MICROCIRCULATION

Volume I

Edited by **Gabor Kaley** and **Burton M. Altura**

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PREFACE

The purpose of this treatise is to present a comprehensive view of the field of microcirculation. The study of small blood vessels, which forty short years ago was the domain of morphologists only, has grown in the intervening years into a most important subject from physiologic, pharmacologic, and pathologic as well as clinical points of view. Microcirculation is currently an intensively investigated field and yet a comprehensive approach to this subject, one that would focus on its functional entities and interrelatedness to other disciplines, has not yet, to our knowledge, been attempted.

Our concept concerning individual sections of this treatise was to evaluate critically work done in the past, to describe the present state of the art, and to point out future directions that seem profitable and challenging. It is hoped that *Microcirculation* will not be merely a collection of monographs and a reference source but that it will facilitate a synthesis of all the information available and will provide new approaches to the study of small blood vessels. We also hope that the sheer size of *Microcirculation* will not discourage students, research workers, and biologists in related areas, as well as clinicians, from becoming acquainted with the field of microcirculation.

It is inevitable that some duplication of material will occur in a work of this size. It is also not possible, mostly because of limitations of the size of this treatise, to include among the authors all investigators who have contributed significantly to this research field. Nevertheless, we have been fortunate in being able to bring together so many active and outstanding workers in this field to join us in this endeavor.

There is another, equally compelling reason to put together a volume on microcirculation. It is to honor Benjamin W. Zweifach, the individual who, more than any other, has left his personal mark on this research field. It is rare in science for any one man to become as influential as he has through the years. Almost everyone who has contributed significantly to the field of microcirculation has taken a turn in Dr. Zweifach's laboratory and has been enriched by his exceptional knowledge of, and insight into, research problems. His own contributions, which span four decades and a host of scientific disciplines, encompass every important new development in the field of microcirculation and are the cornerstones of our knowledge in this area of biology. The measure of his success is also exemplified by the number and quality of his students, all of whom, including the editors of this treatise, are proud to trace their lineage to him. This book is a collaborative effort of his students and colleagues, to whom he served as mentor and for whom he continues to be a constant source of help and inspiration.

We are proud to dedicate this treatise to Benjamin W. Zweifach.

G. Kaley and B. M. Altura

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INTRODUCTION: Perspectives in Microcirculation

Benjamin W. Zweifach

The broad outlines of the microcirculation as a separate entity were established more than half a century ago primarily on the basis of direct observational studies. Much of the information was perforce descriptive in nature. As new procedures were developed for the in vivo examination of different tissues, it was recognized that the terminal portion of the vascular tree was, in fact, an independent organic unit with intrinsic mechanisms for the local regulation of blood flow. The minute size and inaccessibility of the capillary vessels have made it difficult to utilize conventional quantitative methods to define these activities. For the most part, investigators had to be satisfied with quantitative data obtained by indirect approaches–particularly for exchange processes–using averaged values for whole organs or comparatively homogeneous tissues, such as skeletal muscle.

The substantial advances that have been made in our knowledge of the microcirculation are attested to by the very size of the present treatise. Some 25 years ago, it would have been impossible to put together so comprehensive a treatment of the small blood vessels. A combination of circumstances has made it possible to describe microcirculatory behavior in more precise quantitative terms: the application of electron microscopy, major advances in cell biology, and the development of electronic instrumentation and modern data handling procedures. These advances have, in turn, led to more rigorous theoretical and

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physical analyses of the basic features governing tissue homeostasis. In view of the extensive coverage of microcirculatory phenomena presented in these volumes, there is little that can be added in an introductory sense, aside from a critical discussion in a historical perspective of as-yet-unresolved issues, particularly those biological characteristics that enable the microcirculation to perform as the keystone of bodily homeostasis.

Microtechniques (Intaglietta, Pawula, and Tompkins, 1970) and computer-assisted analysis of video images (Intaglietta, Tompkins, and Richardson, 1970) have made it possible to use intravital microscopy to subject individual segments of the blood capillary system to more precise analysis and to use such information to reconstruct the operational characteristics of an entire microbed. There are considerable differences in opinion as to the best approach to the problem. Some investigators (Wayland, 1973; Grafflin and Bagley, 1953) believe that the random nature and diversity of capillary patterns preclude the use of data on single vessels as a productive approach for a systematic appraisal of the capillary bed as a whole. They favor instead studies of groups of vessels representing what may be considered basic or modular subunits.

There has been a tendency to emphasize differences between species and tissues rather than similarities. Nevertheless, a meaningful discussion of the capillary bed as a discrete organic unit requires that certain common organizational and functional features be identified. The only other alternative would be to treat the myriads of vascular beds separately.

Our approach to the problem (Zweifach, 1961) has been based on the premise that all circulatory beds share certain common structural features and that these are modified by the peculiar terrain of the various parenchymal structures supplied by these vessels. Because of its two-dimensional format, the mesentery seemed to be a particularly appropriate starting point where the entire microvascular bed could be examined unencumbered by parenchymal tissue limitations.

Perhaps the most valuable asset of such two-dimensional tissue preparations is that pressure, flow, reactivity, and permeability data for single microvessels can be obtained with full knowledge of their location and structural makeup. Past attempts to handle data on single vessels have been fraught with difficulties because they were compared by setting up categories on the basis of vessel diameter alone.

In a continuously branching system, this criterion is not reliable and classification must be based on other characteristics, such as the location of the vessel in the arborizing sequence. Without a framework of this kind, it is not possible to develop models of the microcirculation that can be used to analyze blood flow through the many solid tissues of the body where intravital microscopy cannot be applied.

The term "microcirculation" would serve no useful purpose if it merely referred to the microscopically small blood vessels. The striking differences

between the behavior of the large and small blood vessels cannot be explained by obvious physical features such as the lesser distensibility of the thick walled arterioles, the non-Newtonian blood flow through the narrow capillaries, or the repeated dichotomies and interdigitation of the microvasculature. Two key functions of the microcirculation require special intrinsic mechanisms: (a) the capacity to adjust blood flow in line with the changing metabolic requirements of the tissue, and (b) the local autoregulatory adjustments that serve to stabilize flow as well as pressure.

Earlier concepts depicted the capillary bed as a set of microscopic irrigation channels interposed between the arterial and venous conduits with no active participation in local regulation. In such a framework, the only important intrinsic variable was the permeability of the blood–tissue barrier. It has become obvious that the mere act of transporting a given volume of blood to the tissue was not enough to sustain tissue vitality and that a whole array of pathologic conditions are either initiated by or sustained by the failure or loss of active microcirculatory adjustments.

The literature is replete with observations on different tissues which demonstrate that the complex of minute blood vessels displays a considerable degree of local control or autonomy (Mellander and Johansson, 1968; Nicoll, 1969). Substantive data defining the mechanics of such local readjustments are not always available, although it is obvious that in some way the controls must be related to the metabolic requirements under different conditions.

We are obviously only beginning to unravel the complexities of microcirculatory behavior and, despite substantive agreement on broad principles, fundamental details remain controversial. Krogh, in his classical monograph (Krogh, 1922), presented a fairly convincing argument that under basal conditions microcirculatory flow is intermittent; this point of view has been more or less accepted by contemporary investigators. On the basis of injection studies in skeletal muscle, Krogh proposed that only a fraction of the available microvessels are perfused in so-called resting muscle and that with an active flow, the number is then increased at least four- to fivefold when higher volume flow rates are required to meet the metabolic demands of the contracting muscle. This type of local adjustment goes hand in hand with observations in other tissues that show a waxing and waning of flow in different portions of the same structure. On the other hand, in still other tissues including several skeletal muscle preparations, all of the available capillaries appear to be perfused, so that with vasomotion of the feeding arterioles the flow in all of the vessels is sped up or slowed accordingly. The question at issue is particularly germaine to the discussion of blood flow in skeletal muscle or cardiac muscle where the total number of capillaries seems to be much greater than would be needed to sustain the metabolic requirements of the tissue at rest.

A direct corallary of the unresolved issue of intermittency is the mechanism responsible for the ebb and flow of the microcirculation. Structural and func-

tional evidence (Folkow, Sonnenschein, and Wright, 1971) has led to the concept that on the proximal or precapillary side, muscular sphincters are the structural elements whose contraction and dilation modulates local blood flow. There is no question but that such sphincters are present in many tissues. In other tissues, however, the same homeostatic adjustments appear to be performed by the terminal arterioles (Eriksson and Myrhage, 1972). With the controls located more proximally in the microcirculatory system, the net effect would be an overall shifting of flow through the capillary network as a whole. Such a mechanism would preclude active adjustments within the tissue, except for minor differences due to the distribution of pressure and flow. In contrast, separate controls more distally in the precapillaries would make such adjustments independent of the resistance function of the arterioles, which are subject to continuous modulation in line with the maintenance of systemic blood pressure. Let us examine some of these questions in greater detail.

STRUCTURE–FUNCTION RELATIONSHIPS

In view of their common nutritive function in most tissues, it would seem plausible to assume that all microcirculatory beds share certain fundamental features that permit them to fulfill these basic functions. In broad operational terms, the purpose of the microcirculation is to deliver blood to the parenchymal constituents of the tissues in accord with their metabolic activity. This is accomplished by allowing a given volume of blood to perfuse the terminal network of vessels at a rate that is compatible with an adequate exchange of fluids and materials across the blood–tissue interface. Because parenchymatous organs display a range of activity, some provision must be made to vary the volume and distribution of blood accordingly. The volume flow of blood to resting as contrasted to working skeletal muscle may differ by as much as tenfold. Furthermore, local mechanisms must exist to permit pressure, flow, and resistances to be maintained in a range appropriate for steady-state conditions. Inasmuch as the kinetics of exchange differ from tissue to tissue, it is highly probable that some structural basis exists for such a selective process.

The layout for particular microvascular networks is modified by the peculiar architecture of each tissue to the extent that some investigators have concluded that there was no overall structural design and that microcirculatory networks are more or less randomly distributed (Hammersen, 1970). The strongest argument for a structural module at the capillary level of organization was originally made on the basis of studies on mesenteric tissues (Zweifach, 1957). Despite the fact that these tissues are not made up of a mass of specialized parenchymal cells that exhibit extremes in metabolic demands, they possess the functional attributes of other microcirculatory beds in large parenchymatous organs such as skeletal muscle. They exhibit an ebb and flow of microcirculation, an intrinsic capacity to redistribute blood flow, and a distinctive local autonomy.

From the structural point of view, the most prominent landmark of the terminal vascular bed is its arteriolar parent trunk. When the direct extensions of these feeding vessels penetrate into the microvascular network, they are already of capillary dimensions, but can be recognized by the high velocity of the blood stream and their scalloped appearance due to the presence of vascular smooth muscle. In some tissues, such as the mesentery, anatomic pathways can be traced from arteriole to venule, and have been referred to as preferential channels (Zweifach, 1957). In other tissues, the arteriolar stem is distinctive but its extensions do not appear to have selective pathways to the collecting venules (Eriksson and Myrhage, 1972). It is interesting to note that developmental studies (Bar and Wolff, 1973) have shown the capillary networks in major tissues such as the brain, skin, and skeletal muscle to originate as preferential channels and only secondarily to develop side branches that form the capillary network proper.

The general construction of the capillary bed using the arteriolar stem as the central framework carries with it a number of ancillary features that contribute to local regulation. The smooth muscle of the distal continuations of the terminal arterioles is progressively thinned out and within the microcirculation is found only on the extremely fine terminal arterioles (10–12 μ) and the immediate junctional portions of their branches. These muscular junctions, which serve as sluice gates, have been termed precapillary sphincters (Wiedeman, 1967). Beyond this, the capillary network proper consists of endothelial tubes that show no vasomotor activity. The precise point within the microcirculation where vascular smooth muscle no longer occurs varies somewhat in the different tissues.

In most tissues, the precapillary branch has a muscular investment for only a short distance (some 20–50 μ), while in others the muscular branch may be as long as several hundred microns. These longer vessels usually distribute as many as seven to eight capillaries, which in turn dichotomize, so that in effect vasomotor adjustments of one parent vessel directly influence up to 20–30 capillaries, whereas in most tissues the activity of a short precapillary will effect the flow in only some four to six capillaries. The disposition of smooth muscle on these delicate arterioles can be determined in intravital preparations only by the spontaneous vasomotor activity and responses of these vessels. None of the capillaries and earliest venules show physiologic evidence of smooth muscle activity (Clark and Clark, 1943).

The structural keystone to the regulatory activities of the arteriolar-precapillary functional complex is the physics of the branching complex (Zweifach, 1974). The pressure drop and resistance in a branching system are governed by the relative size of the parent and daughter vessels. Because most of the precapillary side branches are of capillary dimensions, the ratio of the branch diameter to that of the parent trunk (40–50 μ wide) is between 0.3 and 0.35. In addition, such branchings have a neck-like configuration so that entry conditions

into the branch contribute substantially to the resulting pressure drop (Vawter, Fung, and Zweifach, 1974). Branching vessels with ratios of 0.3 and below are in the critical range where only a slight narrowing of the entry is sufficient to cut off flow completely into the offshoot.

Earlier concepts emphasized an all-or-none effect, a critical pressure below which precapillaries narrowed to shut off flow into the downstream capillaries (Nichol et al., 1951). Other recent studies indicate that the branching complex as a whole, rather than a sphincter per se, represents the important regulatory mechanism (Zweifach, 1974). The most appropriate term for this structural unit would be the arteriolar-precapillary junctional complex; most of the terminal arterioles have from five to ten such complexes. Minor changes in entry conditions (narrowing of terminal arteriole) or in size of the branch (narrowing of precapillary) can cut off capillary perfusion temporarily and lead to the intermittency observed in many tissues.

Another structural feature, which has been reported in some tissues but not in others, is the presence of anatomic "shunts" at the microvascular level (Chambers and Zweifach, 1944). Here again there has been a tendency to oversimplify and to cast aside the functional implications of the preferential flow channels because of variations in the distribution of small blood vessels to different tissues. There is, however, indirect evidence for the presence of preferential paths even in skeletal muscle (Hyman, 1971). For example, simultaneous recording of pressure in arterioles and venules that supply and drain a common area of the spinotrapezius muscle of the rat, or the mesentery of the cat, shows that a small percentage (15–20%) consistently have an AV pressure drop of as little as 10–12 cm H_2O, whereas in the majority of vessels, the pressure drop is 26–30 cm H_2O. Even in a random network of capillaries, as in the cat mesentery, not all of the capillaries have the same diameter. Several low-resistance paths are always present that allow a greater convective flow and in an operational sense can be considered as shunts. Low resistance AV paths of this kind are especially numerous in the mesentery, the omentum, the skin, and the ear microcirculation.

Other two-dimensional preparations, such as the bat wing and the hamster cheek pouch, do not show a definitive thoroughfare pattern (Webb and Nicoll, 1954). Nonetheless, the fact that even here the direct extensions of the arterioles form the backbone of the microcirculation and penetrate well into the capillary network, allows for the distribution of parallel precapillary offshoots that can confine blood flow almost entirely to the parent trunk. In skeletal muscle, the orderly parallel array of striated muscle fibrils is matched by a comparable alignment of the capillaries (Spalteholz, 1888). Thoroughfare channels are not a striking feature here, although the arrangement of the terminal arterioles in a transverse direction to the muscle fibers and their associated capillaries permits a high percentage of the flow to be restricted to a small percentage of the available channels.

Several other structural modules for the microcirculation have been described. In the cat mesentery, circumscribed areas of tissue are demarcated by pairs of interarcading arteriole-to-arteriole and venule-to-venule connections (Frasher and Wayland, 1972). The tissue within these walled-off zones is supplied by delicate arteriolar offshoots of these arcades. Although the arrangement of capillaries within this type of module is more or less random, differences in the caliber and length of the different vessels allow for a rapid shunt-like flow through paths that offer the least resistance. It is obvious that an arcading configuration by itself cannot serve as modular building blocks in three-dimensional arrays.

The term "functional shunting" has been used to describe an increase in regional blood flow that is not associated with a proportionate increase in exchange (Renkin, 1971). Various explanations have been proposed to account for this phenomenon. Such a discrepancy can arise if different groups of vessels have different permeability properties, e.g., throughfare type channels. Another possible mechanism would involve diffusional short circuiting, either between paired arterioles and venules, or between adjacent capillary networks (Crone, 1970). Finally, changes in pressure and flow may by themselves result in shifts in the permeability of the capillary barrier, either through changes in wall tension, or modification of the sieving properties of the vessel barrier.

In view of the existence of capillary vessels with substantially different permeabilities, selective shunting requires the presence of some type of regulation by means of which flow could be diverted selectively into or away from particular vessels. The observation that a reduced permeability to hydrophilic substances analogous to shunting develops at increased flow rates in skeletal muscle suggests that the restriction to diffusion through porous channels in the capillary wall may become more pronounced as blood flow is increased. It has been suggested that some form of pore plugging by plasma proteins may be responsible for such an effect (Trap-Jensen and Lassen, 1971). On the other hand, there is good evidence that "functional shunting" is present in skeletal muscle for gases (hydrogen) that presumably penetrate the vessel wall along its entire cell surface and do not require aqueous channels for their diffusion into the tissue compartment (Grunewald, 1968). Equally plausible alternatives would be either some type of redistribution of blood within the capillary network, or a change in the permeability of the vessel wall.

VASOMOTOR CONTROL OF MICROCIRCULATION

Endothelial Contractility

It is generally accepted that active vasomotor adjustments within the microcirculation of mammalian tissues occur only in those vessels with recognizable