The Peripheral Circulations

Edited by
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Introduction

Students of cardiovascular physiology and medicine learn quite early that their course concerns the *cardio*vascular rather than the cardio*vascular* system. The natural glamour of studying cardiac physiology, and diseases of the heart can only partially explain this emphasis in teaching. Another equally important factor is the sheer complexity of the problem. By the time the student has considered the basic principles governing control of the circulation, little time is left to consider how these basic control mechanisms must be tailored to meet the individual requirements of each specific regional circulation. The purpose of this monograph is to consider in depth the normal circulatory control mechanisms operative in regulating perfusion of a variety of the major regions and how they are altered by some diseases. The monograph is not intended to be all-inclusive; a number of circulations are not covered. By and large the venous system is only considered minimally. Similarly, the section on the abnormal circulations serves largely to accentuate how normal regional circulatory mechanisms are altered by disease.

INTRINSIC CONTROL MECHANISMS

Theories of Autoregulation

Autoregulation of blood flow can be defined as the capacity of a circulation to alter vascular resistance in order to maintain flow relatively constant over a wide range of perfusion pressures (Fig. 1). In a rigid tube of constant radius, flow is related directly to perfusion pressure. An increase in pressure results in a proportional increase

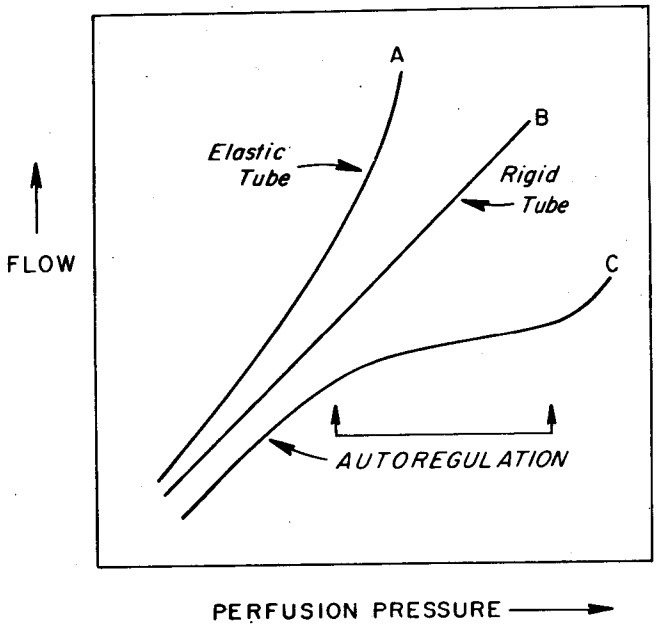

Fig. 1. Schematic representation of pressure-flow curves in three types of systems: (A) represents a curve typical for flow in an elastic tube, (B) represents the pressure-flow characteristics for a rigid tube, and (C) represents flow in a vessel capable of autoregulation. The bracket encompasses that portion of the autoregulation curve (C) in which autoregulation is taking place.

in flow. By contrast, in elastic tubes in which the radius progressively increases as perfusion pressure is raised, flow generally increases out of proportion to alterations in the pressure head. In other words there appears to be a fall in resistance secondary to the increase in radius. On the other hand, in a circulation that has the capacity to autoregulate flow, vascular resistance changes in the same direction as perfusion pressure in an effort to maintain the flow constant. Thus as perfusion pressure is increased the vessels constrict to minimize the increase in flow. Not all circulations have the capacity for autoregulation; for example, the cutaneous circulation appears to lack this property.

In those circulations that do have the capacity to autoregulate flow, two major theories that are not mutually exclusive have been postulated to explain this phenomenon. These are the myogenic and

metabolic theories of autoregulation. The myogenic theory has as its basis the observation that when vascular smooth muscle is stretched it responds by active contraction of smooth muscle cells, resulting in a reduction in vascular radius. In contrast, the metabolic theory of autoregulation postulates that when perfusion pressure to a region increases there is a transient increase in flow that washes away products of local metabolism having vasodilator characteristics. The vessels then respond to this altered level of vasodilator metabolites by contracting. Either one or both mechanisms may predominate in an individual region. A third theory of autoregulation, the tissue-pressure theory, has received less wide acceptance as being a major factor in regulating regional blood flow except under unusual circumstances. This theory suggests that an increase in perfusion pressure causes an enhanced extravasation of fluid into the interstitial space; this fluid acts to increase interstitial pressure and partially collapse distensible vessels, thereby increasing resistance to flow. Whereas the metabolic theory best explains autoregulation in the coronary circulation, the myogenic theory is more applicable to the renal and perhaps the cerebral circulations. On the other hand, it is more likely that myogenic and metabolic mechanisms are both operative in skeletal muscle. It is less likely that the tissue-pressure theory plays a major autoregulatory role under physiologic conditions; however, in edematous states it may play an important role in altering blood flow to skeletal muscle.

Special Characteristics of the Regional Circulations

Many of the regional circulations have special characteristics that play an important role in regulating flow. For example, in the heart where intramyocardial tension increases markedly during ventricular systole, there is such an increased resistance to blood flow that coronary perfusion of the left ventricle is largely a diastolic event. Similar mechanisms are operative in skeletal muscle during static or "isometric" exercise. Another example of a special characteristic is that circulation to the brain must "go uphill" in the upright subject. Furthermore, blood flow to this highly metabolic organ also serves a cooling function. The splanchnic circulation, because of its large flow and blood volume, can be operative as a vascular reservoir. These are but a few examples that serve to illustrate that the special characteristics of a regional circulation must be considered when one is trying to understand the principles regulating blood flow in each specific regional circulation.

NEUROHUMORAL CONTROL MECHANISMS

Most regional circulations have a greater or lesser population of α-adrenergic receptors that induce arteriolar constriction when postganglionic sympathetic adrenergic nerves are stimulated to fire. Dilation in a vascular bed, however, can be a complex phenomenon. For example, it can occur through a reduction in α-adrenergic vascular tone or through stimulation of β-adrenergic, dopaminergic, histaminergic, or cholinergic receptors through a neural or humoral mechanism. Thus an increase in blood flow can result from a passive process, or it can be secondary to an active process induced by increased neural activity or an increased concentration of a circulating hormone.

An important concept is that when "sympathetic neurogenic vascular tone" is altered, the various regional circulations do not necessarily respond uniformly. A vascular efferent reflex response is generally specific for the afferent mechanism that is stimulated. Thus the activation of afferent fibers from the carotid sinus baroreceptors produces quite a different regional vascular reflex response than activation of afferent fibers from carotid body chemoreceptors. Similarly, the activation of one reflex arc can modify the reflex vasomotor response when a second reflex arc is activated, and vice versa. This is an important point that should be considered in trying to understand the responses of the various regional circulations to the complex stimuli controlling neurogenic vasomotor tone in normal and diseased states.

Principles of Regional Control—A Synopsis

One simplified approach to understanding the basic control mechanisms governing the circulation to a certain region is to consider the "purpose" of the circulation to that organ system. A simple way to approach this is to evaluate the relationship of its oxygen requirements to its blood supply. In Fig. 2 the percentages of cardiac output to the various regional circulations are compared to the percentages of oxygen utilized by the organs in those regions. For example, it is readily apparent that the coronary and cerebral circulations have a large oxygen requirement in proportion to their blood flow. Blood flow through these highly metabolic organs might be expected to be predominantly regulated by intrinsic local rather than neurohumoral control mechanisms. In the coronary circulation, in particular, the metabolic theory of autoregulation would appear to be most dominant.

On the other hand, the function of the cutaneous circulation is for body-temperature regulation. It has little capacity to autoregulate,

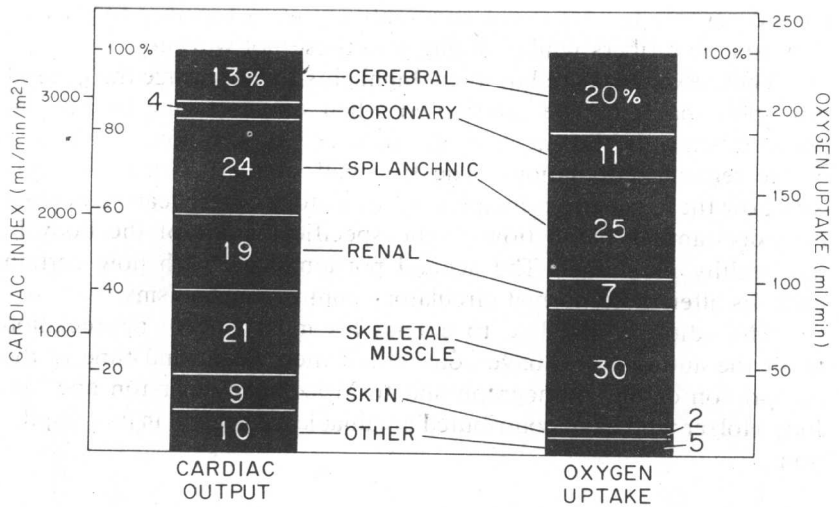

Fig. 2. The distributions of the cardiac output to and the oxygen consumption of the regional circulations of the body. The bar to the left represents the percentage distribution of the cardiac output to each of the regional circulations, and the bar to the right represents the fractional oxygen consumptions of the organs served by these circulations.

has a low metabolic requirement, and is primarily under neurogenic control. The anatomic arrangement of the arteries and veins and venous valves provides an effective mechanism for diverting blood toward the skin or toward the limb core so that body heat can be dissipated or conserved, respectively. Similarly, when the body is subjected to an acute physiologic stress such as exercise superimposed on a severe chronic pathologic stress such as anemia or heart failure, the renal and cutaneous circulations are the ones most likely to be "turned off," since they are under a high degree of neurogenic control and have relatively low oxygen requirements in relation to their blood supply.

In skeletal muscle a complex system operates to control blood flow. The circulation must respond rapidly to meet tremendous metabolic requirements during periods of skeletal-muscle activity, but yet have the capacity to restrict flow during periods of inactivity. As one might expect, resting blood flow is controlled by neurogenic and myogenic factors; whereas during exercise where blood flow can increase 20-fold or greater, metabolic factors appear to be the dominant regulators of the circulation. During submaximal exercise, metabolic

and neurogenic factors might cooperatively work together to provide flow to active fibers while limiting it to those not working.

These examples are but a few highlights to emphasize the general principles that must be considered when one is trying to gain an understanding of the mechanisms involved in the control of each of the regional circulations. The first half of this monograph deals with how these general principles of circulatory control can be applied to understanding blood flow to the specific regions of the body in the healthy individual. The second portion deals with how certain diseases alter these normal circulatory control mechanisms.

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Robert Zelis, M.D.

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PART I

Normal Circulations

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Skeletal-Muscle Blood Flow: Neurogenic Determinants

As with blood flow in any vascular bed, the blood flow to skeletal muscles depends on the perfusion pressure and the caliber of the resistance vessels. Changes in caliber are dictated by alterations in nervous activity, by circulating vasoactive agents, and by metabolic changes that originate in the immediate environment of the blood vessels. This chapter is concerned with the changes in caliber that are effected through the nerves to the muscle vessels.

While changes in caliber caused by metabolic events within the muscle provide for local alterations in flow that are proportional to metabolic needs, the reflexly induced changes in muscle are only a part of the total vascular system response that provides the proper balance among cardiac output, blood pressure, and distribution of flow to the different vascular beds. These reflex changes are effected through the sympathetic adrenergic nerves. In special circumstances, neurogenic liberation of acetylcholine and histamine can influence blood flow to muscle (Fig. 1-1).

ADRENERGIC INNERVATION OF RESISTANCE VESSELS IN MUSCLES

Morphology

Conventional staining techniques, as used by Hillarp,[1,2] and, more recently, histochemical techniques for fluorescent staining of catecholamines,[3] have characterized the structure of the postganglionic adrenergic nerve supply to the blood vessels. The innervation of

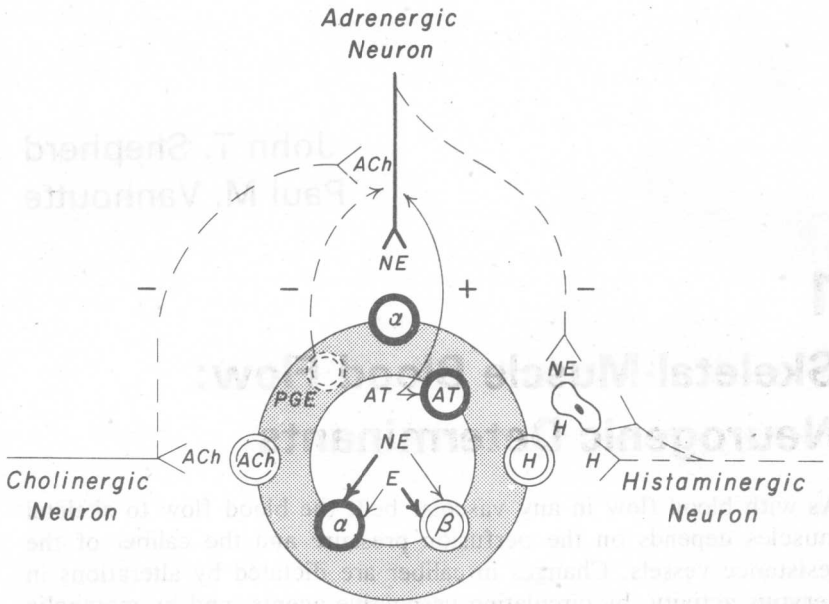

Fig. 1-1. Schematic representation of the major neurogenic and humoral factors affecting vascular smooth-muscle cells and of their possible interactions. Dotted lines indicate more recently proposed interactions. Black circles = receptors whose stimulation causes constriction of the smooth muscle; white circles = receptors whose stimulation causes relaxation of the smooth muscle (for details see text). Symbols: ACh = acetylcholine; NE = norepinephrine; E = epinephrine; AT = angiotensin II; H = histamine; PGE = prostaglandins (E type); α = α-adrenergic; β = β-adrenergic.

arterioles is particularly dense in most vascular beds except the brain; the precapillary sphincters are relatively poorly innervated. The majority of nerve bundles in arterial and arteriolar tissue consist of nonmyelinated nerve fibers surrounded by Schwann cells. The nerve bundles form a dense plexus in the adventitia but do not penetrate into the media. Hence only the outer layer of smooth-muscle cells is in contact with the adrenergic nerves.

The terminal portions of the adrenergic axons form a reticulum of slender processes (about 0.1 μm in diameter) with widening at regular intervals into varicosities (about 1 μm in diameter). The varicosities, which usually are denuded of Schwann cells, contain vesicles for storage of neurotransmitter. They are in close apposition to the vascular smooth-muscle cells they innervate, although a minimal distance of 800 Å persists between the axon profile and the smooth

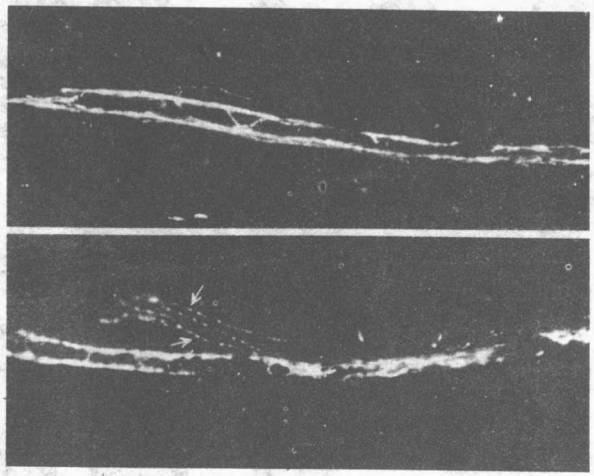

Fig. 1-2. M. tibialis anterior of cat in longitudinal section, showing adrenergic fibers passing along arterioles. In lower figure single varicose fibers can be seen in relation to a small side branch of the arteriole (arrow). Fluorescence microphotograph; ×165. (Reproduced from Fuxe F, Sedvall G: The distribution of adrenergic nerve fibres to the blood vessels in skeletal muscle. Acta Physiol Scand 64:75-86, 1965, by permission of Karolinska Institutet.)

muscle. In richly innervated blood vessels the individual smooth-muscle cells probably have several close contacts with varicosities of one or more adrenergic fibers.[4-10] Although few studies deal specifically with muscle vessels, Fuxe and Sedvall[11,12] have confirmed that arterioles of skeletal muscle are richly supplied with adrenergic nerve endings (Fig. 1-2).

Neurotransmission

The impulses passing down to the adrenergic nerve terminals liberate transmitter from the successive varicosities *en passant*. It has been calculated that each impulse liberates approximately 400 to 500 molecules of norepinephrine per activated varicosity.[13-15] The neurotransmitter diffuses to the smooth-muscle cells and, although the closest cells are likely to be the first targets, diffusion may be effective up to 1 μm from the liberation site. Whether diffusion is sufficient to activate all cells of the media facing each varicosity is still debated, especially in the case of larger blood vessels. In