One important basic consideration in the study of circulatory regulation is an understanding not only of how any given component reacts but also the manner in which its activity will vary with changing circumstances. Central to the general thesis that nutrient supply is appropriate to the level of activity, at least in certain tissues, is the necessity for considering the means by which this is achieved.

One objective of this communication will be to present data in support of the position that the function of the baroceptor can, in general, be characterized by likening it to a voltage regulating element in a complex electronic system in which the numerous power-consuming elements independently vary their power output and requirements.

The numerous reflex circulatory effects of carotid sinus activity are aimed at maintaining the arterial pressure within relatively narrow limits. If one of these reflex effects, general peripheral vasoconstriction in response to carotid hypotension, were to be as effective in an active area as in one at rest, a vastly more complicated circuitry would be required to accomplish the same objective than if such were not the case.

The experiments to be described herein were aimed at a re-examination of the circumstances under which the vascular bed in muscle will or will not react to direct and reflexly engendered adrenergic stimulation and, further, an attempted correlation between the level of activity in that muscle and its responsiveness to such stimulation. Preliminary reports have been made.

Methods

Mongrel dogs were used throughout this study and received chloralose (60 mg./Kg.) and urethane (600 mg./Kg.) intravenously with intermittent subsequent doses as required. Following an initial dose of 75 mg. heparin intravenously, 10-mg. doses were given hourly to prevent clotting. Respirations were maintained constant by means of a Jefferson ventilator attached to a tracheal cannula. A constant slow intravenous infusion of blood was given as necessary to maintain arterial blood pressure within normal limits. It was occasionally necessary to restore the arterial pH with an intravenous infusion of 1.0 M NaHCO₃ buffer solution.

The experimental preparation used in this study is shown in figure 1. The lower aorta was cannulated just above the trifurcation and the flow led through a pair of 600-cc. Shipley-Wilson rotameters and back into the external iliac arteries, thus providing a measure of the flow to each leg. The lowest vertebral and common internal iliac arteries were ligated. Arterial pressure was recorded in a brachial artery with a Statham P23Gb strain gauge. Pressure was also frequently recorded in the tubing distal to each rotameter so that the pressure-flow relation could be determined for the vascular bed supplied by each rotameter. Occasionally, both lower legs were stimulated and the combined flow measured by a single rotameter; in this situation, a second rotameter was placed in a subclavian artery to measure flow in a control resting area distant from the stimulated area. Heart rate was monitored from the pressure pulse by a Waters cardiotachometer.

Sources of arterial and venous blood were provided for continuous recording of certain parameters: Arterial blood was obtained from a port in the lower aortic line, and venous blood was obtained from a T-cannula placed in either the left common iliac vein (hypogastric ligated) when the left leg alone was exercised or in the lower inferior vena cava when both legs were exercised. The arteriovenous oxygen difference (A-V O₂) of these samples was continuously recorded with a Guyton analyzer which was calibrated over its full range with more than 200 arterial and venous samples.
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analyzed by the technique of Van Slyke and Neill.\textsuperscript{5} Arterial and venous pO$_2$ were recorded by means of Clark\textsuperscript{6} polarographic electrodes which had been determined to have a linear calibration; pH was recorded with Beckman \textit{G} electrodes calibrated with known solutions of buffer. This blood line assembly was in a bath, the temperature of which was adjusted to that of the experimental animal. Blood was pumped at a constant rate of 35 ml./min. through each line of this assembly, and both lines returned to the left brachial vein. Thus, a constant arteriovenous shunt of 35 ml./min. occurred. All values were simultaneously recorded on an eight-channel direct-writing Sanborn oscillograph.

Simulated exercise was induced in either one or both extremities by means of electrical impulses delivered from a stimulator.* In essence, an electronic circuit changed the 60-cycle wall current into intermittent diamond-shaped impulses which could be delivered at a frequency from 0.5 to 3/sec. and at an amplitude of 0 to 40 volts. Impulses most commonly used were of 25 volts delivered at 2.5/sec, as monitored on an oscilloscope. These were delivered directly in the muscles via needle electrodes placed in the quadriceps. Either a needle or a flat, subcutaneous plate served as the indifferent electrode. The legs were usually restrained by ropes in the position shown in figure 1, allowing only slight motion of the leg with each stimulus. Occasionally, the legs were affixed to a T-bar at the end of the table by means of threaded pins through the paws. Other investigators have employed a similar method and an evaluation of the merits and limitations of this technique of simulating exercise is included in their papers.\textsuperscript{7-10}

*Developed by Frank Noble, M.E.E., Laboratory of Technical Development, National Heart Institute.
Mean arterial pressure (MAP) was obtained from the electronically integrated mean except where this was not available; in such instances, MAP was calculated as diastolic pressure + 1/3 pulse pressure. With the availability of continuously recorded A-VO\(_2\) difference as well as flow, \(O_2\) uptake could be calculated for any given point as the quotient:

\[
\frac{\Delta\text{A-VO}_2 (\text{volume per cent}) \times \text{flow (ml/min.)}}{100}
\]

**Results**

The following results were obtained from the 44 experiments which yielded data judged to be adequate for analysis of the particular experimental objective.

**EXERCISE RESPONSE**

Figure 2 shows a recording obtained before and during exercise of both lower extremities. A single rotameter measured the lower aortic flow (LAF), and a second rotameter measured the flow to the left forelimb (LSF). The arrow marks the onset of exercise in both hindlimbs. It can be seen that the flow in the exercising area (LAF) rose promptly and sharply and then leveled off at a high value. Systemic arterial pressure, except for a slight initial fall, remained essentially constant. After an initial increase, the flow in the resting forelimb (LSF) fell to below the resting level. A progressive widening occurred in the A-VO\(_2\) difference across the exercising area, and a concomitant drop in the pO\(_2\) of the venous blood coming from the hindlimbs took place. The pH of this blood initially rose for a short time and then exhibited a slow progressive fall.\(^{11}\) The responses shown in this figure are similar to those observed when exercise was produced under the experimental conditions described, but with the following exceptions: Arterial pressure sometimes rose or fell by varying amounts, the venous pH did not always show the initial rise before falling (fig. 9), and the relative contribution to \(O_2\) uptake of the increase in flow and the widening of the A-VO\(_2\) difference varied considerably with the frequency and intensity of stimulation.

Figure 3 shows data from one experiment.
which is representative of 29 studies in 13 preparations. The determination of \( O_2 \) uptake was made both at rest and at varying levels of exercise. PRU fell sharply with relatively slight increases of \( O_2 \) uptake and thereafter declined more gradually. The shape of the curve did not appear to be influenced by whether the increase in \( O_2 \) uptake was accomplished predominantly by an increase in flow or by a widening of the \( A-VO_2 \) difference. Directly comparable responses and curves were obtained from experiments in which the skin of the exercising extremity had been preliminarily removed and the paw excluded from the circulation.

**EFFECTS OF LUMBAR SYMPATHETIC CHAIN STIMULATION**

When the lumbar sympathetic chain was stimulated with a hindlimb at rest (first black bar in channel LLF of fig. 4, upper), a decrease in flow and an increase in resistance were seen. The resistance increase, induced by sympathetic stimulation, was markedly diminished while the limb was being exercised (second and third, and fourth and fifth black bars). As can be seen, the resistance increase is influenced by the intensity of exercise and

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EFFECTS OF NOREPINEPHRINE

Norepinephrine was injected into the tubing supplying the arteries to two extremities at rest in doses which produced a constrictor response in both. The same or sometimes even multiples of this dose did not evoke a constrictor response during exercise of one of these extremities while the control extremity still responded with the same constrictor response. It was felt, however, that the change in flow during exercise made such experiments difficult to interpret.

To test the response to infused norepinephrine more critically, a previously described time-dissociation technique was used. The preparation was one in which an infusion of norepinephrine was given intravenously at a constant rate, so that blood reaching each of the vascular areas under study contained the same concentration of the drug regardless of flow (fig. 5). Both hindlimbs were exercised; flow was measured in the lower aorta (LAF), as well as the left subclavian artery (LSF) which served as the resting control. At the arrow, the norepinephrine infusion was begun. The initial rise in arterial pressure was due both to the cardiac effect of norepinephrine and the effect on those vessels not supplied by either rotameter system. As a consequence of the arterial hypertension, the vascular beds of both the resting (LSF) and active extremities (LAF) showed an initial flow increase, since blood containing the drug had not yet traveled through the rotameters and arrived at these vascular beds. When blood containing the norepinephrine had traversed both rotameter circuits, it caused a marked vasoconstriction in the resting area (LSF), but no constrictor effect in the vessels of the active muscular area (LAF), in spite of the fact that much more norepinephrine was being presented to it per unit of time.

EFFECTS OF CENTRAL VAGUS STIMULATION

Figure 6 shows typical results from the type of experiment in which sympathetic stimulation, reflexly induced by central vagus stimulation, was examined. With both lower extremities at rest, arterial hypertension and hindlimb vasoconstriction took place during central vagus nerve stimulation. When the left hindlimb was then exercised, the flow in it appeared to be essentially pressure-dependent when the central vagus was again stimulated while the contralateral resting extremity retained its control response. At rest, central vagal stimulation reduced O2 uptake; during exercise, the same stimulus produced an increase in O2 uptake. The reciprocal of the
results shown in figure 6 was obtained when central depressor vagal stimulation was performed.

EFFECTS OF CHANGING CAROTID PRESSURE

Studies were done in which a comparison was made of the flow response to changing carotid pressure at rest and during exercise. An example of this is shown in figure 7. Lowering carotid sinus pressure at rest is shown in panel A and during exercise in panel B. At rest, there was an increase in arterial pressure, tachycardia, and a fall in blood flow. A narrowing of the A-VO₂ difference occurred. In contrast, when carotid sinus pressure was lowered while the hindlimbs were exercising, accompanying the increase in arterial pressure and tachycardia, there was a marked increase in blood flow. A narrowing of the A-VO₂ difference also occurred in this instance. At rest, lowering carotid sinus pressure resulted in a decrease in O₂ uptake. When carotid sinus pressure was lowered during exercise, there was an increase in O₂ uptake. The muscle contractions were unequivocally weaker by visual observation during the periods of high carotid sinus pressure and strengthened promptly when blood flow and O₂ uptake rose during low carotid sinus pressure. It is of note that, in this type of experiment, lowering carotid sinus pressure produced a narrowed A-VO₂ difference across the legs both at rest and during exercise, although perhaps for different reasons, and that the different changes in flow in the two situations accounted for the difference in the direction of change in the O₂ uptake. One other finding should be noted regarding the changes observed in this type of experiment. At rest, lowering carotid pressure most frequently lowered flow, as seen in figure 7, but in other instances flow was maintained or was slightly elevated at least initially, as shown in figure 8.

Figure 9 also shows the effects of carotid sinus activity on an exercising extremity. In this experiment, exercise was begun (arrow) while there was a high systolic and pulse pressure in the carotid sinuses. In the exercised extremity (LLF) flow rose, the A-VO₂ difference widened, and venous pO₂ and pH fell. After a steady state was attained, pressure in the carotid sinuses was lowered. This produced a further flow increase, narrowing of
FIGURE 8
Effects of lowering carotid arterial pressure at rest. Carotid arterial pressure in mm. Hg (CP); systemic arterial pressure in mm. Hg (AP); left hindlimb flow in ml./min. (LLF); right hindlimb flow in ml./min. (RLF). Paper speed was 0.5 mm./sec.

the A-VO₂ difference, and a rise in venous pO₂. O₂ uptake changed little. The declining venous pH became level. As can be seen, these changes were found to be sustained, reversible, and consistent. The strength of the contractions did not appear to change with changing carotid pressure in this experiment.

The geometrical considerations developing from the law of Laplace, plus certain of the limitations implicit in basing conclusions solely on resistance calculations, made it advisable to examine the total obtainable relation between pressure and flow before and during carotid hypotension at rest and during exercise. It was largely for these reasons that the donor dog isolated leg preparation was employed. Representative data from one of the four experiments of this type are shown in figure 10. It can be seen that, at any given flow, pressure was substantially higher in the limb at rest when the carotid arteries were occluded but that this was not observed when the limb was exercised.

The foregoing data indicated that the blood vessels of an exercising extremity behaved as if they had been partially or completely deprived of their sympathetic supply. This position was strengthened by making a direct comparison of the reactions in a sympathectomized extremity with one in which the sympathetics were intact. In figure 11, at rest (panels A and C), raising carotid pressure produced a pressure-dependent decrease in flow accompanying the systemic arterial hypotension on the surgically sympathectomized side; flow was slightly increased on the intact side. During exercise, elevating the carotid pressure produced the same pressure-dependent flow pattern on both sides.

Figure 12 indicates that the responsiveness of the vascular bed of an extremity to the reflex effects of carotid sinus stimulation is gradably related to the O₂ uptake in that extremity. The response to both raising and lowering carotid arterial pressure was observed to approach zero as O₂ uptake was increased. The major part of the diminished responsiveness occurred with a small increase in O₂ uptake above the resting level. This finding was consistent and noteworthy.

Discussion

Although the type of stimulation used in this study produces a strong muscular contraction, it obviously does not mimic the contraction of voluntary exercise. It should be emphasized that the relative contributions to the increased O₂ uptake of the increased flow and the widening of the A-VO₂ difference vary with the specific parameters of muscular contraction produced and are unlikely to be directly comparable to the phenomena observed during normal exercise. However, since the muscular activity produced a substantial increase in local O₂ uptake, it was felt that certain helpful observations and correlations could be made.

The possibility was considered that the Lovén reflex could explain the results obtained. This spinal reflex produces vasodilation locally in a stimulated area and also arterial hypertension. Both the frequent
Effects of lowering carotid arterial pressure during exercise. Carotid arterial pressure in mm. Hg (CP); systemic arterial pressure in mm. Hg (AP); left hindlimb flow in ml./min. (LLF); right hindlimb flow in ml./min. (RLF); heart rate in beats/min. (HR); arteriovenous O\textsubscript{2} difference in volumes per cent across left hindlimb (A-\textit{V}O\textsubscript{2} [LL]); directional changes in oxygen tension of left hindlimb venous blood (\textit{V}pO\textsubscript{2} [LL]); pH of left hindlimb venous blood (\textit{pH} [LL]). Hematocrit = 55.0 per cent. Arterial pH = 7.44. At arrow, exercise begun in left hindlimb; right hindlimb at rest throughout. During high carotid sinus pressure, LLF A-\textit{V}O\textsubscript{2} difference = 13.7 volumes per cent, and LLF O\textsubscript{2} uptake = 23.8 ml./min.; during low carotid sinus pressure, LLF A-\textit{V}O\textsubscript{2} difference = 10.9 volumes per cent, and LLF O\textsubscript{2} uptake = 27.0 ml./min. Paper speed was 0.5 mm./sec.

absence of hypertension with the onset of muscular stimulation, and the fact that the vascular bed of an extremity to which the autonomic supply had been surgically interrupted still exhibited the same decreasing responsiveness to sympathetic stimulation when exercise was increased (fig. 4, lower), excluded the Lovén reflex from consideration as the causative mechanism in such experiments.

The data presented above confirm the numerous studies showing that vasoconstriction, resulting either from direct stimulation of the sympathetic or the administration of norepinephrine, is diminished during muscular activity.\textsuperscript{17-20} They also establish two additional facts. The first is that the major diminution in the calculated resistance to flow occurs at that level of exercise which produces a relatively small increase in O\textsubscript{2} uptake and that thereafter, with further substantial increases in O\textsubscript{2} uptake, relatively little further decrease in calculated vascular resistance takes place (fig. 3). The second fact of importance (which would appear to be related to the first) is that

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Pressure-flow curves in an isolated perfused hindlimb. The connected open circles represent the pressure-flow curve with the limb at rest; the solid circles show the values obtained while the common carotid arteries were occluded, also with the limb at rest. The connected open triangles show the pressure-flow curve obtained during exercise with the carotid arteries open; the solid triangles show the values obtained during exercise with the carotid arteries occluded.

Whatever the mechanism which produces the diminished responsiveness to sympathetic stimulation during exercise, this mechanism also exerts the major portion of its potential influence with relatively small increases of \( O_2 \) uptake when exercise is induced (figs. 4, lower, and 12). The shape of the curves describing both the resistance changes and the responsiveness changes lends support to the supposition that the observed phenomena are concentration dependent and augment the opportunity for future biochemical correlation.

Rein and his collaborators, using a thermostromuhr, investigated the reactions of vessels in resting and exercising areas and studied the effects of reflexly induced vasomotor impulses to ascertain their effect on the level of local \( O_2 \) uptake. With bilateral common carotid occlusion, Rein observed a rise in systemic arterial pressure, a decrease in blood flow, \( A-V_O_2 \) difference, and the calculated \( O_2 \) uptake of the hindlimbs during rest. The data presented herein, in general, confirm Rein’s observations on the response of the resting extremity to carotid hypotension, although, as noted above, in some experiments limb flow remained the same or rose slightly, as found by Charlier and Vandermussen. One outstanding divergence from Rein’s findings apparent in our data is that, in the exercising extremity, during carotid hypotension blood flow rose more than in Rein’s reported data and frequently resulted in a marked increase in \( O_2 \) uptake.

At rest, marked hyperperfusion of an extremity apparently does not result in any substantial increase of \( O_2 \) uptake or consumption, even though \( O_2 \) availability is, of course, increased; the \( A-V_O_2 \) difference narrows (W. N. Stainsby and A. B. Otis, personal communication). During exercise, however, an increased blood flow due to an increased perfusion pressure can be thought to have three important consequences. The first is that the increased \( O_2 \) availability tends to return the \( A-V_O_2 \) difference and venous \( p_O_2 \) toward their resting values (fig. 9). The second consequence is that, by virtue of the narrower
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Δ-VO₂ difference and higher venous pO₂, a larger O₂ availability reserve for a further increase of the activity of that extremity is maintained. Finally, it can be supposed that, when the activity of an extremity is such as to lead to substantial oxygen debt, the increased O₂ availability and O₂ uptake due to a higher perfusion pressure limit the rate of development of debt to a level lower than that which would occur if the perfusion pressure were low. This position is supported by the findings in those experiments in which there was visible weakening of contractions when carotid pressure was elevated (fig. 7) and their becoming stronger again when carotid pressure was lowered, the latter resulting in an increased blood flow and O₂ uptake. It seems fair to assume that under such circumstances the O₂ utilization of the exercising limb, as well as its O₂ uptake, was increased during the period of carotid hypotension.

The other simultaneously occurring reflex effects of carotid sinus hypotension are of interest in this connection. The effect on heart rate and resistance in visceral and resting areas,27 the effect on venous tone,28-30 and the recently described reflex influence of carotid sinus pressure on atrial and ventricular myocardial contractility31 are all relevant; each tends to promote a reconstitution of arterial pressure when carotid sinus pressure is lowered. When viewed in relation to the data presented above, it seems likely that these reflex effects of the carotid sinus contribute in an important and unified manner to the ability of the organism to maintain an appropriate distribution of blood flow in varying states. It appears that the baroreceptor functions much like a voltage-regulating element which insures an adequate current flow to a system-complex of power-consuming elements when, in such a system, the power requirements of each of these elements can vary independently and in opposite directions.81,82

Summary

The effects of both direct and reflexly induced increases in sympathetic activity on the blood flow to an extremity at rest and during muscular activity have been studied. When the O₂ uptake of an extremity is increased during muscular activity, its vascular resistance falls sharply with a small increase in O₂ uptake and thereafter declines only slightly. The responsiveness of a vascular bed to adrenergic stimulation diminishes sharply with a small increase in O₂ uptake and thereafter diminishes only slightly. The role of the carotid sinus as a sense organ which helps to regulate blood flow to the various tissues of the organism in accordance with their varying metabolic requirements in accordance with their varying metabolic requirements rather than one which acts only as a receptor that helps to safeguard flow to the vital organs has been discussed.

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Functional Sympatholysis During Muscular Activity: OBSERVATIONS ON INFLUENCE OF CAROTID SINUS ON OXYGEN UPTAKE
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