Handbook of Physiology

a critical, comprehensive presentation of physiological knowledge and concepts

SECTION 2:

The Cardiovascular System

Formerly SECTION 2: Circulation

VOLUME IV.
MICROCIRCULATION, PART 2

Volume Editors: *EUGENE M. RENKIN*
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Preface

Three hundred and fifty years ago, the microcirculation was a hypothesis, a necessary link between the arteries and veins in Harvey's theory of the circulation of the blood. Although capillaries were observed by Malpighi three years after Harvey's death, two centuries elapsed before the cellular nature of the capillary wall was conclusively demonstrated. Since the middle of the nineteenth century, knowledge of the structure and function of small blood vessels has steadily increased, and the pioneering work of Müller, Poiseuille, Ludwig, Cohnheim, Starling, and Krogh has been sustained and developed by their many notable successors.

Although hemodynamics and transport in the minute blood vessels have always been recognized as topics of major importance, it is only recently that large numbers of investigators have been attracted to work on the microcirculation. Since publication of the first edition of the *Handbook of Physiology* on circulation more than twenty years ago, societies and journals dedicated to the microcirculation have proliferated, and the subject has become one of the most active and challenging areas of cardiovascular research.

Modern study of the microcirculation is an interdisciplinary exercise. It has long been a field where physical principles have been broadly and fruitfully applied, and at times the search for physical explanations of observed phenomena has led to the discovery of new physical relationships. For example, Poiseuille discovered a law that forms the basis of our understanding not only of microvascular flow but also of transport through porous membranes such as the capillary wall. Until twenty years ago, physical principles had been successfully applied to the microcirculation by only a few outstanding physiologists. In the mid-1960s, however, an influx of engineers and mathematically inclined biologists imparted a strong biophysical character to the field. This did much to enhance theoretical developments, particularly in the areas of rheology and transport. Somewhat earlier, electron microscopists had turned their attention to the microcirculation, and their contributions continue to increase. The early advances are admirably described by Majno in volume III of the first edition of the *Handbook* on circulation, but subsequent developments have drastically altered our ideas about the relationships between structure and function. Most recently there has been an upsurge of interest in the cellular biology of endothelium, and this promises to be one of the most important stimuli for further advancement.

Preparation of this edition of the *Handbook of Physiology* on the cardiovascular system has provided an opportunity for consolidation of essential concepts and new developments of microvascular physiology. Each chapter introduces the scope and principles of the topic it describes and offers to more experienced investigators a critical assessment of the status of current ideas and techniques. It is also hoped that this volume will help cardiovascular physiologists to correlate phenomena at the macrocirculatory and microcirculatory levels.

The volume begins with a historical review of the contributions of Poiseuille to our understanding of microvascular flow. This is followed by two chapters on the structure of the microcirculation, a chapter on endothelial cell biology, and one on microvascular growth and adaptation. The next two chapters are devoted to microcirculatory dynamics of blood and lymph. Six chapters on material transport in and around the microcirculation cover the mechanics and thermodynamics of transport, movement of fluid, movements of small solutes and of macromolecules, transport in the interstitium, and transport modeling. A chapter on control of the microcirculation and exchange forms a bridge between these chapters and the rest of the volume. The next eight chapters describe microcirculation and exchange in selected organs and organ systems: liver and spleen, heart, gastrointestinal system, lungs, synovial joints, adipose tissue, brain, and eye. Finally there are chapters on capillary portal circulations and on disseminated intravascular coagulation. We have not covered all the topics that might have been included, nor have we covered certain topics to the extent that some readers and authors might desire. However, this volume is larger than we originally expected, and an end had to be made somewhere.

We are grateful to the many contributors to this volume for their time and effort.

EUGENE M. RENKIN
C. CHARLES MICHEL

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CHAPTER 14

Control of microcirculation and blood-tissue exchange

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CHAPTER CONTENTS

THIS CHAPTER REVIEWS present knowledge of the mechanisms controlling peripheral circulation at the microcirculatory level and their influence on fluid exchange and solute transport. In the past 20 years the literature on this subject has expanded enormously, and it is not possible to examine all aspects of microvascular control or to cite all the important papers; coverage is restricted to the most general aspects. Special functions of the microcirculation and microcirculation control in specific organs and organ systems are dealt with in other chapters of this *Handbook* and its companion volumes (61, 489a). The reader's attention is also directed to recent symposia (189, 277, 295, 399a, 462), reviews (209, 391), and monographs (142, 278, 307, 438, 538).

Structures that may participate in the control of microvascular function include smooth muscle cells, pericytes or adventitial cells, and endothelial cells.

SMOOTH MUSCLE

Smooth muscle is responsible for major microvascular adjustments of pressure and flow. Relaxation or contraction of spirally arranged fibers controls the circumference and compliance of the vessel wall. Small changes in smooth muscle fiber length distributed over a large part of the microvasculature have a strong influence on total blood flow. Localized changes have important effects on blood flow distribution within the microvascular network. Smooth muscle fibers are present in arteries and arterioles down to the smallest branching order (terminal arterioles) in many tissues. In some instances single smooth muscle cells extend beyond arteriolar junctions with otherwise nonmuscular capillaries and control the entrances to those capillaries. They are termed *precapillary sphincters* (456, 552). The presence of true precapillary sphincters has been reported in many tissues and organs: frog mesentery (552), mouse mesentery (553), rat mesoappendix (18, 94), rat intestinal mucosa (201), dog

omentum (94), bat wing (413), frog retrolingual membrane (42), rabbit muscle fascia (456), and rat liver (388, 437). Zweifach and Metz (560) described precapillary sphincters in the spinotrapezius muscle of the rat. However, others have reported that vascular smooth muscle does not extend beyond the second or third level of arteriolar branching preceding the true capillaries in mammalian skeletal muscles (145, 146, 229, 515). The smallest unit of controlled flow distribution is thus a bundle of capillaries supplied by a muscular terminal arteriole (301). Wiedeman (in this *Handbook*; also ref. 537) and others (388) have suggested calling such an arteriole, or the last smooth muscle cell on it, a precapillary sphincter on functional grounds. Whatever the nomenclature, the distinction between control of capillary blood flow in single capillaries and control in bundles of adjacent capillaries is important. For a given fraction of perfused capillaries, maximum blood-to-tissue diffusion distances will be greater if the perfused capillaries are arranged in bundles rather than distributed individually (450).

In most mammalian tissues, smooth muscle cells reappear at the level of 30- to 50-μm-diameter venules and occur along the rest of the venous tree [(457, 534); see the chapter by Wiedeman and the chapter by Simionescu and Simionescu in this *Handbook*]. Because postcapillary resistance is generally much less than precapillary resistance, changes in dimensions of venules have only a small influence on total resistance and blood flow. However, they have an important effect on hydrostatic pressures in capillaries and smaller venules (425) and on vascular volume (390).

OTHER MICROVASCULAR EFFECTORS

Interest has returned to possible roles of microvascular pericytes (adventitial cells, Rouget's cells) and endothelial cells as agents of microvascular control. The early literature was reviewed by Krogh (337), who was convinced that both these elements were actively contractile and were involved in control of capillary blood flow. Later investigations support only limited or special roles for these "effectors" [(231, 534); see the chapter by Wiedeman in this *Handbook*].

Pericytes

Krogh (337, Lecture IV, Figs. 24–27) illustrates the difficulty in distinguishing microvascular pericytes from smooth muscle cells by vital microscopy. Clark and Clark (98) showed that noncontractile pericytes on capillaries growing into the rabbit's ear chamber were capable of differentiating into precapillary and arteriolar smooth muscle cells as growth proceeded. They did not observe contraction until the change was complete. A recent study of microvascular pericytes in rat skeletal and cardiac muscle showed weak "contractile" responses of the former but not the latter on perfusion with angiotensin, norepinephrine, or vasopressin (512). The morphology of the pericyte–endothelial cell contact was altered in a way that suggested shortening, but there was no indication that capillary diameter changed near the location of the cell. Pericytes are widely and characteristically distributed in practically all microvascular networks (337, 534). Their structure and association with capillaries in various organs have been studied in detail (174, 407, 457, 530, 542). However, except as precursors of microvascular smooth muscle cells, their functions remain unknown.

Endothelial Cells

Demonstration of fibrils resembling those of contractile cells (41, 430) and identification of proteins similar to those in skeletal and smooth muscle (37) have redrawn attention to the contractile properties of microvascular endothelial cells. There is no question of endothelial cell motility in growing capillary sprouts and in remodeling of the microvascular pattern by local growth and regression [(97a); see the chapter by Hudlická in this *Handbook*]. Direct mechanical stimulation (e.g., by microneedle) may cause endothelial cells to change their shape (552). Specific morphological changes reported include cell swelling with luminal narrowing (no change in outer diameter) and bulging of endothelial nuclei into the capillary lumen, partially obstructing it (430). Krogh (335–337) and many early investigators were convinced that capillary contraction was responsible for many aspects of capillary blood flow control. However, Clark and Clark (99) considered all diameter changes of microvessels not supplied with smooth muscle to be passive. Zweifach (552) and Illig (282) did not observe endothelial contractions in response to known vasoactive stimuli. Zweifach (558) wrote: "It is generally accepted that active vasomotor adjustments within the microcirculation of mammalian tissues occur only in those vessels with recognizable smooth muscles in their walls."

However, endothelial motility may serve functions other than general control of microvascular pressure and flow. Lübbers and colleagues (367, 531) recently identified local sites in capillaries of frog and rabbit mesentery responding to electrical stimulation by endothelial contraction. They suggested a special role in distribution of capillary flow in response to physiological stimuli (nervous, humoral, or chemical). Another special role may be regulation of endothelial permeability. Majno and associates (306, 381) reported morphological changes in endothelial cells of postcapillary venules after application of histamine that suggested cell contraction: thickened cell nuclei with indented surface contours and sizable gaps between adjacent cells. Their interpretation of these changes as consequences of contraction has been contested by Hammersen (231), who suggests that the changes may

result from detachment of junctional processes holding the cells together and consequent elastic recoil of the cells. The mechanisms by which endothelial cells influence microvascular permeability can include more subtle variations in intercellular contact: changes in surface membrane characteristics and changes in vesicular turnover, size, or surface properties (see the chapter by Michel, the chapter by Crone and Levitt, and the chapter by Taylor and Granger in this *Handbook*).

SERIES AND PARALLEL MICROVASCULAR COMPONENTS

Folkow, Mellander, and their collaborators (100, 169, 390, 391) introduced the concept of consecutive vascular sections to emphasize the influence of location of microvascular smooth muscle on its function. Arterioles were termed *resistance vessels* because they are the most important effectors for control of hemodynamic resistance and local blood flow. Arteries and larger arterioles were also called *Windkessel* (windchest) *vessels* because their compliance contributes to distribution of energy from cardiac systole to propulsion of blood during diastole. Capillaries and nonmuscular venules were designated *exchange vessels*. The degree to which total exchange capacity is utilized depends on the extent to which these vessels are open to blood flow and is thus controlled by terminal arterioles and precapillary sphincters. Muscular venules and small veins are the site of *postcapillary resistance*. Although their contributions to total resistance are small compared with arterioles, the ratio of postcapillary resistance to precapillary resistance is an important factor in control of capillary pressure and fluid exchange. These venules and small veins were also termed *capacitance vessels* because they contain a large fraction of microvascular blood volume and because contraction of venular smooth muscle can divert blood from peripheral to central circulation. The concept of consecutive sections has been enormously useful in interpreting the effects of specific vasomotor mechanisms on microvascular functions. However, the boundaries of microvascular smooth muscle action are not as sharp as this description implies, and the functions of resistance, capacitance, and exchange are shared by all parts of the vascular bed.

Many vascular networks have anatomical distinctions among alternate parallel pathways at the level of terminal arterioles and capillaries. Zweifach (552) described preferential arteriovenous (AV) pathways (thoroughfare channels, central canals, metarterioles) in the microvasculature of frog mesentery. They start as terminal branches of the arteriolar system, but their coat of smooth muscle cells gradually thins out and disappears as they continue their course, and they eventually join other vessels to form venules. Along their course they give rise to several capillaries; those from the muscular, arteriolar end of the preferential channel have smooth muscle sphincters at their junctions (282, 456). In states of low overall flow, blood flow may be restricted largely to these central channels. Extension of flow to the rest of the network depends on the opening of precapillary sphincters. Similar arrangements have been reported in the mesenteric microcirculation of mice (553), rat mesentery (282), rat mesoappendix (94), and dog omentum (94). Anatomically differentiated preferential channels corresponding to metarterioles do not appear characteristic of the microcirculation in rabbit mesentery (282), bat wing (413), skeletal muscle (134, 146, 515), or intestinal wall (201).

In a few parts of the body, notably certain regions of skin and dog tongue, true AV anastomoses are found (232). They are short, wide, muscular vessels connecting arterioles and venules of moderate size bypassing the exchange vessels. Their function seems to be maintenance of extremity temperature in a cold environment or facilitation of heat loss. Less specialized AV channels are reported in bat wing (413) and in skeletal muscle (560). They are often shown in illustrations, but invariably the text points out that their numbers are too small to account for a significant fraction of total blood flow (27, 230, 560). Attempts to measure AV shunt flow by transit of large microspheres have yielded values below 5% of total flow, except for organs like dog tongue and paw in which well-differentiated AV anastomoses are known to be present (120, 148, 432). Note that this method measures flow through connections exceeding a specified width (somewhat smaller than the diameter of the spheres used) and will not show the presence of short, narrow connections.

PHYSICAL FACTORS CONTROLLING FLOW AND EXCHANGE

Temporal Flow Patterns and Velocities

Early vital microscopic observations emphasized intermittence of flow in individual capillaries, with constantly shifting perfusion of a variable fraction of the microvascular network (282, 336, 337, 343, 376, 413, 552, 553). Anatomical differentiation of constant and intermittent flow pathways has been described for some tissues (552, 553). The older studies do not provide quantitative descriptions of spatial or temporal flow variability or of the fraction of microvessels perfused at a given time. Limited data on heterogeneity of perfusion have been derived from microscopic examination of fixed or frozen tissue samples with the use of endogenous red blood cells (RBCs) (274, 275) or infused dye or India ink (102, 334, 385, 526) to identify perfused vessels. By these methods the fraction of capillaries perfused at any time in resting skeletal muscles has been estimated to be as little as

1% (334) or as high as 90% (526). Table 1 lists some of these measurements. Although histological methods are valuable because they can be applied to bulk tissues inaccessible to vital microscopy, the variability of results obtained suggests more serious technological problems than have generally been recognized. The distribution of RBCs or more finely particulate tracers (India ink) may differ from that of moving blood or plasma (21, 504). Furthermore the degree of filling of the microvascular bed with exogenous dye or ink depends on the total blood flow rate and the time of exposure to the marker, as well as on the fraction of vessels open (450).

Recent vital microscopic studies attempted to quantify microvascular flow patterns by measuring local RBC flow velocities. On the basis of such measurements, Johnson and Wayland (303) described five kinds of temporal flow variability in capillaries of cat mesentery (Fig. 1). In only one capillary of type C and the two of type E did RBC velocity fall to zero at any time. Periodic and pulsatile flow patterns in individual capillaries were unrelated to flow patterns in adjacent capillaries and were attributed to the action of precapillary sphincters. In cat mesentery, spatial and temporal variations in capillary pressure appear to be much smaller than variations in flow (557).

Burton and Johnson (88; see also 192, 247) described three RBC velocity patterns in capillaries of cat sartorius muscle: *1*) steady flow with small variations (no more than 25% in any 15-s interval), 65% of 57 capillaries observed; *2*) periodic variations in velocity (10- to 15-s period; with amplitudes only occasionally going to zero) 10%; and *3*) irregular variations in velocity (going down to zero for brief intervals) 25%. These patterns persisted through 15-min observation periods. Individual capillaries in muscle showed only irregular, nonperiodic oscillations, which Fung (186) attributed to random distribution of the formed elements of blood. Periodicity, where present, was not localized to single capillaries but generally to a group of 6–12 capillaries sharing the same periodic pattern, which was supposed to originate at the level of their common arteriolar origin (301). Periodic flow was present in 26% of the capillaries of cat mesentery and in only 10% of the capillaries of skeletal muscle in the studies of Johnson and colleagues. Other workers found no periodic variations in capillary flow other than those synchronous with the arterial pulse in cat omentum (283), frog skeletal muscle (519), or rat cremaster muscle (495). In the preparations described by Johnson and colleagues (88, 192, 247, 299, 303), apparently all the capillaries were accounted for. In skeletal muscles no more were observed to become perfused during reactive hyperemia (88, 247, 297). These observations present a picture of microvascular beds fully or almost fully perfused but with widely varying flow rates in different channels. Only a small fraction of the capillaries in either mesentery or skeletal muscle were intermittent in the sense used by Krogh (337).

Still more recent reports describe substantial fractions of the total capillary population in resting skeletal muscle as either devoid of RBCs or containing a few stationary cells (197, 359, 434, 507). The fraction of perfused capillaries varied with environmental or partial pressure of O_2 (P_{O_2}) in the tissue. Sullivan and Johnson (507) reported that as P_{O_2} was increased, the number of terminal and preterminal arterioles per-

TABLE 1. *Open-Capillary Densities in Skeletal Muscles: Histologic Measurements*

Muscle	Conditions	Open Capillaries/mm²	Open Fraction, %	Method	Ref.
Frog sartorius	Rest	10–90	3–28	India ink	334
Guinea pig abdominal	Rest	31–270	1–11		334
Rat abdominal	Rest	[a]	90	FITC-dextran	526
Rat gracilis anticus	Rest	[b]	61	Fluorescein	102
	Contracting, tetani/min				
	4		73		
	8		82		
	12		100		
Dog gracilis	Rest	1,050[c]	41	India ink[d]	385
	Postcontraction	2,000	78		
	Maximum vasodilatation	2,580	100		
	Rest	655	34 (57)[e]	RBC	275
	Contracting, 4 twitches/s	1,123	59 (100)[e]		

"Open" is defined as containing ink, dye, or RBCs. (See ref. 450 for critique of histological methods of identifying open capillaries.) [a] Reported capillaries/fiber 0.76–0.89 rest, 0.81–1.00 exercise. Assume 100% open in exercise. [b] Reported capillaries/fiber 0.57 rest; 0.69, 0.77, 0.94 exercise. Assume 100% open in maximum exercise. [c] Absolute capillaries/mm² too high because uncorrected for shrinkage (cf. 477). Capillaries/fiber (unaffected by shrinkage) 0.64 rest, 1.23 exercise; 1.57 maximum vasodilatation (amyl nitrite). [d] Perfusion for 10 s at prevailing flow rate directly after blood. [e] Values in parentheses are calculated assuming 100% open in maximum exercise vasodilatation. Authors applied arbitrary shrinkage corrections of 20%–30% to data of Martin et al. (385) to obtain total capillary density of 1,800–2,000/mm² for comparison with their measured densities; they concluded that only 34% of capillaries were perfused at rest, 59% during contractions at 4/s. However, Schmidt-Nielsen and Pennycuik (477) corrected their values for shrinkage by direct measurement of blocks during processing and reported lower densities for dog muscles (~800 capillaries/mm²). Thus the value of 1,123 represents nearly all capillaries present.

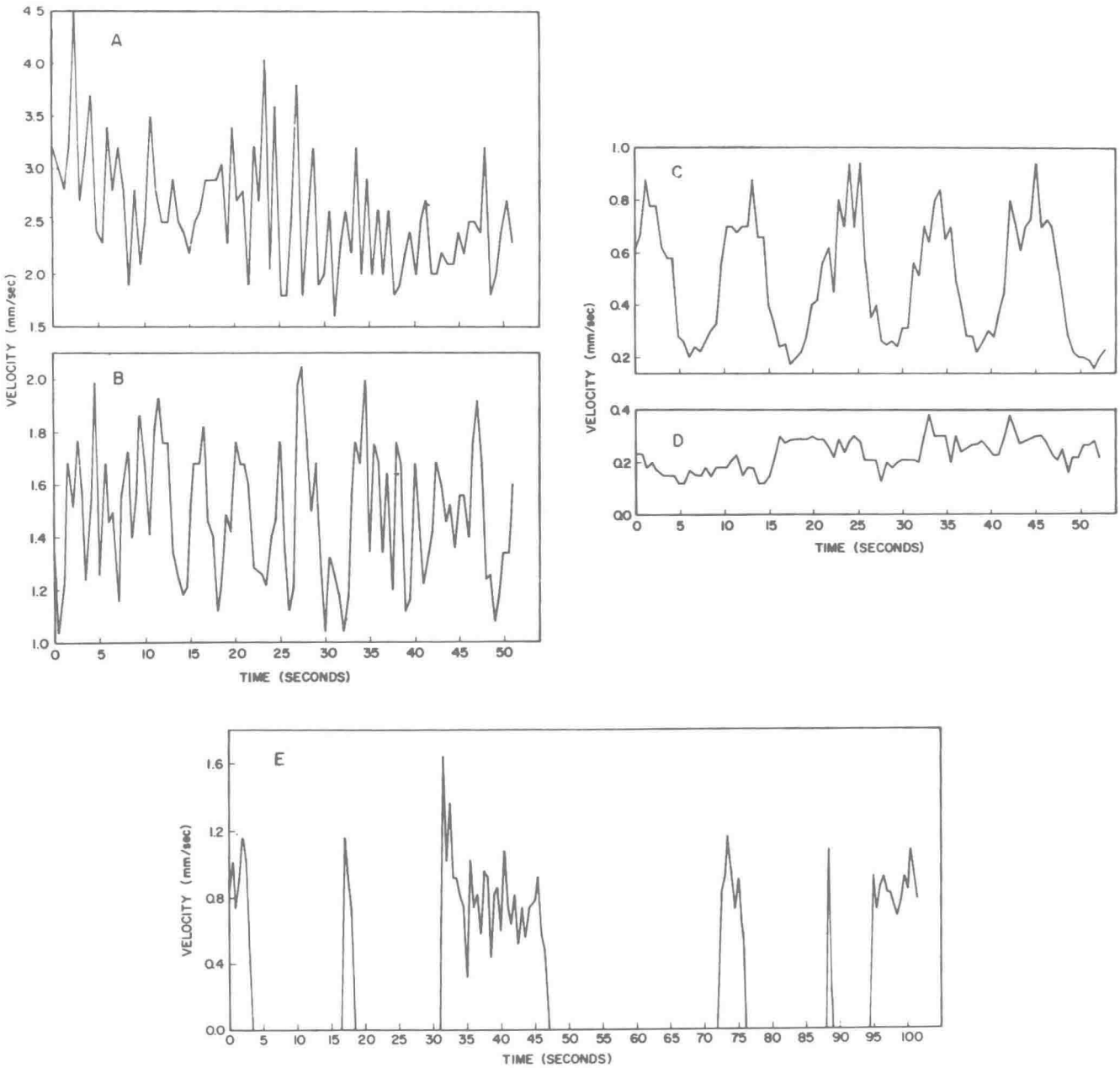


FIG. 1. Patterns of red blood cell (RBC) flow in single capillaries of cat mesentery. *A*: thoroughfare channel, high RBC velocity with irregular and random variation (2 of 27 capillaries studied). *B*: nonperiodic flow with large velocity variations (13 of 27). *C*: periodic flow, 5- to 15-s periods (7 of 27). *D*: low RBC velocity with irregular small variations (3 of 27). *E*: intermittent flow (on-off), nonperiodic (2 of 27). [From Johnson and Wayland (303).]

fused decreased along with the number of perfused capillaries, though not to the same extent. These reports describe both steady and periodic flow patterns with simultaneous periodicity in groups of capillaries but do not classify flow patterns or give their frequency of occurrence. Table 2 lists some values of open-capillary density and mean RBC flow velocities measured by vital microscopy.

Descriptions of microvascular flow patterns may represent normal microcirculation only if associated mean flow velocities and open-capillary densities are compatible with physiological flow rates measured at the whole-organ level. For a given bulk flow rate (q), there is an inverse relation between mean capillary flow velocity ($\bar{v}$) and the number of open capillaries per unit volume of tissue. For a bed of uniform parallel

TABLE 2. *Open-Capillary Densities and RBC Flow Velocities in Skeletal Muscles: Direct Vital Microscopic Measurements*

Muscle	Conditions		Open Capillaries/ mm²	Open Fraction, %	RBC Velocity,† mm/s	Ref.
Frog pectoralis	Rest				0.46 ± 0.37 (0.2–7.0)	192
Rat cremaster	Rest		1,300	65–100	0.70 (0.2–1.0)	495
Hamster cremaster	Rest, P_{O_2} 8 mmHg*		410		0.21	323
	Rest, P_{O_2} 10–17 mmHg			51		197
	Contracting, twitches/s					
	1			68		
	2			76		
	4			100		
Rabbit tenuissimus	Rest; P_{O_2}, mmHg; P_{CO_2}, mmHg*					
	5	40	269 ± 22	48	0.29 ± 0.14	359
	22	40	232 ± 16	41	0.24 ± 0.13	
	35	40	177 ± 30	32	0.23 ± 0.13	
	65	40	97 ± 56	17	0.21 ± 0.12	
	100	40	6 ± 10	1	0.18 ± 0.06	
	150	40	0	0		
Cat tenuissimus	Rest		650	100	0.50 (0–1.5)	146
Cat sartorius	Rest			70–100	0.38 (0–1.8)	88, 297
	Rest		310	23	~0.73	340

"Open" is defined as containing moving RBCs. * Superfusate P_{O_2}, P_{CO_2}. † Means ± SD, range in parentheses.

capillaries, as in skeletal muscles, this relation can be expressed as (450)

$$\bar{v}(\text{blood}) = \frac{ql}{N(\pi/4)d^2} \quad (1)$$

where N = number of open capillaries per square millimeter of tissue cross section, $\pi = 3.14$, d = capillary diameter, and l = average depth of tissue traversed by a capillary between arteriole and venule (if capillary is not straight, l = capillary length ÷ path tortuosity). Figure 2 is a nomogram of this relation. The RBC velocity is assumed to be 1.25 blood velocity (21, 323, 504). The central line represents the level of blood flow in resting skeletal muscle (6 $ml \cdot min^{-1} \cdot 100\ g^{-1}$). For a capillary density of 600/mm², $\bar{v}$ (RBC) = 0.11 mm/s. Comparison of this chart with some of the values in the literature (Table 2) shows that the regions observed must have been hyperemic.

Microvascular Pressures and Resistances

Within a network of interconnected vessels, the distribution of resistance or the location of principal sites of resistance can be inferred from the steepness of the fall in pressure in the direction of flow. Figure 3 shows selected examples of microvascular pressure gradients measured directly by micropuncture under presumably basal conditions. These are mean pressures averaged over temporal and spatial variation for vessels of each class. In most examples the greater part of total resistance lies in small arteries and arterioles.

There is often a substantial pressure drop in arterioles and venules >100 μm in diameter. This does not appear to be a special characteristic of any particular bed but may be related to the level of arterial pressure. Table 3 lists values of large- and small-vessel resistances (as fractions of total resistance) calculated from direct micropuncture measurements. These figures are supported by macroscopic data obtained by direct, obstructive, retrograde cannulation of arteries and veins 300–500 μm in diameter (224, 225). Table 4 gives resistance values (as fractions of total resistance) for small arteries (0.17–0.57), microvascular segments (0.31–0.80), and small veins (0.03–0.12) obtained for several experimental preparations.

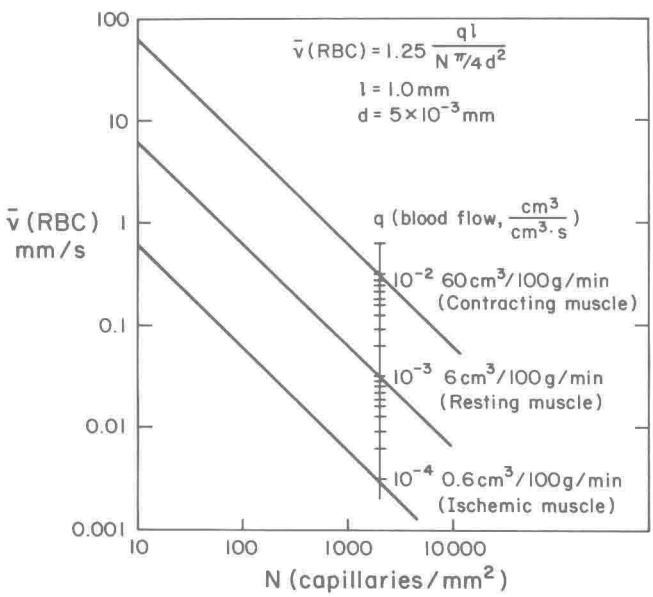
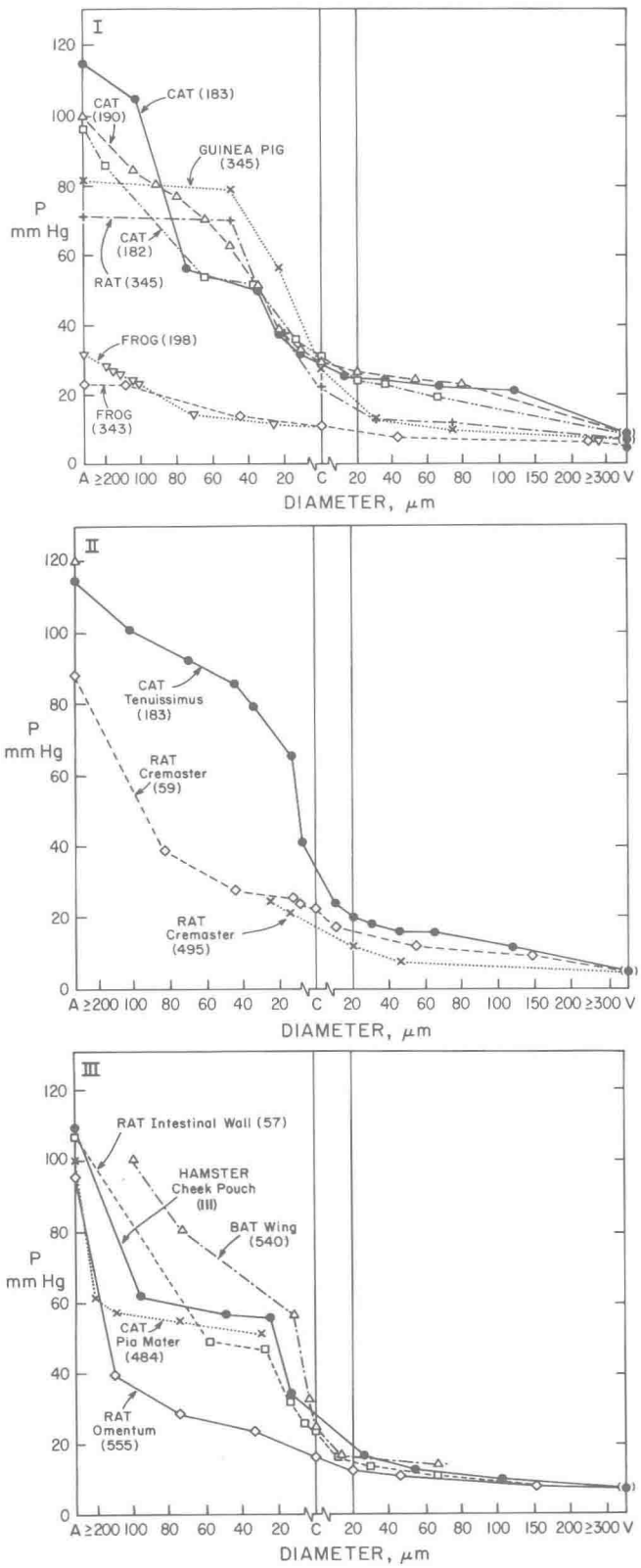


FIG. 2. Nomogram of relation between mean RBC velocity [$\bar{v}$(RBC)], capillary density (N), and total blood flow per unit tissue volume (q). Calculated for parallel array of capillaries (5 μm diam) between arterial and venous connections (l) 1.0 mm apart, assuming $\bar{v}$(RBC) = 1.25$\bar{v}$(blood). All scales are logarithmic. Units of q are s^{-1} (= $cm^3 \cdot cm^{-3} \cdot s^{-1}$). If l is more or less than 1.0 mm, or if $\bar{v}$(RBC) is more or less than 1.25$\bar{v}$(blood), the scales must be adjusted accordingly.

Within arteriolar microvessels <100 μm in diameter, there are often two regions of different slopes: vessels > 40–60 μm in diameter (which may be considered as a continuation of large-artery category) and vessels < 40–60 μm in diameter.



The pressure drop across the capillaries (and hence their share of total resistance) is small but not negligible. This is not evident in Figure 3 because only mean capillary pressures are given. Table 5, derived from micropuncture data, divides total resistance for several vascular beds into fractions: large artery to capillary, capillary, and capillary to large vein. Except for the pulmonary vascular bed, in which the capillaries may be the major component of total resistance (51, 74), values of capillary resistance from 0 to 0.59 of total resistance have been reported. Some of the higher values may be due to inclusion of terminal arterioles and/or postcapillary venules with true capillaries, but ratios between 0.1 and 0.2 are frequently observed. Variations of capillary resistance must depend largely on the number of capillaries perfused.

Resistance of the venules and small veins (Table 5, R_{cv}/R_{tot}) seems to be comparable in magnitude to that of the capillaries. Comparison with the ratios for large vein resistance in Table 4 shows that 25%–50% of total venous resistance is attributable to large vessels.

Hydrostatic pressures in anatomically defined ("true") capillaries (Fig. 3*C*) are with few exceptions greater than what one would predict for maintenance of fluid balance according to Starling's hypothesis

$$P_{c,iso} = \Pi_P - \Pi_{ISF} + P_{ISF} \qquad (2)$$

where $P_{c,iso}$ = isovolumetric or isogravimetric capillary pressure, Π_P = colloid osmotic pressure of plasma, Π_{ISF} = colloid osmotic pressure of interstitial fluid, and P_{ISF} = hydrostatic pressure of interstitial fluid [(344, 348, 425); see also the chapter by Michel in this *Handbook*]. For systemic capillaries in mammals, reasonable values of Π_P, Π_{ISF}, and P_{ISF} might be taken as 25, 10, and −1 mmHg, respectively, leading to an estimate of $P_{c,iso}$ = 16 mmHg (13). Measured mean pressures in true capillaries of mammalian mesentery, omentum, and skeletal muscle range from 19 to 36 mmHg. In intestinal wall, P_c = 24 mmHg, but in the mucosa (an absorbing organ) P_c = 14 mmHg (201). Perhaps the omentum and mesentery are normally filtering organs (182, 283), with reuptake of fluid occurring elsewhere in the abdominal cavity. However, this does not seem likely for intestinal wall or skeletal muscle, in which most of the fluid lost from the capillaries must be taken up in vessels downstream with lower pressures. Pressures close to estimated $P_{c,iso}$ values are found in postcapillary venules 20–100 μm in diameter. Some of the measured microvascular pressures may be elevated due to vasodilatation on exposure or mechanical interference with venous outflow, but even the lowest measured values support the

FIG. 3. Examples of microvascular pressure gradients measured directly by micropuncture in mesentery (*I*), skeletal muscles (*II*), miscellaneous tissues (*III*). (More examples may be found in refs. 51, 57, 541, 556, 557.) A, large-artery pressure; V, large-vein pressure; C, mean capillary pressure.

concept that postcapillary venules are an important site of "transcapillary" fluid exchange.

Because the resistance vessels are distensible (87, 166), total vascular resistance tends to fall with increasing transmural pressure in the absence of compensatory smooth muscle responses. Blood flow will thus vary more than in proportion to perfusion pressure. Diameters of apparently passive arterioles and venules of cat mesentery (199) and rat intestinal wall (57) decreased as arterial pressure was lowered from 110 to 20 mmHg. At normal levels of arterial pressure, pressures within arterioles of different sizes appear to lie on the flat upper limb of their distensibility curves (low compliance). For venules, however, normal operating pressures are on the steeply rising limb (high compliance). In most microvascular beds, only passive responses of venules to increasing transmural pressure have been reported even when the arterioles show active constriction (18). The venules of the bat wing (71, 413) are an exception. (Of course, venular smooth muscle can respond to other stimuli.)

TABLE 3. *Resistance of Vessels Larger Than 100 μm Diameter Calculated From Micropuncture Pressure Measurements*

	Arterioles ≥100 μm diam	Venules ≥100 μm diam	Ref.
Frog mesentery	0*	0*	343
	0.28	0.08	541
	0.31	0.07	198
Rat omentum	0.63		555
Rat cremaster		0.06	59
Hamster cheek pouch	0.46	0.05	111
Cat mesentery	0.10		182
	0.17		199
	0.09	0.13	183
Cat tenuissimus	0.13	0.07	183
Cat pia mater	0.45		484

Values are ratios of resistance in large vessels to total vascular resistance (R/R_{tot}). * No measurable pressure drop from large artery or to large vein.

Microvascular Volume

Capacitance represents the ability of a blood vessel or assemblage of vessels to change its volume and thus its potential contribution to control of venous return. The volume of a blood vessel (V) as a function of transmural pressure ($P_T = P_{inside} - P_{outside}$) can be represented by two components: an unstressed volume (V_0), which is the volume contained at zero P_T, and the product of P_T and volume compliance (C).

$$V = V_0 + CP_T \quad (3)$$

Over a wide range of P_T values, C is not constant but tends to decrease as P_T increases (87, 202). Both V_0 and C may be altered by contraction or relaxation of the smooth muscle in vascular walls; contraction tends to decrease both. The capacitance function of a vascular bed includes changes in both terms. It is possible to specify an active capacitance function by eliminating those changes due to P_T alone. This can be done precisely for single vessels for which inside and outside pressures can be measured directly. However, for networks of vessels only crude approximations to P_T can be made, such as $(P_{sa} + P_{sv})/2$ for the whole microvascular bed or $(P_c + P_{sv})/2$ for the postcapillary section (166); P_{sa} = small-artery pressure and P_{sv} = small-vein pressure.

All elements of the microvasculature contribute to the capacitance function of the network. Arterial and all but the smallest venous vessels are provided with smooth muscle cells and can undergo active changes in volume and compliance as well as passive changes. Capillaries and nonmuscular collecting venules can participate in passive volume changes. Volume changes in small arteries, arterioles, and capillaries are not entirely negligible, but because both V_0 and C are much greater for venules and small veins, these vessels are believed to be responsible for the greater part of active and passive volume changes observed during cardiovascular regulation (87, 169). The extent

TABLE 4. *Resistance of Large and Small Vessels Measured in Whole Organs by Cannulation of Arteries and Veins (0.5–0.3 mm Diam)*

	P_a, mmHg	P_v, mmHg	Q, ml·mm^{-1}·100 g^{-1}	R_{tot}, mmHg·ml^{-1}·min^{-1}·100 g^{-1}	R_{sa}/R_{tot}	R_{mv}/R_{tot}	R_{sv}/R_{tot}	Ref.
Dog								
Hindleg	123	4.2			0.49	0.42	0.09	225
	125	7*			0.21	0.75	0.04	310
Foreleg	113	7.5	15.0	6.9	0.49	0.43	0.08	224
	122	6.0	14.2	18.2	0.37	0.58	0.05	223
	117	4.0			0.17	0.80	0.03	143
Foreleg skin	129	5.1	13.0	9.5	0.21	0.75	0.04	480
Foreleg muscles	126	5.7	10.7	11.7	0.22	0.74	0.04	480
SD	8	1.8	2.0	1.4	0.06	0.05	0.02	
Intestine	101	8*			0.44	0.51	0.04	510
	100	1.9	18.2	5.4	0.18	0.75	0.07	298
Cat hindleg muscles	110	6.0	8.9	11.7	0.57	0.31	0.12	373

P_a, large-artery pressure; P_v, large-vein pressure; Q, blood flow; R_{tot}, total vascular resistance [$R_{tot} = (P_a - P_v)/Q$]. If P_{sa} and P_{sv} are pressures measured in small-artery and small-vein cannulas, then $R_{sa}/R_{tot} = (P_a - P_{sa})/(P_a - P_v)$, $R_{mv}/R_{tot} = (P_{sa} - P_{sv})/(P_a - P_v)$ and $R_{sv}/R_{tot} = (P_{sv} - P_v)/(P_a - P_v)$. * Estimated value. [Method of Haddy et al. (225).]