The Microcirculation in Clinical Medicine

EDITED BY Roe Wells

THE MICROCIRCULATION IN CLINICAL MEDICINE

Edited by

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Peter Bent Brigham Hospital and
Harvard Medical School
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Erratum

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Roe Wells, Editor

In the List of Contributors (pp. xiii-xiv) the following information should appear:

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FOREWORD

The history of medicine illustrates that remote or esoteric studies of the basic science laboratories eventually find their way to the clinical arena, whether by integration into a larger clinical subject or by the development of a clinically feasible test procedure that leads to a whole new series of clinical entities, e.g., the flame photometer and the spectrum of serum electrolyte abnormalities.

Over 50 years ago Augustus Krogh reported his observations of blood flow in the mesenteric membranes of small laboratory animals. Five years later Eugene Landis quantitated the pressures in the microvasculature. Today the clinician is faced with a rapidly increasing flow of laboratory and clinical reports describing microvascular involvement or reactions in a wide variety of important new clinical phenomena. The term microcirculation now appears repeatedly in the literature of shock, transplantation, diabetes, cancer, and many other disorders.

It becomes apparent therefore that some unifying or integrated overview of this vascular system would be of great value to clinicians. This should not only provide a better perspective for those already interested in the subject, but should also provide, as Dr. Wells notes, a broad introduction for clinicians who may not have realized how often they must refer to the microcirculation in their deliberations on the pathophysiology of disease.

I am confident this book will accomplish its purpose of stimulating the clinician to consider the hemodynamics of the microcirculation in his day-to-day thoughts about diagnosis and therapy. It is but another example of how investments in basic science research eventually play a role in better medical care for the consumer and the community.

ROBERT EBERT, M.D.
Harvard Medical School

PREFACE

The clinician who must often consider disease in terms of organ systems has rarely had occasion to think of the microcirculation as either an organ system or as a primary site of pathologic phenomena. This is due to the fact that the microcirculation is not often considered as a functional component of the cardiovascular system. This misconception plus the lack of published information on the clinical aspects of the microcirculation have combined to leave the clinician unprepared to evaluate disease processes in terms of microvascular reactions or pathology. This book is designed to introduce the clinician to the concept that the microcirculation is an important and dynamic vascular system, consideration of which can fruitfully be applied in both differential diagnosis and therapy.

The bulk of the research in this field has generally been reported in the basic science literature, yet it contains many findings that have direct application to contemporary clinical problems such as shock, thrombosis, organ transplantation, and hemoglobinopathies. One of the aims of this work, therefore, is to bring to the clinician's attention contemporary research findings that will be useful to him in the analysis of clinical problems. References are recorded for those wishing to pursue any given subjects in greater detail.

The present rate of accumulation of new knowledge is such that accomplishment of these goals by a single author would occupy such time that a major portion of the material would require revision by the time the last chapter was written. Multiple authorship appears to be the best solution to this problem, acknowledging that it tends to produce variation in style and method of presentation.

The nature of the subject is such that most readers will likely utilize this book with reference to that disease state or organ system which is most pertinent to their primary interest. The possibility of this variable usage notwithstanding, the larger goal remains the illustration that the microcirculation is a dynamic component of the total cardiovascular system and is involved either primarily or secondarily in a wide variety of clinical conditions.

ROE WELLS

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Kenneth H. Falchuk

1 ANATOMY

MARY P. WIEDEMAN, Ph.D.

I. Historical Introduction

The smallest blood vessels, those that represent the microcirculation, were first mentioned as a concept rather than as a reality. They were conceived in the mind of William Harvey, whose experimental and speculative conclusions were published in 1628 and remained as a product of Harvey's logical reasoning until magnifying lenses in the hands of Marcello Malpighi, a professor of medicine in Bologna in 1661, revealed to him "tubules" through which blood flowed from arterial to venous vessels (Young, 1929).

Information regarding the microcirculation was collected sporadically as interest waxed and waned. Among the notable contributors during the nineteenth century was Leeuwenhoek, who drew the vascular patterns he saw in various aquatic forms and documented the continuity between arteries and veins. Definitive terminology had still not been accepted (as it has not today) in the nineteenth century, which made it difficult for historians to describe the progress that was being made in unraveling the structure and function of microscopic vascular networks (van Leeuwenhoek, 1964).

The first attempt to differentiate between arterioles, capillaries, and venules was made by Marshall Hall in 1831 who defined arterial vessels as those which divided to become smaller and smaller, and venous vessels as those which enlarged as a result of confluences. He saw capillaries as being different from both in that they maintained a uniform diameter. He also reasoned that, functionally, capillaries served as nutritional beds. His observations were made on fishes and frogs. In 1852, T. Wharton Jones presented a paper containing microscopic observations on blood vessels in the wing of the bat and focused his attention on the veins, describing in detail their spontaneous contractile activity and the action of venous valves. Müller, in 1838, published a review of the literature extant at that time and included diameters of capillaries in various tissues. He noted that vascular beds assumed different patterns depending on the tissues, taking on special characteristics to accommodate to specific areas. It must be surprising to current students of microcirculation to discover, in researching the literature, that there is such an extensive and detailed background of descriptive material, and yet, in 300 years of microscopic observations of small blood vessels, there are still many deficiencies in regard to both architecture and function.

After the flurry of activity in the middle 1800's, little of consequence appeared until a new interest was generated by August Krogh whose book "The Anatomy and Physiology of Capillaries," published in 1922, promised to be the source book and the irrefutable reference for all things pertaining to the subject matter, about which, in view of such an encompassing title, all was known, all problems solved. The reaction was not one of total acceptance, however, and a new era of investigation began with more sophisticated equipment and the introduction of new techniques utilizing *in vivo* microscopy. Many of the techniques are in use today.

In general, there are four basic methods. One technique employs the fused quartz rod, fiber optics, or some other means of transmitting light to relatively inaccessible areas, and by this means tissues can be observed *in situ*. Such tissues are lung, spleen, and liver. Another method is the preparation of tissues for transillumination by the implantation of transparent chambers, as has been done in the rabbit ear, the hamster cheek pouch, and the skin of various mammals. A third method consists of the exteriorization of suitable tissues for direct microscopic observation, such as the cecal mesentery of the rat, the omentum and mesentery of the dog and cat, and the cremaster muscle of the rat. A fourth method is the utilization of superficial structures whose vasculature can be easily seen with transmitted or direct light, such as the wing membrane of the bat or conjunctival vessels in man. Detailed descriptions of these and other methods can be found in the current literature (Wiedeman, 1967).

The development of new methods, the refinement of older ones, and their current widespread use in both clinical and basic science laboratories attest to the continued interest in the microcirculation as a site for discovering the solution to problems related to the cardiovascular system.

II. Terminal Vascular Beds

A. Components

The final ramifications of the arterial distribution represents the beginning of the terminal vasculature. Between the large, thick-walled aorta, heavily endowed with elastic and fibrous tissue, and the pure endothelial tube which is the capillary, there is a gradual thinning of elastic and fibrous tissue. Wall thickness decreases and also the diameter of the vessels, from approximately 25 mm in the aorta to 5 μm in the capillary. The relationship between wall thickness and the internal diameter varies with the distribution of smooth muscle and this is determined by the functional role of the different categories of vessels. The details of wall structure will be considered in the chapter dealing with ultrastructure.

The vessels which are recognized as components of the microcirculation are arterioles, terminal arterioles, capillaries, postcapillary venules, and venules.

B. Definition of Components

Although there is no universally accepted nomenclature or list of specific characteristics to use as a guide in defining the vessels of the microcirculation, there are generalizations which can be made to assist in identification.

The term "microcirculation" is used to designate blood flow through small vessels. The microcirculatory bed is that portion of the vascular system which is concerned with the transfer of gases and nutrients and the removal of metabolic waste products and is referred to as the exchange system. The vessels designed to function in the exchange of materials to maintain the life of tissues and cells are considered separately from the vessels of the macrocirculation which are designed for the maintenance of systemic blood pressure to assure the delivery of blood to the microcirculation.

The microcirculatory system begins with arterioles. Branches from arterioles are called terminal arterioles, so named because they terminate in a capillary network and have no vascular communication, such as an anastomosis or arcuate structure, with any other arterial or venous vessel. The increasingly familiar "precapillary sphincter" has almost as many definitions as there are investigators who have needed its functional activity to explain their observations. In general, however, it is the portion of the terminal arteriole that contracts or relaxes to monitor blood flow into the capillary network which lies distal to it. Originally, it was placed at the point of origin of a capillary vessel leaving a "preferential channel." The concept of the preferential channel, proposed in early descriptions of terminal beds (Zweifach and Kossman, 1937), was not given much support by subsequent investigators, but the term appears occasionally in current literature. A vessel called the metarteriole is perhaps its counterpart in current usage. Swedish investigators, headed by Mellander (Mellander and Johnson, 1968) have defined the precapillary sphincter on a functional rather than anatomical basis as the most distal point at which changes in peripheral resistance occur. Since we are dealing with anatomy of the microcirculatory system, perhaps the most acceptable definition for the precapillary sphincter is that it is the final smooth muscle cell that separates arterial and capillary vessels, realizing that its location will vary in different vascular beds and from species to species. It affords the ultimate control of blood flow into the capillary circulation.

Defining a capillary vessel is the easiest. It can be stated without fear of contradiction that a capillary vessel is a pure endothelial tube, lying between distributing arterial vessels and collecting venous vessels. Details regarding the ultrastructure of the different types of capillaries will be discussed in Chapter 2, so it is sufficient to say here that most capillaries originate from terminal arterioles either singly or as a burst of vascular pathways to form interconnecting networks that ultimately end where two vessels converge to form a postcapillary venule. In some instances, the determination of the beginning and ending of a capillary vessel that acts as a conduit between the arterial and venous systems may be difficult when observed with the light microscope because there are vascular connections, sometimes U-shaped and sometimes straight, sometimes long and at other times short, that join a terminal arteriole with a postcapillary venule. Some portion of the vessel is pure endothelium, and by definition, a capillary, but it remains for the electronmicroscopist to identify the proximal and distal limits. It is this configuration, lacking the design of a network, that has been designated as a thoroughfare channel, a preferential channel, or an arteriovenous capillary (Zweifach and Kossman, 1937). The arteriovenous capillaries were described as being muscular throughout and parent vessels for true capillaries. It seems undesirable to introduce additional terminology to the microcirculation, already overladen with descriptions of vessels. In some cases different names have been given to the same vessels and in others the same names have been used for different types of vessels.

The convergence of short capillary vessels marks the formation of the postcapillary venules which may be described as nonmuscular venous vessels whose diameter is noticably larger than that of the capillaries which form them. Each further convergence results in larger diameters, smooth muscle cells reappear, and, finally, with the appearance of venous valves, the venules are reached.

C. Relationships between Arterial and Venular Vessels

There are certain relationships between the components of the microvascular beds that are appropriate to mention here. The information comes from observations made on the vascular bed in the wing membrane of the little brown bat *(Myotis lucifugus)* (Wiedeman, 1962), but, because of general similarities in the vascular beds which have been studied in recent years, may be considered as acceptable for relative relationships in any terminal vascular configuration.

Arterial and venous vessels accompany one another except in the final ramification of the arterial vessels in the capillary network. There are also no arterial counterparts for postcapillary venules. The arterial vessels are smaller in diameter than their venous companions. Arterioles have an average diameter about one-third that of their accompanying venules. Capillary vessels are the smallest in diameter, having an average diameter of 3.7 μm, while the postcapillary venules formed from them average 7.3 μm in diameter. Postcapillary venules convene to form the venules with an average diameter of 21 μm. (See Fig. 1.) It must be made clear that the exact diameter should not be the basis on which a vessel is placed in any

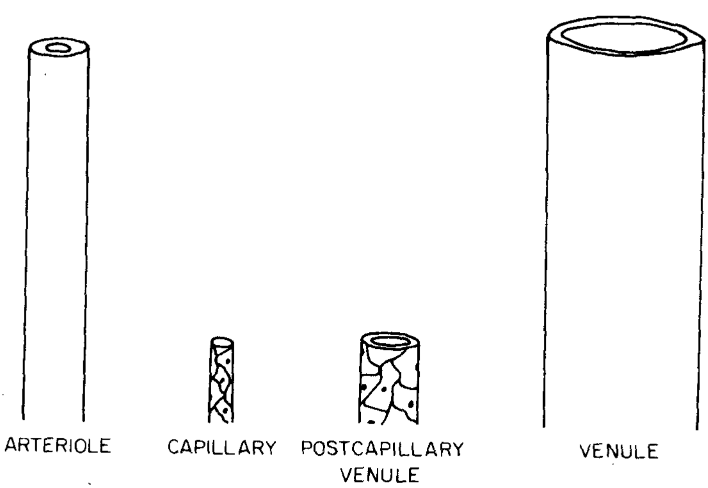

Fig. 1. Comparison of lengths, wall thickness, and diameter of four components of the capillary network.