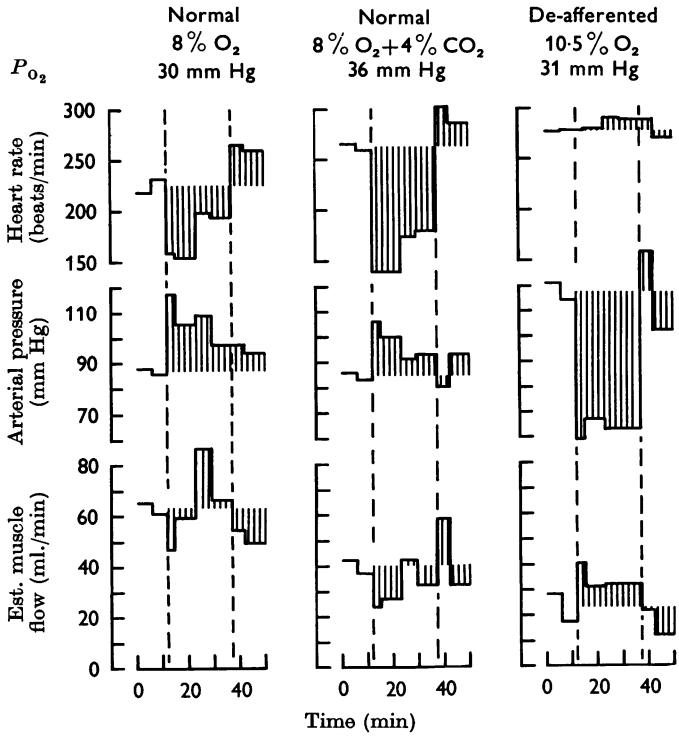


Fig. 5. Effects on the heart rate (beats/min), arterial pressure (mm Hg), and the estimated muscle blood flow (ml./min) produced in one rabbit by the inhalation of 8% O_2 (left panel), and 8% O_2+4% CO_2 (middle panel) one day before section of the carotid sinus and aortic nerves. The effects on these parameters produced by the inhalation of 10·5% O_2 in the same rabbit one day after section of the nerves is shown in the right panel. Notation as in Fig. 3.

hypoxia (Fig. 6*A*). In others the blood flow decreased on the denervated side, and to a lesser extent on the innervated side, suggestive of a dominance of humoral constrictor effects (Fig. 6*B*). The greater effects observed on the denervated side suggest the development of denervation hypersensitivity to endogenously produced adrenal catecholamines (Barcroft. 1963; Trendelenburg, 1963).

The lack of uniformity in circulatory response indicates that the above preparation is not suitable for detailed analysis of the efferent adrenergic pathways in the muscle circulation during hypoxia since too many uncontrolled factors (e.g. variation in relative contribution of increased neural and humoral activity, as well as variation in the hypersensitivity response of the denervated limb to the latter) apparently contribute to the response. This problem of variable response in the sympathectomized

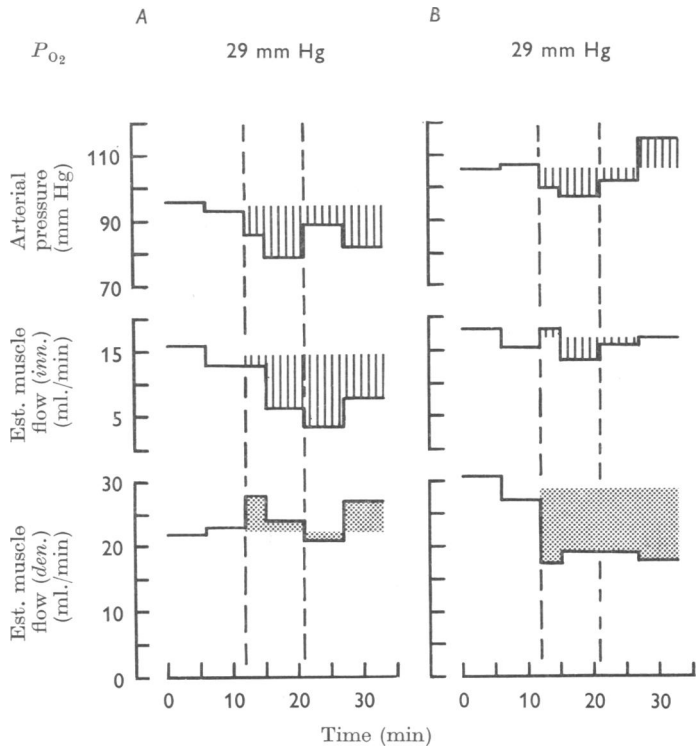


Fig. 6. Effects of breathing 8% O_2 in two rabbits (*A* and *B*) with unilateral lumbar sympathectomies on the arterial pressure and estimated muscle blood flow of the innervated limb (*inn.*), and of the denervated limb (*den.*). Notation as in Fig. 3.

animal with intact adrenals was avoided by testing the effects of hypoxia on the muscle blood flow in adrenalectomized rabbits with unilateral lumbar sympathectomy and in normal rabbits before and after administration of the β-adrenergic blocking drug propranalol.

The effects of reducing the arterial P_{O_2} to 23–34 mm Hg before and after β-adrenergic block with propranalol were examined in seven animals (Fig. 7, Table 1). Before administration of the drug there was the usual initial vasoconstriction in muscle, followed by either a return to, or an

increase above, initial control values depending on the severity of hypoxia. After administration of propranalol there was intense vasoconstriction in the muscle bed which was sustained throughout the entire period of hypoxia. The fall in muscle flow was relatively greater than the fall in cardiac ouput.

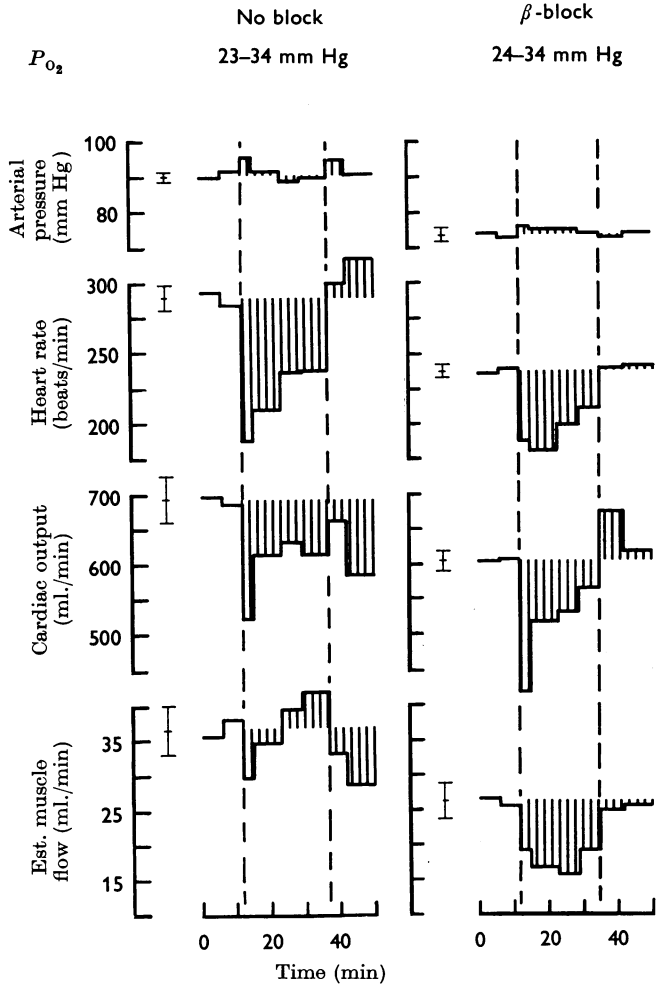


Fig. 7. Mean effects of breathing 8 % O_2 on arterial pressure heart rate, cardiac output and estimated muscle blood flow of seven rabbits, before and after administration of β-adrenergic blocking agent (propranalol). Notation as in Fig. 3.

These results indicate that following the initial vasoconstriction in normal animals (with no blocking agent), the return of muscle blood flow to control values during moderate arterial hypoxia, or above these values in severe hypoxia is prevented by β-adrenergic block. This suggests that

adrenaline release (in doses producing dominant β-effects) during severe hypoxia is a factor in raising muscle blood flow above control values during the 'steady state' of hypoxia in the rabbit. The intensification of vasoconstriction during hypoxia after β-block would result from unmasking of increased α-constrictor activity mediated through the sympathetic constrictor nerves.

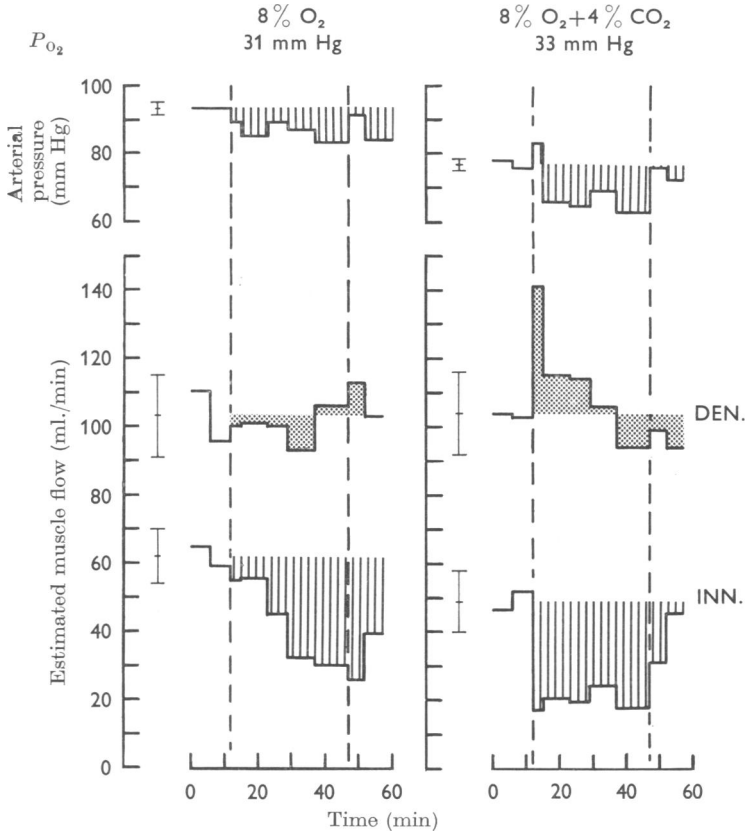


Fig. 8. Mean effects produced by inhalation of 8% O_2, and 8% O_2+4% CO_2 in three adrenalectomized rabbits with unilateral sympathectomy on the arterial pressure and the estimated muscle blood flow in the innervated limb (vertical hatching), and the denervated limb (stippled hatching). Notation as in Fig. 3.

This hypothesis was tested in three adrenalectomized rabbits with unilateral lumbar sympathectomy (Fig. 8, left panel). In these animals arterial hypoxia produced a more intense and sustained vasoconstriction in muscle on the innervated side than in normal animals, and the response obtained was thus similar to that obtained with hypoxia during β-adrenergic block. On the denervated side, however, the initially high blood

flow to muscle remained unchanged during hypoxia. An even greater difference in the response of the two sides was observed after administration of 8% O_2+4% CO_2 (Fig. 8, right panel). These experiments thus demonstrate that during severe hypoxia increased activity of the sympa-

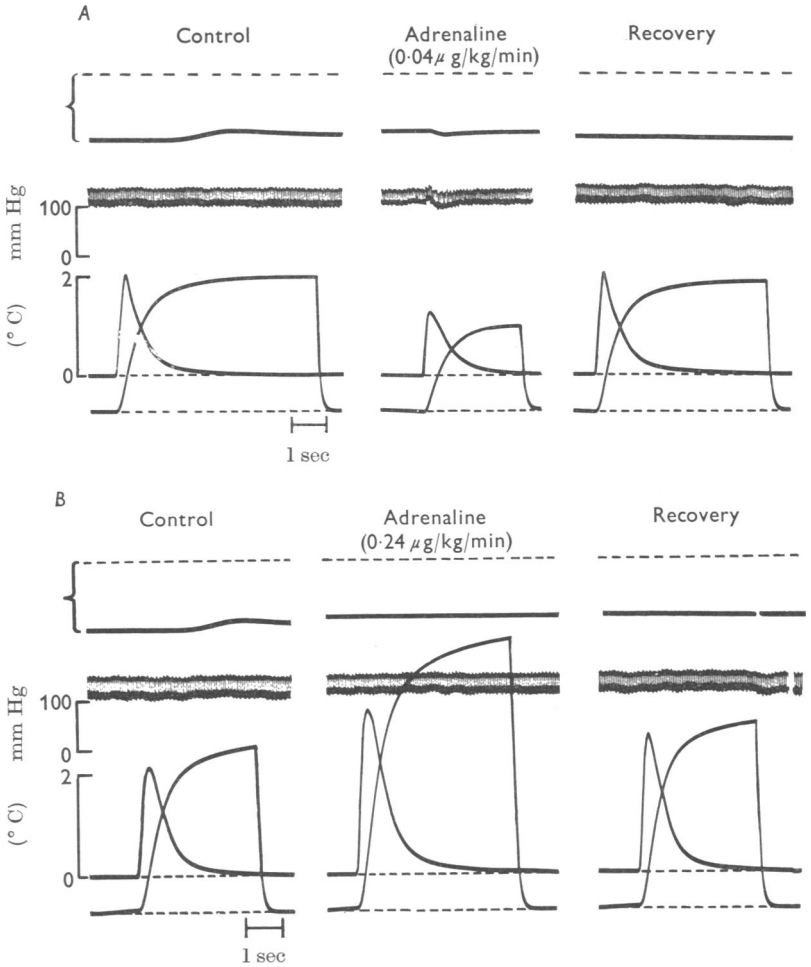


Fig. 9. *A*. Recording of (from above down in each record): heat flow from hind-limb skin (cal/cm²/min), ear artery pressure (mm Hg), temperature changes (° C) in common iliac vein immediately after injection of room temperature injectate (local thermodilution curve), and of the integrated time temperature curve. The bracket at top left indicates the deflexion produced by the heat flow disk relative to the base line (zero heat flow = interrupted line). The records show these parameters in the control period (left), 2 min after commencing I.A. infusion of 0·04 μg/kg/min adrenaline into the lower abdominal aorta (middle), and in the recovery period (right).

B. Records from a similar experiment in the same animal showing the effects of continuous I.A. infusion of 0·24 μg/kg/min of adrenaline.

thetic constrictor nerves to muscle can be readily observed in the adrenalectomized animal at a time when vasodilatation is seen in the normal animal.

In order to see whether adrenaline could produce such a vasodilatation in the unanaesthetized rabbit, intra-arterial infusions of adrenaline at different rates were administered to two normal animals. Maximal vasodilatation was observed with infusions of adrenaline of 0·04 μg/kg/min (Fig. 9*A*), whilst with larger doses vasoconstriction was observed (Fig. 9*B*). The findings in normal rabbits are thus in agreement with the results of Celander (1954) in the cat. In one adrenalectomized rabbit administration of 0·04 μg/kg/min of adrenaline during hypoxia elevated the muscle blood flow on the innervated (constricted) side from 27 to 40 ml./min, and on the denervated (dilated) side from 140 to 165 ml./min.

The effects of *mild* degrees of arterial hypoxia (P_{O_2} 37–45 mm Hg) on muscle blood flow were examined before and after the administration of propranalol in three rabbits and in these the response to hypoxia with no drug was not significantly different from that observed after β-block. This suggests that with this degree of hypoxia there is relatively little increase in sympathetic constrictor activity.

DISCUSSION

In the present experiments the changes in muscle blood flow only paralleled the changes in cardiac output during moderate arterial hypoxia. In mild hypoxia muscle blood flow did not change although the cardiac output increased, whilst in severe arterial hypoxia there was a large increase in muscle blood flow, at a time when the cardiac output had barely returned to control values. The participation of the circulation of muscle in the overall redistribution of blood flow during arterial hypoxia thus varies in relation to the severity of hypoxia.

The sympatho-adrenal discharge to muscle increases relatively little during *mild* arterial hypoxia in the rabbit (cf. Chalmers *et al.* 1965), and the increase is probably just sufficient to oppose the small local vasodilator effects of this degree of hypoxia (Ross *et al.* 1962). On the other hand, in *moderate* and *severe* arterial hypoxia both α- and β-adrenergic activity are increased. The increased α-adrenergic activity is predominantly mediated through the sympathetic vasoconstrictor nerves and accounts for the vasoconstriction observed in the normal rabbit during the early phase of moderate arterial hypoxia. However, during the 'steady state' of moderate arterial hypoxia, or during severe arterial hypoxia, the effects of increased α-adrenergic constrictor nerve activity are masked in the normal rabbit by the β-adrenergic vasodilator effects of increased adrenaline secretion and can only be demonstrated in β-blocked or adrenalectomized animals.

Adrenaline is the major adrenal medullary hormone of the rabbit (Hökfelt, 1951; Shepherd & West, 1952; Malmejac, 1964). It appears to be the main factor in restoring muscle blood flow to normal in moderate hypoxia and elevating it above resting values during severe hypoxia, since the experiments in β-blocked and adrenalectomized animals demonstrate that the increase in α-constrictor activity is more than sufficient to overcome the local vasodilator effects of hypoxia on muscle. The results of Fukuda & Kobayashi (1961) show that in the rabbit during severe arterial hypoxia the adrenaline secretion rate is of the order of 0·04 μg/kg/min, which is in the range of maximum vasodilator (dominant β-adrenergic) activity on muscle vessels. During moderate hypoxia the rate of adrenaline secretion is smaller. This may explain the relatively slow restoration of muscle blood flow in moderate hypoxia, since a greater period of action is necessary to produce vasodilatation when the adrenaline secretion rate is only slightly increased (Golenhofen, 1962; Glover & Shanks, 1963). During severe hypoxia the rate of adrenaline release appears to be optimal for producing dominant β-activity so that the α-constrictor effects become rapidly masked and the muscle blood flow is elevated above control values. No increase in activity of the sympathetic vasodilator nerves could be demonstrated during severe hypoxia, so that the hypothalamic mechanisms involved in the 'defence reaction' of Abrahams, Hilton & Zbrožyna (1964) do not appear to be activated in hypoxia.

The arterial chemoreceptors are the chief afferents involved in the increase in sympathetic vasoconstrictor tone in the muscle bed during arterial hypoxia. This is evident from the abolition of constriction and marked vasodilatation observed in this bed during hypoxia after section of the carotid sinus and aortic nerves, and intensification of vasoconstriction in normal rabbits in which hypercapnia was superimposed on hypoxia. Hypercapnia potentiates the increased chemoreceptor discharge produced by reduction in arterial P_{O_2} (Heymans & Neil, 1958; Eyzaguirre & Lewin, 1961; Neil & Joels, 1963) and also potentiates the circulatory effects of chemoreceptor stimulation in the rabbit (Korner, 1965*a*). The baroreceptor reflexes probably do not contribute to the increased vasoconstrictor activity of moderate hypoxia where the blood pressure is raised, though they may have done so during severe hypoxia in the present experiments, since the blood pressure fell slightly. It is not clear from the present experiments whether increased chemoreceptor stimulation directly determines the release of adrenaline during moderate and severe arterial hypoxia. Potentiation of the circulatory chemoreceptor effects of moderate arterial hypoxia by hypercapnia results in increased vasoconstriction (Fig. 5) rather than vasodilatation. It seems likely that a

different reflex mechanism may be involved in the release of adrenaline. In severe arterial hypoxia the baroreceptor reflexes, stimulated by the small fall in blood pressure, probably contribute to the elevation of adrenaline secretion (Heymans & Neil, 1958; Malmejac, 1964).

The changes in the circulation in muscle observed in the rabbit during arterial hypoxia differ in several respects from the effects observed in other species. In man, but not in the rabbit, there is vasodilatation during relatively 'mild' hypoxia (P_{O_2} > 35 mm Hg). This vasodilatation in the muscle bed in man is clearly related to hyperventilation, as is also in part the rise in cardiac output (Clarke, 1952; Black & Roddie, 1958; McGregor, Donevan & Anderson, 1962). The rise in cardiac output at this level of hypoxia is smaller in the rabbit than in man (Korner, 1959; 1965*a*) and the development of tachycardia is slower. Since the local vasodilator effects of hypoxia on the muscle bed are similar in the two species the findings suggest that the overall level of sympathetic activity in the rabbit at this level of hypoxia, though slight (Chalmers *et al.* 1965), is greater than in man. The reflex accompaniments of hyperventilation appear to oppose the circulatory effects of chemoreceptor stimulation (Daly & Scott, 1962, 1963*a*, *b*; Daly & Hazzledine, 1963) more successfully in man and the dog, than in the rabbit (Korner, 1959; 1965*a*).

During moderate and severe arterial hypoxia, the changes in muscle blood flow in the rabbit have features in common with the responses of both man and the diving animals. The early constrictor response seen in the rabbit is also present in diving animals, but in the latter constriction is sustained throughout the period of hypoxia (Scholander, 1964). In man, on the other hand, this constrictor response is absent even during severe hypoxia, but the time course of the vasodilatation at this level of hypoxia is of similar, gradual onset to that observed in the rabbit (cf. 'non-fainters' of Anderson *et al.* 1946) and may well have a similar basis. The secretion of small quantities of adrenaline is probably an important mechanism in many terrestrial animals for the maintenance of high muscle blood flow during the marked increase in sympathetic activity which occurs during severe arterial hypoxia.

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