

# Factors That Influence Blood Flow in Skeletal Muscle and Skin

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CARDIOVASCULAR RESPONSES are often complex, with profoundly different responses in various vascular beds. These complex responses can be better understood if we first consider those factors which control blood flow to each vascular bed. This review, therefore, describes some of the factors which regulate blood flow in skeletal muscle and skin in physiologic and pathologic states and points out some of the unique features of these vascular beds.

Blood vessels in skeletal muscle and skin play an essential role in regulation of circulation during exercise and in thermoregulation. They also are involved in compensatory adjustments to hemodynamic stresses and in pathologic states. Because these vascular beds are readily accessible for study in man as well as in experimental animals, an imposing body of knowledge has accumulated.

Several concepts are emphasized: First, differences in vascular structure, in innervation, in responses to humoral stimuli, and in metabolism permit specialized functions in different vascular beds. For example, the presence of arteriovenous shunts in skin facilitates heat dissipation, while differences in capillary density and innervation of red and white muscle fibers are related to their metabolism and function. A second concept relates to the vascular segments which control vascular resistance and blood flow. As is generally known, arterioles account for the largest portion of vascular resistance. Recent studies indicate that large arteries also regulate vascular resistance, particularly during reflex stimuli, and venules contribute importantly to vascular resistance.

A third concept relates to distribution of blood flow within an organ. Not only do

stimuli cause different responses in different vascular beds, so that there is a redistribution of blood flow within the body, but appropriate stimuli can also cause redistribution of blood flow within an organ. This effect can be mediated through arteriovenous shunts or precapillary sphincters, and can dramatically alter oxygen consumption of an organ with little change in vascular resistance.

Four general areas are considered: 1) regulation of blood flow in skeletal muscle; 2) regulation of cutaneous blood flow; 3) effects of pathophysiologic states on muscle and skin flow; 4) effects of anesthetics on blood flow.

## Regulation of Blood Flow in Skeletal Muscle

### GENERAL CONSIDERATIONS

Skeletal muscle constitutes about 40 per cent of the total body weight in man. The cardiovascular system might justifiably regard the large mass of resting skeletal muscle as a sleeping giant. At rest, blood flow to muscle is about 1 liter/min; strenuous exercise provides the most severe cardiovascular load which man experiences, as blood flow to muscle may reach 20 to 30 liters/min. It is clear that skeletal muscle has an enormous vasodilator capacity.

There are two types of muscle fibers, red (tonic) and white (phasic), which are present in various proportions in different muscles. Tonic fibers have characteristics which allow sustained contractions and are numerous in muscles involved in maintenance of posture. Phasic fibers predominate in fast-contracting muscles. Resting blood flow, capillary density, and innervation appear appropriately related to the metabolism and function of these muscles.<sup>1</sup> Tonic muscle depends predominantly on aerobic metabolism and receives three times as much blood

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flow per gram as phasic muscle, which depends on glycolytic metabolism and can accumulate an oxygen debt. Innervation and reflex responses are different in the two types of fibers; for example, the "defense" reaction, induced by hypothalamic stimulation in animals, increases blood flow to phasic fibers by almost threefold without altering flow to tonic fibers.<sup>2</sup>

In addition to supplying substrate, vessels in skeletal muscle play an important role in regulation of blood pressure and distribution of blood flow. Vasodilatation in muscle protects against hypertension; vasoconstriction compensates for arterial or venous hypotension and also provides a mechanism for redistribution of blood flow to organs which are more vulnerable to ischemia than skeletal muscle.

Blood flow to skeletal muscle is determined by vascular resistance in muscle and arterial pressure. Vascular resistance is regulated predominantly by arterioles, but recent studies indicate that large arteries as well as arterioles are important in regulation of vascular resistance, particularly during reflex stimulation. Electrical stimulation of sympathetic nerves causes constriction of large arteries in the forelimb of the dog.<sup>3</sup> The "diving reflex" results in constriction of large arteries in both experimental animals and man.<sup>4,5</sup> Constriction of large arteries provides an efficient mechanism for diversion of blood flow away from the large vascular beds of the extremities, which results in conservation of oxygen and diversion of flow to central organs.

Precapillary sphincters do not contribute significantly to peripheral vascular resistance, but they play a major role in directing blood flow through nutritional capillaries. They are regulated by humoral factors and, more importantly, by tissue metabolites. Venules may contribute a significant proportion of total resistance (10–25 per cent) but their major influence is on capillary pressure and filtration. Studies in animals indicate that small veins in skeletal muscle are rather poorly reactive to neurogenic and humoral adrenergic stimuli, and have thinner walls with fewer smooth muscle layers than small veins draining cutaneous beds.<sup>6</sup>

## TECHNIQUES

Numerous techniques have been used to study blood flow to muscle. In experimental animals, responses of perfused limbs or changes in iliac blood flow (measured with a flowmeter) have been used to evaluate vascular responses in skeletal muscle. A limitation of these techniques is that they reflect responses in skin as well as muscle. Better techniques for studying blood vessels in muscle include perfusion of an isolated muscle, isotope clearance techniques, and measurement of venous outflow from muscles. In man, muscle or limb blood flow can be measured by isotope (for example, <sup>133</sup>Xe) clearance, dye-dilution techniques, measurement of deep-vein oxygen tension, and venous occlusion plethysmography of a limb.

Several recent studies concerning effects of anesthetic agents have equated forearm blood flow, measured with limb plethysmography, with muscle blood flow. Flow to the forearm goes to both skin and muscle. If an anesthetic or other stimulus causes profound vasodilatation in skin and moderate vasoconstriction in muscle, the result might be an increase in total forearm flow; if the increase in forearm flow were interpreted as indicating an increase in flow to muscle, the conclusion would be incorrect. The limitation of limb plethysmography for measurement of muscle flow is serious when skin and muscle of the limb respond in opposite directions.

We should consider one other point in relation to techniques for determining vascular resistance in muscle. Plethysmography and dye-dilution techniques in man and perfused muscle preparations in animals reflect total vascular resistance in an organ or a region. These techniques are adequate in evaluating regulation of blood pressure and regional distribution of blood flow. If one wishes to know capillary or "nutritional" blood flow, however, these methods are not adequate and one must resort to other techniques, such as rubidium clearance or indirect evaluation of aerobic metabolism. An estimate of a change in capillary surface area would provide some estimate of nutritional flow and the state of precapillary

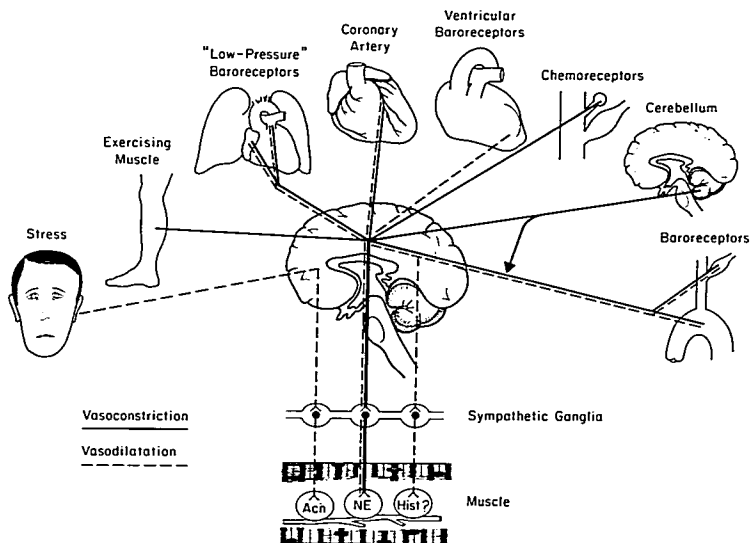


FIG. 1. Major reflex pathways to blood vessels in skeletal muscle. Some reflexes (such as from chemoreceptors) activate vasoconstriction only and some (such as stress) activate vasodilatation only; other reflexes (from "low-pressure," carotid, and aortic baroreceptors) activate either constriction or dilatation, depending on the nature of the afferent stimulus. The major efferent pathway releases norepinephrine (NE) from nerve endings on vessels in muscle: vasoconstriction occurs during activation of this adrenergic pathway, vasodilatation occurs during withdrawal of adrenergic tone. The cholinergic pathway, which releases acetylcholine (ACh), produces vasodilatation when activated during stress. Release of histamine (Hist) may contribute to vasodilatation during stimulation of baroreceptors. These reflexes produce direct effects on vessels in muscle and in addition may interact with other reflexes, for example, reflexes from the cerebellum may modulate the baroreceptor reflex.

sphincters and may be obtained by measuring capillary filtration coefficient.<sup>7</sup> An important point to recognize is that stimuli which cause similar increases in total blood flow to an organ may have very different effects on nutritional blood flow.<sup>8,9</sup>

#### NEUROGENIC FACTORS

Sympathetic adrenergic fibers provide the neural mechanism which mediates reflex vasoconstriction. The extent of innervation and the catecholamine content of vessels correlate with their responsiveness to stimulation of sympathetic nerves<sup>10</sup> but not with the

level of sympathetic tone. Sympathetic tone is a function of neural discharge rate and is best evaluated by measurement of norepinephrine turnover or circulating dopamine  $\beta$  hydroxylase.<sup>11</sup>

In contrast to the presence of only one neural noradrenergic vasoconstrictor pathway, there are several mechanisms which may contribute to reflex vasodilatation in muscle (fig. 1). First, withdrawal of adrenergic constrictor tone is a major mechanism for vasodilatation such as that seen during stimulation of arterial baroreceptors (by elevations of arterial pressure). Second, "active" vaso-

dilatation (in contrast to withdrawal of adrenergic constrictor tone, which may be considered "passive") mediated by a sympathetic cholinergic pathway has been demonstrated in a variety of situations. Third, it has been reported that vasodilatation may occur in the hindlimb of an experimental animal by a histaminergic mechanism, especially during stimulation of baroreceptors.<sup>12,13</sup> A histaminergic vasodilator pathway has not yet been demonstrated in man. Fourth, neural release of norepinephrine can result in slight vasodilatation in skeletal muscle by stimulating beta-adrenergic receptors,<sup>14</sup> but this effect is masked by the simultaneous vasoconstrictor effect of norepinephrine.

#### Reflex Vasoconstriction in Muscle

Skeletal muscle can incur an oxygen debt and is less vulnerable to ischemia than the myocardium or the brain. Therefore, reflex vasoconstriction in muscle in response to numerous stimuli is a protective mechanism which tends to maintain arterial pressure and perfusion of vital organs. Reflex vasoconstriction in muscle has been demonstrated in

animals during chemoreceptor stimulation,<sup>15</sup> in resting muscle during exercise of other muscles,<sup>16</sup> during activation of the baroreceptor reflex by arterial hypotension,<sup>17</sup> and during coronary occlusion.<sup>18</sup>

Recent findings in man modify the earlier concept<sup>19</sup> that receptors which are located in the atria and pulmonary vessels have minimal reflex effects on vessels in muscle. Lower body negative pressure, a reflex vasoconstrictor stimulus which at low levels of suction activates "low-pressure" but not arterial baroreceptors,<sup>20</sup> has been shown to have profound reflex vascular effects on muscle<sup>20,21</sup> (fig. 2). These findings suggest that vasoconstriction in muscle is an important compensatory mechanism during upright posture which, like lower body negative pressure, activates reflexes triggered by "low-pressure" baroreceptors.

Carotid-artery compression in man, which decreases pressure in the carotid sinus baroreceptors, might be expected to cause reflex vasoconstriction in muscle. This, surprisingly, is not the case. Carotid compression which is sufficient to cause reflex hypertension causes little change in forearm vascular re-

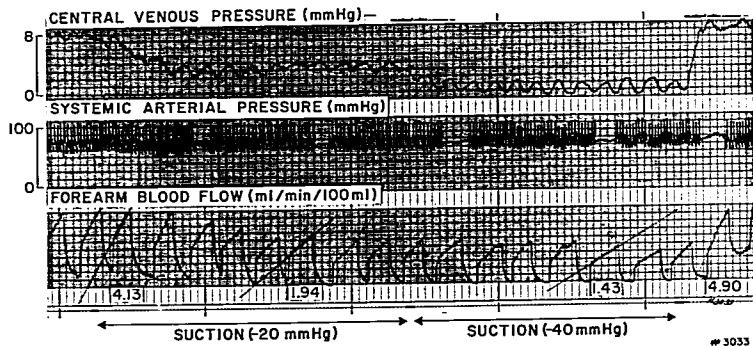


FIG. 2. Responses to lower body negative pressure (at  $-20$  and  $-40$  mm Hg). Forearm blood flow was measured by plethysmography. Slopes of the increase in forearm volume were obtained during intermittent venous occlusion and were used to calculate forearm blood flow. Suction at  $-20$  mm Hg decreased central venous pressure and forearm blood flow, with little change in heart rate or arterial pressure. It appears that, at this low level of suction, arterial baroreceptors were not affected and the forearm vasoconstriction was initiated by "low-pressure" baroreceptors. At higher levels of suction (e.g., at  $-40$  mm Hg), arterial baroreceptors as well as "low-pressure" baroreceptors may initiate forearm vasoconstriction. (Reprinted with permission from *J Clin Invest.*<sup>22</sup>)

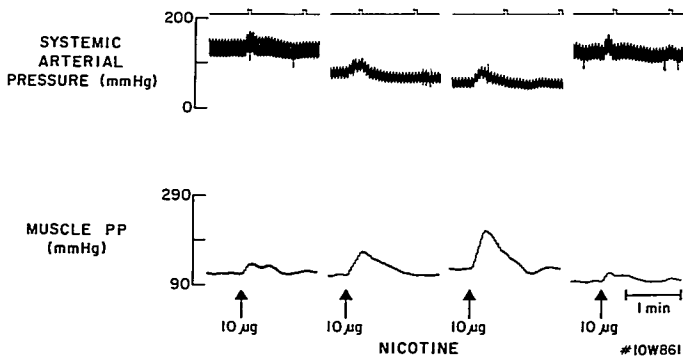


FIG. 3. Effects of hemorrhagic hypotension on responses to chemoreceptor stimulation. Muscle perfusion pressure (*lower panels*) was recorded during perfusion of the gracilis muscle of a dog at constant flow; because flow was constant, an increase in perfusion pressure indicates vasoconstriction. This record shows responses to repeated injections of 10  $\mu$ g nicotine into the carotid artery to stimulate carotid chemoreceptors. When systemic pressure was lowered by bleeding, vasoconstrictor responses to chemoreceptor stimulation in the muscle were augmented (*middle two panels*). The chemoreceptor reflex was potentiated during hypotension. (Reprinted with permission from J Clin Invest.<sup>29</sup>)

sistance.<sup>23</sup> This study suggests that in man, unlike animals,<sup>17</sup> hypotension in carotid baroreceptors may have little effect on vessels in muscle. In man, exercise causes vasoconstriction in resting muscle.<sup>24</sup>

#### Reflex Vasodilatation in Muscle

Withdrawal of sympathetic adrenergic constrictor tone causes vasodilatation in skeletal muscle in animals during stimulation of arterial and ventricular baroreceptors.<sup>25-27</sup> Because of the enormous vasodilator capacity of muscle, this is an effective mechanism for compensating for acute arterial hypertension. This mechanism is also important in the response to ventricular stretch, which may be activated during myocardial ischemia,<sup>27,28</sup> in patients with aortic stenosis,<sup>29</sup> and in heart failure.

In man, elevation of the legs raises venous pressure and results in withdrawal of sympathetic tone in forearm vessels, presumably by stretch of low-pressure baroreceptors.<sup>30</sup> This effect is opposite to that which occurs with pooling of blood in the legs.<sup>20</sup>

Injection of nicotine or veratridine into a coronary artery produces reflex hypotension and vasodilatation in skeletal muscle by activation of the Bezold-Jarisch reflex. This reflex is not activated by hypoxia and hypercapnia, which suggests that distal coronary arteries and the myocardium do not contain true chemoreceptors.<sup>31</sup> This reflex is nevertheless of clinical importance since it can be activated by injection of contrast medium during coronary arteriography.<sup>32</sup>

Active vasodilatation in muscle which is mediated by sympathetic cholinergic fibers has been demonstrated in experimental animals during the defense reaction in response to hypothalamic stimulation.<sup>33</sup> Similar cholinergic vasodilatation occurs in man during emotional stress,<sup>34</sup> during the Valsalva maneuver and application of ice to the forehead after adrenergic blockade, and possibly in diabetic patients with postural hypotension.<sup>35</sup> This suggests that the "defense reaction" of hypothalamic stimulation in animals may have important physiologic counterparts in man.

### *Interaction of Reflexes*

Recent studies in animals have demonstrated that there are important interactions of reflexes within the central nervous system. The "defense reaction" to hypothalamic stimulation is suppressed by simultaneous cerebellar stimulation.<sup>36</sup> Orthostatic reflexes in the cat appear to be profoundly affected by the cerebellum and the vestibular apparatus.<sup>37</sup> This study suggests that, in experimental animals, the vestibular apparatus acts in concert with the baroreceptors to initiate vasoconstriction in muscle and participate in maintenance of arterial pressure during upright posture. This hypothesis has not yet been tested in man.

Studies in experimental animals indicate a profound interaction between chemoreceptor and baroreceptor reflexes.<sup>38</sup> During hypotension the chemoreceptor reflex causes marked vasoconstriction in muscle and hypertension (fig. 3). We speculate that potentiation of the chemoreceptor reflex during hypotension would promote a favorable redistribution of blood flow when oxygen availability is limited by hypoxemia and hypotension.

Activation of ventricular baroreceptors by distending the left ventricle produces reflex vasodilatation and hypotension.<sup>38</sup> One would expect arterial hypotension and the arterial baroreceptor reflex to attenuate the reflex vasodilatation during activation of ventricular baroreceptors. The attenuation is minimal, however, which suggests that activation of ventricular baroreceptors may override and suppress the baroreceptor reflex initiated by arterial hypotension.

### HUMORAL FACTORS

#### *Vasoconstrictor Compounds*

Cardiovascular and metabolic effects of catecholamines are produced by activation of adrenergic receptors. Pharmacologic differentiation of receptors is based on differences in relative potency of different catecholamines and demonstration of selective receptor antagonists.<sup>39</sup> Adrenergic receptors are currently classified as: 1) alpha receptors, which produce vasoconstriction and are blocked by

phenolamine or phenoxybenzamine; 2) beta-1 receptors, which activate beta receptors in myocardium but not in peripheral vessels, and are blocked by practolol<sup>40</sup>; 3) beta-2 receptors, which activate beta receptors in peripheral vessels but not myocardium. Propranolol blocks both beta-1 and beta-2 receptors.<sup>40</sup>

Catecholamines produce different responses in various vascular beds. Differences in responses to a drug may be ascribed to different affinity for receptors in various vascular beds and to differences in number of receptors present in each bed. These factors may account for different responses to norepinephrine and epinephrine in various vascular beds.

Norepinephrine activates predominantly alpha and beta-1 adrenergic receptors and causes vasoconstriction in muscle, but the constriction is less than in some other vascular beds, such as skin<sup>40</sup> and kidney. The population of alpha adrenergic receptors may be less in vessels of skeletal muscle than in skin.<sup>40</sup> Epinephrine, which activates alpha, beta-1, and beta-2 receptors, is a powerful vasodilator in skeletal muscle of man<sup>41</sup> and a vasoconstrictor in skin and kidney.

Normally the level of circulating catecholamines is not sufficient to affect blood flow in muscle. In some circumstances, such as shock, pheochromocytoma, vasovagal syncope, and severe postural hypotension, blood levels of catecholamines may be elevated sufficiently to affect blood vessels in muscle.

Two non-adrenergic hormones which have intense vasoconstrictor effects on skeletal muscle are vasopressin (antidiuretic hormone) and angiotensin.<sup>42-44</sup> Vasopressin is released in high concentrations during general anesthesia, cardiopulmonary bypass, and hypotension.<sup>45</sup> The renin-angiotensin system may contribute to normal homeostasis, to compensatory adjustments in hypotension and to the pathogenesis of renovascular hypertension. In addition to the direct vasoconstrictor effects of vasopressin and angiotensin, these hormones contribute to further constriction by potentiating responses to norepinephrine or facilitating the release of endogenous

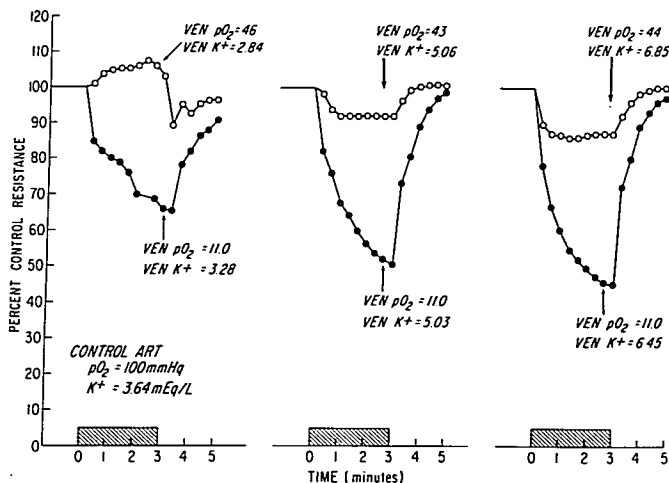


FIG. 4. Interaction of vasoactive substances in regulation of vascular resistance in skeletal muscle. Resistance was plotted as percentage of control. When venous  $P_{O_2}$  was normal ( $\circ-\circ-\circ$ ), hyperkalemia produced mild vasodilatation. When venous  $P_{O_2}$  was reduced ( $\bullet-\bullet-\bullet$ ), hyperkalemia produced profound vasodilatation. Studies such as this suggest that combinations of vasoactive substances may account for vasodilatation during exercise and ischemia. (Reprinted from *Circ Res*<sup>24</sup> by permission of the American Heart Association, Inc.)

catecholamines during neural stimulation.<sup>19,16,17</sup>

precapillary "sphincters" may increase both total and nutritional flow.

#### Vasodilator Compounds

Skeletal muscle is very responsive to humoral vasodilator stimuli. Isoproterenol, nitroglycerin, phentolamine, acetylcholine, and nitroprusside cause profound vasodilatation in muscle. These stimuli have been shown to increase total muscle blood flow in experimental animals, but they may have differing effects on nutritional blood flow in muscle, as reflected by differing effects on oxygen consumption of muscle.<sup>18</sup> The differing effects on nutritional blood flow may reflect different sites of vasodilator action. For example, dilatation of arteriolar resistance vessels may increase total flow with little change in nutritional flow, while opening of

#### METABOLIC FACTORS

The ability of blood vessels to regulate blood flow independently of systemic neurogenic and humoral factors is called autoregulation of blood flow. Muscle has a limited autoregulatory capacity: less than kidney, heart, and brain, but more than skin. Two theories have been suggested to explain autoregulation, the pressure theory and the metabolic theory. The pressure theory proposes that stretching vascular smooth muscle during a rise in pressure initiates contraction in the vascular muscle and thereby limits blood flow. The metabolic theory proposes that the rate of oxygen delivery or accumulation of metabolites resulting from a change

in arterial pressure affects arteriolar resistance and blood flow.

Numerous studies have sought to identify factors which are important in local regulation of blood flow in muscle and which might account for the hyperemia of exercise and following ischemia. Release of adenosine,<sup>48</sup> hypoxemia,<sup>49</sup> hyperosmolarity, hyperkalemia, and combinations of some of these factors<sup>50</sup> have been suggested as important local mediators of hyperemia. It seems likely that hyperemia in skeletal muscle is not the result of release of one major factor, but instead is caused by multiple factors (fig. 4).

Acute systemic hypoxemia in man causes vasodilatation in the forearm,<sup>52</sup> even though studies in animals indicate that stimulation of chemoreceptors by hypoxemia produces reflex vasoconstriction in muscle.<sup>54</sup> We speculate that vasoconstriction in muscle (induced by chemoreceptor stimulation) is attenuated by hypoxemia itself, which is known to attenuate reflex vasoconstriction,<sup>53</sup> or by activation of pulmonary stretch receptors during the hyperventilation caused by hypoxemia.<sup>54</sup> The forearm vasodilatation during hypoxemia in man appears to be the result of a humoral rather than a neurogenic mechanism, since the vasodilatation occurs in the nerve-blocked as well as in the intact forearm.<sup>52</sup> The vasodilatation is not the result of release of catecholamines during hypoxemia<sup>55</sup> and is not the result of hypocapnia which may accompany hypoxemia.<sup>56</sup> The vasodilatation may be due to a local effect of hypoxemia on arterioles<sup>57</sup> or to local release of a vasodilator substance.

Hypercapnia causes vasodilatation in muscle. This effect appears to be related to the change in  $P_{CO_2}$  rather than the simultaneous acidosis.<sup>58</sup>

#### PHYSICAL FACTORS

Vessels in skeletal muscle are not important in thermoregulation. Local or total-body heating in man causes minimal or no vasodilatation in skeletal muscle.<sup>59</sup> Local cooling increases muscle blood flow in experimental animals.<sup>60</sup>

Blood flow in muscle, as in other vessels, is affected by viscosity of blood. Polycythemia, hyperlipidemia with excessive chylomicrons,

or macroglobulins in Waldenström's macroglobulinemia increase blood viscosity substantially and increase resistance to blood flow.

### Regulation of Cutaneous Blood Flow

#### GENERAL CONSIDERATIONS

Skin in man weighs about 2 kg. Total body skin blood flow ranges from about 20 ml/min in the cold to 8 l/min during maximal heating. Clearly the most important function of cutaneous vessels is thermoregulation; other stimuli, such as the baroreceptor reflex, may affect cutaneous vessels, but when blood flow to skin is increased by a heat load, cutaneous vessels become minimally responsive to reflex stimuli.<sup>61,62</sup>

Cutaneous vessels have unusual features which serve their thermoregulatory function. One feature is the presence of arteriovenous shunts, particularly in the fingers, toes, and ears. Because of the large surface area of skin in these sites, patency of the shunts favors heat dissipation. A second feature is the presence of sweat glands. Neurogenic activation of sweat glands apparently causes local release of bradykinin<sup>63</sup> and vasodilatation.

In considering factors which affect blood flow to skin, we should point out again that constriction of arteries as well as arterioles affects blood flow.<sup>3-5</sup> In addition, small veins may contribute significantly to regulation of blood flow in skin. Studies in experimental animals indicate that venous constriction during sympathetic nerve stimulation or infusions of norepinephrine contributes significantly to increases in vascular resistance.<sup>64</sup>

#### TECHNIQUES

Techniques to study cutaneous vessels in animals include perfusion of a paw, measurement of venous effluent from a paw, and microsphere techniques. In man, skin blood flow can be estimated by venous occlusion plethysmography in a finger or hand or by isotope clearance techniques. There is no serious objection to using finger or hand flow as a reflection of skin flow, if one accepts limitations on quantitative accuracy



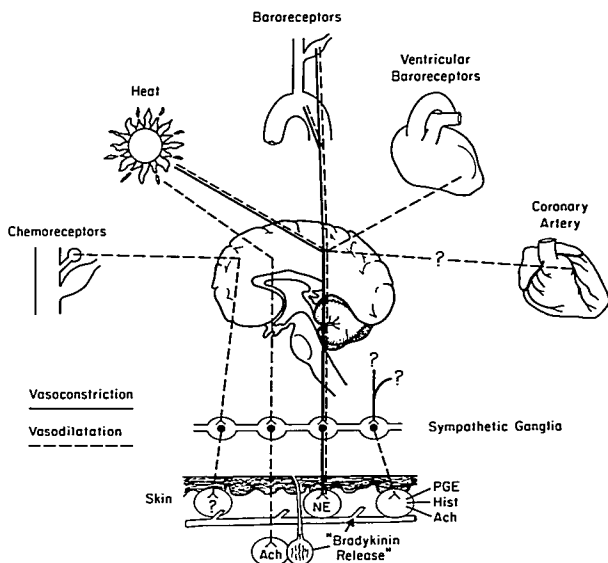


FIG. 5. Several reflexes which affect vessels in skin. Chemoreceptor stimulation causes active vasodilatation by release of an unidentified neurotransmitter. Heat activates a cholinergic pathway to sweat glands; the sweat glands release a bradykinin-forming enzyme which activates bradykinin which, in turn, produces vasodilatation. An important efferent pathway is adrenergic (*i.e.*, releases norepinephrine); cutaneous vasodilatation, which has been demonstrated in experimental animals during coronary occlusion, may be produced by withdrawal of adrenergic vasoconstrictor tone. In animals, stimulation of sympathetic nerves causes cutaneous vasodilatation, which appears to be mediated by release of prostaglandin E, histamine, and acetylcholine; reflexes that can activate these efferent pathways to cutaneous vessels have not yet been identified.

imposed by two considerations: First, arteriovenous shunts are particularly common in the fingers, so cutaneous vessels of the finger are more responsive to vasoactive stimuli than cutaneous vessels in other areas. Second, the hand is only about 30 per cent skin by weight; despite the predominance by weight of muscle and bone, blood flow to the hand is a reasonable reflection of skin flow because flow to skin normally greatly exceeds flow to muscle and bone.

#### NEUROGENIC FACTORS

Sympathetic vasoconstrictor fibers to skin supply both arteriovenous anastomoses and

arteries and arterioles. There is a definite pattern of neural and vascular responses during heating or cooling in man. Vasodilatation or vasoconstriction may begin in the arteriovenous anastomoses of the fingers and ears, progress to the feet, and spread to the proximal skin areas.

Vasodilatation in skin is accomplished by several mechanisms (fig. 5). First, withdrawal of sympathetic constrictor tone is the primary mechanism of dilatation, particularly in arteriovenous shunts. Second, "active" vasodilatation occurs during heating as the result of activation of a cholinergic pathway to sweat glands which apparently releases bradykin-

forming enzymes from sweat glands.<sup>63</sup> Third, a vasodilator pathway mediated by release of prostaglandin E has been proposed on the basis of studies in experimental animals.<sup>65</sup> Fourth, a noncholinergic nonhistaminergic reflex pathway in the hindlimb of dogs is possibly activated by stimulation of sympathetic nerves and causes sustained dilatation in cutaneous but not muscular vessels.<sup>66,67</sup> This mechanism may be involved in the cutaneous vasodilatation during chemoreceptor stimulation.<sup>15</sup>

#### *Reflex Vasoconstriction in Skin*

The most effective reflex vasoconstrictor stimulus in skin is cold. Local or central cooling initiates profound cutaneous vasoconstriction. The hypothalamus appears to initiate the reflex response to "core" cooling.<sup>68</sup>

Lower body negative pressure in man, which activates arterial baroreceptors and "low-pressure" baroreceptors (in atria and pulmonary vessels), results in significant vasoconstriction in skin as well as muscle.<sup>21</sup> The arterial baroreceptor reflex affects cutaneous vessels, but less than vessels in muscle. It is interesting that cutaneous vessels are less responsive to the baroreceptor reflex than one would predict from the extensive adrenergic innervation of the vessels. This, again, reflects the predominant thermoregulatory function of cutaneous vessels.

In man, painful stimuli or a deep breath cause profound cutaneous vasoconstriction.

#### *Reflex Vasodilatation in Skin*

Heating initiates reflex vasodilatation in skin mediated by withdrawal of sympathetic constrictor tone to arterioles and arteriovenous anastomoses and probably by neural release of bradykinin-forming enzymes from sweat glands. Vasodilatation in the hand during heating appears to be the result of withdrawal of adrenergic tone and vasodilatation in the skin of the forearm appears to be produced by reflex (cholinergic) release of bradykinin-forming enzymes from sweat glands.

Studies in experimental animals have demonstrated that some stimuli which cause vasoconstriction in muscle cause vasodilatation

in skin. Chemoreceptor stimulation<sup>15</sup> and coronary occlusion<sup>18</sup> cause cutaneous vasodilatation and vasoconstriction in muscle. Cardiovascular reflexes do not produce qualitatively similar effects in different organs; the opposite responses in paw and muscle when the same stimulus is applied provide a striking example of dissimilar reflex effects in different vascular beds. Vasoconstriction in muscle and vasodilatation in skin provide a reflex mechanism for redistribution of flow away from muscle and toward skin during hypoxia and coronary occlusion. Because oxygen utilization is higher in muscle than skin, vasodilatation in skin favors conservation of oxygen and also prevents an excessive increase in arterial pressure (and cardiac work) during vasoconstriction in muscle.

Cutaneous vessels dilate in response to stimulation of arterial or ventricular baroreceptors. The vasodilator response is far less in skin than in muscle.<sup>26</sup> It also appears that stretch of "low-pressure" baroreceptors by raising the legs causes much less vasodilatation in skin than in muscle.<sup>69</sup>

#### *Interaction of Reflexes*

Fainting while standing is not uncommon during hot weather. Apparently cutaneous vessels remain dilated, which suggests that reflex effects of baroreceptors on cutaneous vessels are minimal in the face of the heat load. This effect may be due at least in part to a central interaction of baroreceptor and thermal reflexes<sup>62</sup>; as a result of this interaction, reflex vasoconstrictor responses are depressed during heating.

#### HUMORAL CONTROL IN SKIN

Epinephrine stimulates both alpha and beta adrenergic receptors. Because epinephrine activates beta-2 vasodilator receptors in coronary vessels and vessels of skeletal muscle, one might expect epinephrine to cause vasodilatation in skin. This is not the case. A preponderance of alpha adrenergic receptors in cutaneous vessels of man and animals results in vigorous cutaneous vasoconstriction in response to epinephrine as well as norepinephrine.<sup>40,41</sup> Serotonin and prostaglandin F<sub>2α</sub> also cause marked vasoconstriction in skin.<sup>41,70</sup>

In contrast to the profound vasoconstrictor response to catecholamines, serotonin and prostaglandin F<sub>2α</sub>, cutaneous vessels are less responsive to vasopressin<sup>43,44</sup> and angiotensin<sup>44</sup> than are vessels in skeletal muscle.

#### METABOLIC FACTORS

It appears that autoregulation of cutaneous vessels may be primarily a response to changes in pressure; isolated cutaneous vessels exhibit a constrictor response to distention.<sup>71</sup> Autoregulation is not as prominent in cutaneous vessels as in skeletal muscle, where metabolic requirements are greater (fig. 6).

Systemic hypoxemia or hypercapnia in man has both reflex and local effects. Hypoxemia or hypercapnia decreases blood flow to the hand by a reflex effect.<sup>32,72</sup> The local effect of hypercapnia in cutaneous vessels is dilatation.<sup>72</sup>

#### Effects of Pathophysiologic States on Muscle and Skin Flow

##### SHOCK

Hypotension causes marked vasoconstriction in skeletal muscle and even more profound constriction in cutaneous vessels.<sup>73</sup> Circulating catecholamines, rather than angiotensin or increased neural sympathetic tone, appear to account in large part for the constriction in skin.<sup>74</sup> The more profound vasoconstriction in skin compared with muscle during shock is presumably related to the greater sensitivity of skin to catecholamines.<sup>40</sup>

Prolonged shock may result in vasodilatation in skeletal muscle and loss of reactivity to vasoconstrictor stimuli.<sup>75</sup> The vasodilatation and decreased reactivity may be the result of local acidosis and accumulation of metabolites which counteract and oppose effects of neurogenic and humoral vasoconstrictor factors on arterioles. The constrictor effect of catecholamines on small veins appears to be sustained during prolonged shock. Arteriolar dilatation<sup>75</sup> and venous constriction would increase capillary pressure and filtration. Because the vascular bed in skeletal muscle is large, increased capillary filtration in shock may result in loss of a large volume of intravascular fluid and contribute significantly to shock. In this situation, phen-

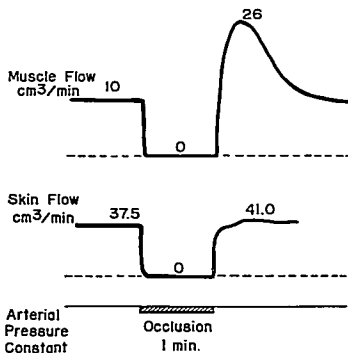


FIG. 6. Autoregulation of blood flow in skeletal muscle and paw (a cutaneous bed) of the dog was occluded for one minute. Reactive hyperemia was much greater in skeletal muscle than skin. (Reprinted with permission from Handbook of Physiology.<sup>117</sup>)

tolamine, which inhibits venous constrictor responses to norepinephrine more effectively than arteriolar vasoconstrictor responses,<sup>76,77</sup> may be beneficial in reducing capillary filtration.

##### HYPERTENSION

There is an interesting changing hemodynamic pattern in patients with hypertension.<sup>78-80</sup> In early labile hypertension cutaneous resistance increases, but there appears to be vasodilatation in skeletal muscle. The vasodilatation in muscle may compensate for constriction in other organs, such as the renal and splanchnic beds, and may result in normal total peripheral resistance. In established hypertension, there is increased resistance in both cutaneous and muscle vascular beds, although the constriction is relatively greater in skin.

Blood vessels are not only constricted in hypertension, but they are also more responsive to superimposed vasoconstrictor stimuli.<sup>81</sup>

##### ARTERIOSCLEROSIS

Subtotal occlusion of large arteries may not alter blood flow to an extremity at rest,

but when metabolic requirements are increased during exercise or reactive hyperemia, the increase in flow is less than normal and may produce intermittent claudication. As flow increases inadequately, arterial pressure falls distal to an obstruction, and blood flow to distal parts of an extremity may cease; it has been suggested that, in this circumstance, critical closure may occur in cutaneous vessels.<sup>52</sup> An important observation is that the limitation of maximal blood flow in the forearm of patients with hyperlipidemia improves after treatment of the lipid abnormality, which suggests regression of obstructive lesions.<sup>53</sup>

Lumbar sympathetic block or sympathectomy for arteriosclerotic vascular disease causes an increase in cutaneous blood flow with minimal change in resting flow or a decrease in flow to skeletal muscle<sup>54</sup>; after sympathectomy, muscle blood flow during exercise may be reduced and intermittent claudication may be worse.

#### HEART FAILURE

Patients in heart failure have diminished blood flow to skin and skeletal muscle.<sup>55</sup> The decrease in flow may be the result of both augmented sympathetic tone and of local factors limiting flow. During exercise these patients have exaggerated vasoconstriction in skin, which may compromise thermoregulation.<sup>56</sup> It has been thought that the exaggerated vasoconstrictor response to exercise is part of a generalized augmentation of sympathetic vascular responses. Recent studies of animal models of heart failure demonstrate that, although vasoconstrictor responses to exercise are increased,<sup>57</sup> responses to other neurogenic stimuli are not increased and may even be diminished.<sup>58-60</sup> It appears that the increased response to exercise in heart failure may be the result of a greater stress and therefore greater stimulus, and may occur despite reduced responsiveness of peripheral vessels to adrenergic stimuli.

Patients in heart failure also have reduced vasodilator responses. Forearm vessels fail to dilate normally during ischemia, exercise, or heating.<sup>65</sup> The reduced vasodilator responses persist after nerve blockade or alpha adrenergic blockade, which indicates the im-

portance of local factors in the altered responses. Limitation of vasodilatation during exercise may contribute to fatigue in patients with heart failure.

#### AORTIC STENOSIS AND MYOCARDIAL INFARCTION

Distention of the left ventricle in patients with aortic stenosis, by a stimulus such as exercise, may activate ventricular baroreceptors and result in vasodilatation in non-exercising limbs and hypotension.<sup>29</sup> The etiology of syncope during exercise in patients with aortic stenosis has been unclear. It now appears that activation of left ventricular baroreceptors in these patients, which results in vasodilatation and hypotension, may be an important mechanism for the syncope. The vasodilator response has been demonstrated in experimental animals to be more marked in skeletal muscle than in skin.<sup>26</sup>

It is likely that ventricular baroreceptors may be activated in a variety of clinical situations and contribute to hypotension. For example, dyskinesia during myocardial ischemia may activate ventricular stretch receptors in the area of localized bulging and may contribute reflexly to the hypotension which is seen following myocardial infarction. In experimental animals, vagotomy improves hypotension after myocardial infarction (unrelated to changes in heart rate), which suggests that vagal afferent fibers originating in the myocardium may be activated during infarction.<sup>26</sup>

#### DIABETES

Vasomotor abnormalities in diabetic patients may be due to accelerated arteriosclerosis, microangiopathy, or autonomic dysfunction. The arteriosclerotic component is reflected in limitation of muscle flow during reactive hyperemia. The microangiopathy of diabetes is manifested in increased microvascular permeability in skeletal muscle.<sup>61</sup> The autonomic neuropathy of diabetes results in abnormalities in reflex control of cutaneous vessels, with impaired neurogenic sweating<sup>62</sup> and thermoregulation, and in impaired orthostatic reflexes.<sup>25</sup>

TABLE 1. Effects of Anesthetics on Blood Flow in Man

Anesthetic	Effect on Cutaneous Blood Flow (with Reference)	Effect on Muscle Blood Flow (with Reference)
Halothane	Increase in hand <sup>98</sup> in forearm skin <sup>99</sup> in finger <sup>100</sup>	Variable little change in forearm <sup>98,100</sup> no change in forearm muscle <sup>99</sup> decrease in forearm flow at low levels of halothane, increase in flow at high levels <sup>101</sup>
Cyclopropane	Increase in forearm skin <sup>99</sup> in finger <sup>100</sup>	Decrease in forearm muscle <sup>99</sup> in forearm flow <sup>101</sup> or little change in forearm flow <sup>100</sup>
Nitrous oxide	Increase in finger <sup>98</sup>	Probable decrease* no change in forearm flow <sup>98</sup> despite cutaneous dilatation suggests constriction in muscle
Diethyl ether	Increase in finger <sup>100,102</sup>	Probable decrease* little change in forearm flow at first <sup>100,102</sup> despite cu- taneous dilatation suggests constriction in muscle
Forane	Increase in finger <sup>103</sup>	Unclear* increase in forearm flow <sup>103</sup> could be in skin or muscle
Ketamine		Unclear* increase in forearm flow <sup>104</sup> could be in skin or muscle
Thiopental	Increase in forearm skin <sup>99</sup> in hand <sup>98</sup>	Decrease in forearm muscle <sup>99</sup> no change in forearm flow <sup>98</sup> despite cutaneous vasodilatation suggests constriction in muscle

\* See text for discussion.

## RAYNAUD'S PHENOMENON

Raynaud's phenomenon affects cutaneous vessels of the digits, and is characterized by unusual sensitivity to slight cooling. Resting hand and finger blood flow may be either normal or low in a warm environment,<sup>83,84</sup> but flow decreases profoundly with slight cooling. A recent study<sup>85</sup> provides important information concerning the nature of the decrease in flow: capillary ("nutritional") blood flow in patients with Raynaud's phenomenon is significantly depressed in both warm and cool rooms.

## COLLAGEN VASCULAR AND MUSCLE DISEASE

Skin involved by scleroderma usually has diminished capillary blood flow. Some patients, however, may have normal capillary flow to skin despite obvious clinical changes in the skin.<sup>86</sup>

Vasculitis or muscle disease may affect blood flow in skeletal muscle; for example, amyloidosis limits the peak forearm blood flow which can be achieved during reactive hyperemia.<sup>87</sup>

## Effects of Anesthetics on Blood Flow

## GENERAL ANESTHESIA

Most studies of peripheral vascular effects of anesthetics in man have utilized forearm blood flow, as an indication of muscle flow, and finger or hand flow, as a measure of cutaneous flow. Because of limitations of these plethysmographic methods, as discussed earlier, the effects of several anesthetic agents on blood flow (especially to muscle) are not clear. Furthermore, only a few studies have dealt with mechanisms which account for the effects of anesthetics on peripheral blood flow.

A clearly established property of anesthetic agents is cutaneous vasodilatation (table 1). The cutaneous vasodilatation contributes to hypothermia during anesthesia.<sup>105</sup> One would expect that the cutaneous vasodilatation is at least in part an effect initiated in the central nervous system and mediated by withdrawal of sympathetic vasoconstrictor tone. In addition, anesthetics could produce cutaneous vasodilatation by inhibiting ganglionic transmission, depressing release of norepinephrine from postganglionic terminals, or by a direct depressant effect on vascular smooth muscle. These effects have, in fact, been demonstrated with halothane. Halothane in dogs inhibits ganglionic transmission, depresses vascular responses to electrical stimulation of sympathetic nerves, has a depressant effect on vascular smooth muscle, and preferentially blocks vasoconstrictor responses to vasopressin in skin.<sup>106</sup>

The effect of anesthetic agents on muscle blood flow appears to be variable (table 1). We will consider some of these agents individually.

The effect of halothane on muscle blood flow is not clear. In experimental animals, halothane causes vasoconstriction in skeletal muscle, as determined with an isolated muscle technique<sup>106</sup> and by a microsphere technique.<sup>107</sup> The vasoconstriction may be caused by release of vasopressin during halothane anesthesia.<sup>108</sup> In man, resistance in forearm muscle (determined with a heat clearance technique) did not change during halothane anesthesia,<sup>99</sup> but forearm vascular resistance determined with plethysmography may increase or decrease during halothane anesthesia.<sup>98,100,101</sup> In part related to the level of anesthesia.

Cyclopropane causes contraction of aortic strips.<sup>109</sup> It also increases forearm vascular resistance<sup>101</sup> despite a decrease in cutaneous resistance<sup>99</sup> in the forearm (determined with a heat clearance technique). An increase in total forearm resistance, despite cutaneous vasodilatation, indicates that cyclopropane causes vasoconstriction in skeletal muscle.

There is little change in forearm vascular resistance during administration of nitrous oxide<sup>98</sup> or diethyl ether.<sup>100,102</sup> These agents increase finger blood flow<sup>98,100,102</sup> and pre-

sumably produce vasodilatation in the skin of the forearm as well. Since forearm resistance does not change during nitrous oxide or diethyl ether anesthesia, it is likely that cutaneous vasodilatation is associated with vasoconstriction in skeletal muscle.

Forane and ketamine decrease forearm vascular resistance.<sup>103,104</sup> This effect may be the result of vasodilatation in skin or skeletal muscle.

Little is known about the effects of anesthetic agents on blood flow in the presence of occlusive arterial disease. In one study,<sup>110</sup> halothane caused little change in calf vascular resistance in patients with intermittent claudication.

#### REGIONAL AND LOCAL ANESTHESIA

Recent studies provide interesting data concerning the effects of peridural block on peripheral blood flow. Peridural block with lidocaine (without epinephrine) causes marked vasodilatation in the calf,<sup>111</sup> which is presumably the result of withdrawal of sympathetic tone to the skin and muscle of the legs. Simultaneously with vasodilatation in the legs, peridural block causes vasoconstriction in the forearm,<sup>111</sup> the mechanism of which may be reflex in nature.

Epinephrine and phenylephrine have been injected with lidocaine during peridural block. These catecholamines are absorbed and have significant hemodynamic effects. Epinephrine decreases arterial pressure, as the result of vasodilatation, and phenylephrine causes vasoconstriction and a small increase in arterial pressure.<sup>112</sup>

A recent study in animals and man concerned the effect of freezing, in cryosurgery, on cutaneous blood flow.<sup>113</sup> Blood flow, measured by xenon clearance, was not reduced until the tissue froze, whereupon blood flow stopped. Blood flow immediately resumed with thawing.

#### ADJUVANTS

##### *Premedications*

Diazepam causes a small decrease in blood flow in the forearm.<sup>114</sup> Pentazocine and meperidine result in small increases in blood

flow in the forearm.<sup>11,4,15</sup> It is not clear whether these changes resulted from effects on vessels in either skin or muscle.

### Muscle Relaxants

It appears that both *d*-tubocurarine and pancuronium decrease blood flow to the calf in patients with arterial disease of the legs.<sup>119,116</sup> The mechanism for this effect is obscure. Because pancuronium results in a smaller decrease in blood flow than does tubocurarine, it has been suggested<sup>116</sup> that pancuronium may be preferable in patients with obstructive arterial disease.

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