

Defining the Precapillary Sphincter

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Past and present use and abuse of the term precapillary sphincter is reviewed. The advantages of a uniform and functional definition are described, and a definition that is consistent with current information is proposed.

INTRODUCTION

The area of least uniformity in nomenclature, architecture, and function in the cardiovascular system seems to be the territory between the vessels comprising the macrocirculation and the ones designated as belonging to the microcirculation. It seems appropriate to raise, and perhaps answer, questions regarding one of the most conspicuous components of the microcirculation, the precapillary sphincter. If disorders resulting in adequate distribution of blood to tissue are to be rectified, recognition of specific location, function and control of distinct sections of the vascular tree are required.

During the last three decades, the development of sophisticated measuring and recording equipment has given us detailed information regarding the structure, the architectural layout, and the function of the microvasculature. We have investigated the ultrastructure and acquired a good knowledge of how endothelial cells of the blood vessels are put together. We have measured the blood pressure in the smallest vessels, we have determined the rate at which blood flows through them, and we have assigned various substances and structures the responsibility for controlling the amount of blood and the speed at which it enters and leaves the tissues (Johnson, 1972). There is one important area, however, that does not enjoy universal acceptance in terms of a definition of function and perhaps structure and that is the region of the precapillary sphincter.

There are a number of aspects to consider in attempting to resolve the problem. Should the region be defined on a functional or anatomical basis? Anatomically we can say that the precapillary sphincter is the final smooth muscle cell of the arterial distribution. Functionally we can say that it is an important determinant of the distribution of arterial blood into the capillary in tissues or organs in which it appears. Does it also contribute to total peripheral resistance? What causes it to contract and relax? It is innervated or does it depend entirely on local factors to regulate its contractile activity?

Historically, Tannenberg, in 1925, referred to the pfortnerzelle or gate-keeper cell which may be the origin of the concept of a sphincterlike regulation of capillary flow. In 1939, Zweifach described a valvelike fold of endothelium at the point where a

capillary branch leaves an arteriole in the mouse mesentery. He stated that the folds behaved as an endothelial sphincter when the parent trunk contracted, but further stated that in arterioles, closure was aided by muscle cells at the point of capillary exit. Fulton and Lutz in 1940 described a sphincterlike region at capillary origins in small blood vessels of the frog's retrolingual membrane and postulated that modified smooth muscle cells of these areas regulated blood flow in a sphincterlike manner. Fulton and Lutz had caused these muscle cells to contract by electrical stimulation of nerves. In 1942 Chambers and Zweifach presented a motion picture that showed "sphincterlike functioning of the precapillaries at their junctions with the arteriole." One year later the Clarks (1943) published a paper on caliber changes in minute blood vessels, describing muscle cells on newly developed terminal arterioles in the rabbit ear that could not contract unless nerves had also grown into the area. The following year, Chambers and Zweifach (1944) presented a diagram of a functional unit of the capillary bed in which a specific area was designated precapillary sphincter. They stated that their results confirmed the findings of studies in the rabbit ear chamber by Sandison (1932) and the Clarks (1943), as well as earlier observations of Zweifach who had stated that "the muscular elements are limited to specific vascular components which here are termed metarterioles and precapillary sphincters."

In 1955, Nicoll and Webb reported that active vasomotion in terminal arterioles of the bat wing was an independent mechanism of their muscle cells without any direct dependency on nerve connections and that the precapillary sphincters, the final smooth muscle cells of the terminal arterioles, exhibited the greatest degree of independent action of any vascular site. The precapillary sphincter exhibited contractile activity (vasomotion) and by this means controlled the flow of blood into the capillary vessels beyond. There was no agreement at this time regarding innervation or lack of it in these muscle cells.

Future developments obscured the simple definition. While the term "precapillary sphincter" and descriptions of its activity came from direct microscopic observations of the terminal blood vessels in living animals, its adoption was unrestricted. Investigators who studied blood flow and capillary exchange by indirect measurements found the concept of the sphincter cell useful to explain changes in capillary filtration. The distinction between precapillary sphincter and precapillary resistance areas was lost.

Mellander, in 1960, presented a method from which hemodynamic reactions of resistance vessels could be deduced. Using the isolated hind limbs of an animal with nerve supply and major artery and vein intact, arterial inflow pressure and venous outflow pressure was measured. A plethysmograph measured volume of the tissue while regional blood volume was measured by a radioactive isotope dilution technique. It was said that shifts in regional blood volume and transcapillary filtration exchange could be deduced from the continuously recorded changes in tissue volume.

Using this animal preparation, Folkow and Mellander (1960) determined that a decrease in outward filtration rate occurred during stimulation of vasoconstrictor fibers and suggested that it was because of a decrease in the size of the capillary surface area available for exchange, presumably due to closure of some of the precapillary sphincters. They estimated that vasoconstrictor fiber activity reduced the capillary surface area roughly to one-third that of normal. There was, however, no direct evidence that the reduction in blood flow through the capillary networks was the result of closure

of precapillary sphincters rather than a reduction in total flow to the limb by small artery or arteriolar constriction. A short time later (Cobbold *et al.*, 1963) investigators using the Mellander method stressed the fact that "the sphincter section forms a part of the resistance vessels, apart from being a functionally specialized vascular section in its own right," and also stated that the influence of sympathetic stimulation on precapillary sphincters is overcome by metabolites.

One question, then, seems to be, "What controls the contractile activity of the precapillary sphincters?" Uncertainty regarding the answer is expressed in a current cardiovascular text (Berne and Levy, 1972) by the statement that "adrenergic sympathetic fiber stimulation elicits arteriolar and possibly precapillary sphincter constriction" although other recent physiology textbooks state "sphincters exhibit constriction and relaxation in response to local metabolites, externally applied chemicals or sympathetic nerve activity" (Selkurt, 1975) and in another instance, "relaxation of precapillary sphincters is due to a decrease in the activity of the sympathetic vasoconstrictor nerves that innervate smooth muscle" (Ganong, 1973).

Suppose we consider the precapillary sphincters to be shared by both the microcirculation and the macrocirculation and to contribute significantly to control of peripheral resistance. In this case, they should be controlled by the sympathetic nervous system in order to coordinate their activity with changes in cardiac output and changing diameters of the large arterial vessels. If, on the other hand, the precapillary sphincter is primarily responsible for flow and pressure in the exchange circulation, then it must belong to the microcirculation and should respond to local factors related to the nourishment of tissues. To have to interreact with mechanisms that normally support blood pressure through autonomic control would be slow and ineffective. Surely we cannot ask the precapillary sphincter to participate in two major activities of the cardiovascular system, controlling both peripheral resistance and capillary exchange.

In considering the contribution of precapillary sphincters to peripheral resistance, a statement regarding peripheral resistance is in order. Peripheral resistance is a calculated value which is a function of values of blood pressure and cardiac output. It is rightfully assumed that an increase in peripheral resistance occurs as a result of constriction in arterial vessels, but just where the constriction occurs is not well documented. There are several ways to manipulate peripheral resistance, to reduce it or increase it, primarily with drugs that affect the autonomic nervous system. Such responses do not pinpoint the location of change in the arterial vascular diameter.

An argument that major changes in peripheral resistance do not occur at the level of the precapillary sphincters is as follows: When a mathematical determination is made of changes in resistance which occur with a decrease in the diameter of four orders of branching vessels, it can be shown (Mayrovitz *et al.*, 1975) that a greater resistance is developed with closure of first- and second-order vessels than with fourth-order vessels, the site of the precapillary sphincter. It would seem reasonable that changes in vascular diameter having the greatest effect in varying peripheral resistance would be under control of the sympathetic nervous system and would occur in arterial vessels proximal to the terminal arteriole with its precapillary sphincter. These arteriolar vessels are parent vessels to a large vascular network beyond and therefore fewer of them would have to react to produce a change in systemic blood pressure. They could

effectively influence blood flow in the terminal vasculature by changing diameter some distance upstream from the vast total cross-sectional area of the capillary network.

There is positive evidence that favors the selection of the precapillary sphincter as the monitor of blood flow into the capillary network, and also evidence that local factors are primary in controlling its contractile activity. For example, the concept of autoregulation deals with the ability of resistance vessels to respond to maintain adequate nutritional flow in an organ in the face of changing perfusion pressure. Both the myogenic and the metabolic theory of autoregulation are independent of central or peripheral nervous control. Furness and Marshall (1973) presented anatomical studies showing that precapillary arterioles in the rat cecal mesentery lack innervation. Phillips and Wiedeman presented similar findings for bat wing terminal arteriolar vessels (1968). Honig *et al.* (1970) found capillary density in heart muscle to be independent of the nervous system. Physiological or functional evidence is found in the fact that surgical section of a major nerve trunk, as well as adrenergic blocking agents, produces increased diameters of large arterial vessels but does not increase the diameters of terminal arterioles and produces only slight changes in their parent vessels (Wiedeman, 1968). This lack of innervation of the vessels supplying exchange vessels may be the reason for failure of sympathectomies to consistently overcome the difficulties of peripheral vascular disorders. Although not conclusive, the evidence is certainly suggestive that nervous control does not extend to these vessels.

It would be most helpful for current and future investigators if agreement could be reached relative to the precapillary sphincter. Most acceptable and most easily definable would be to state that it was at the location of the final smooth muscle cells on the arteriolar vessels that give rise to capillary networks. Unless refuted by further anatomical studies, it could be recognized as having contractile activity of a myogenic nature and being completely devoid of direct control by the autonomic nervous system. Finally, the precapillary sphincter should assume the role of the monitor of blood flow into distal capillary beds, and should not be included as a factor in the regulation of peripheral resistance that aids in determining systemic blood pressure.

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