PHYSIOLOGY OF THE CIRCULATION IN HUMAN LIMBS IN HEALTH AND DISEASE

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To Henry Barcroft, who started me in cardiovascular research

To Sir George Pickering, who, as Editor of *Clinical Science*, rewrote my first paper

To David Greenfield, who nourished me in the early years

To Earl Wood, who continued the sustaining process

To Bob Whelan, Bertie Marshall and Ian Roddie, for the pleasure and education I obtained in collaborating with them

PREFACE

In the past 10 years, so much information has been added to our knowledge of the circulation in human limbs, with its ramifications to the cardiovascular system as a whole, that this seemed an appropriate time to survey this increasingly complex field and to analyze and correlate the available data. In doing this, I have had in mind especially four groups of people: the graduate student with a major interest in the cardiovascular system; the young investigator who is anxious to survey the general field in order to be better able to decide on fruitful areas for study; the experienced investigator looking for a source book of information; the clinician whose interest is in diseases affecting the vascular system and who wishes to have a basic textbook on the behavior of human blood vessels in health and disease.

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JOHN T. SHEPHERD

CONTENTS

INTRODUCTION

So many excellent articles have been published on the methods used for the study of the circulation of the limbs in man that no attempt will be made in this book to discuss the details of these methods. The principles of the methods are outlined below.

Venous Occlusion Plethysmography. Venous occlusion plethysmography, which was first used by Brodie and Russell (1905), is the standard technic for the study of the circulation through the limbs in man. The principle consists of the measurement of the rate of increase in limb volume during brief arrest of the venous return from the limb; this is the rate of venous collection, which equals the rate of arterial inflow. Prior to venous occlusion the veins are kept relatively empty of blood by maintaining the part to be examined just above heart level, and it is then assumed that the rate of arterial inflow is unaltered by the venous occlusion and that the rate of venous collection immediately after occlusion equals the rate of inflow into the undisturbed limb before occlusion. This method, if properly used, still provides the most reliable quantitative measurement of limb blood flow in man. Frequent measurements can be made, so that rapid fluctuations in flow can be followed. Measurements can be made from the digits, the hand or foot, the body of the hand, and the forearm or calf. Water-filled plethysmographs are used most frequently; water temperatures of 30 to 32° C. for the hands and feet and 34 to 35° C. for the forearm and calf have been found

most suitable for the study of vascular reactivity (Barcroft and Swan, 1953; Greenfield, 1957; Greenfield, 1960).

A strain-gauge plethysmograph consisting of thin rubber or Silastic tubing filled with mercury and encircling the forearm or calf is occasionally used. Changes in the circumference of the limb cause changes in the electrical resistance of the mercury. Changes in volume are deduced from the changes in circumference (Whitney, 1953; Clarke and Hellon, 1957; Clarke et al., 1958).

Skin Temperature. In the proximal part of the limb, the temperature of the skin is influenced by the rate of blood flow, the metabolism of the underlying muscles, and the temperature of the blood returning in the superficial veins from the distal parts of the limb. Hence in these areas the surface temperature is not a reliable index of skin blood flow. It provides, however, a useful measure of the blood flow through the digits, where the temperature can vary from that of the room air to nearly that of the core of the body. The relationship between skin temperature and blood flow is complex, and it must be remembered that the temperature will rise to within a few degrees of the maximum when the blood flow is only about one quarter of the maximum. Thus, at the higher rates of flow, skin temperature is an insensitive and uncertain index of flow (Sheard, 1944; Burton, 1948; Cooper et al., 1949; Felder et al., 1954).

Calorimetry. The principle of the method is the measure of heat exchange between an extremity and stirred water at a temperature below that of the body. This gives a semiquantitative measure of blood flow, provided the metabolic heat is very small in comparison with the heat conveyed by the circulating blood. Thus, blood flow can be deduced from the thermal measurements, especially in the digits, where the amount of metabolic heat is small. If the arrival and departure temperature of the blood is known and if metabolic heat can be neglected, the blood flow can be calculated by the Fick principle (Cooper et al., 1949; Mendlowitz, 1954; Greenfield, 1960; Edwards and Burton, 1960). Hatfield (1950) introduced a convenient way of measuring the heat flow from a small area by means of a copper-tellurium-copper heat flow disk. The disk, which is about the size of a dime, is applied to the skin, usually on the pulp of the terminal phalanx, and the part is immersed in stirred water

at a constant temperature, usually 20 to 30° C. Heat flow is mainly from the blood through the disk to the water. This generates a thermoelectric potential, which is proportional to the flow of heat. The disks are calibrated by the manufacturer, are easy to apply, and provide a reliable index of changes in digital or skin blood flow (Catchpole and Jepson, 1955). Calorimetric methods are usually employed under conditions in which venous occlusion plethysmography may be invalid—for example, when the venous pressure is raised so that venous collection is hindered, or when the arterial pressure is low so that the pressure in the collecting cuff may reduce arterial inflow.

Quantitation of Blood Flow Through the Various Tissues of the Limb. Since the blood flow through normal bone is comparatively small, skin and muscle make the major contribution to the total blood flow through the limb. In the digits, where the flow is almost entirely through the skin, changes in flow have been assessed by skin temperature measurement and calorimetry in addition to plethysmography. In the hand, blood flow through the skin predominates, and total hand flow usually reflects mainly changes in skin blood flow. In the forearm and calf, however, both muscle and skin can make a major contribution, which varies under different circumstances; for example, after muscular exercise the increased flow is mainly through muscle vessels, whereas with increased body temperature it is only the skin flow that is increased.

Since venous occlusion plethysmography measures the volume of blood flowing through the segment of the limb enclosed in the plethysmograph, it does not permit any separation of the flow through the various tissues of the part. Thus, methods have had to be devised to estimate the contribution of skin and muscle to the total change in flow in man; for example, epinephrine has been iontophoresed into the forearm skin to suppress its circulation (Edholm et al., 1956). The clearance rate of heat has been measured from a heated element inserted into the tissues; this consists of a needle about 6 cm. long and 1 mm. in diameter, the tip of which is soldered. The lumen of the needle houses an electric heating system and a thermoelectric measurement system. After the needle has been inserted into the muscle, the tip is warmed with constant alternating current. The thermocouple continuously measures the temperature

difference between the heated tip and a reference junction 1 cm. above the tip in the shaft of the needle. Changes in the absolute temperature of the muscle are eliminated because they influence both the heated and the reference junctions in the same way. The recorded temperature difference in the heated probe is therefore dependent on the heat conductivity of the surrounding tissue. Changes in the conductivity of the tissue are indicative of changes in blood flow (Gibbs, 1933; Hensel and Ruef, 1954; Stow and Schieve, 1959). A heat-conductivity meter has been devised which is placed on the skin and which works on the same principle as the muscle probe (Hensel and Bender, 1956). Changes in the clearance rate of diffusible ions from an injection site in skin and muscle have been followed (Kety, 1949; Hyman, 1960). Under conditions in which oxygen consumption of tissue may be assumed to be constant, changes in flow have been deduced from changes in the oxygen saturation of blood from veins draining mainly skin and muscle (Holling, 1939; Roddie et al., 1956).

Resistance and Capacity Vessels. All blood vessels exhibit both resistance to the flow of blood and capacity to contain blood. The arterioles are the main source of the peripheral resistance but contain relatively little blood, whereas the veins offer little resistance but have considerable capacity. Resistance is evaluated from the relationship between blood flow and the pressure difference across the vascular bed. The resistance to flow depends upon the dimensions of the blood vessels and on the viscosity of the blood. Since the viscosity of the blood varies both with the rate of flow and the dimensions of the vessels, changes in vessel caliber cannot always be deduced with certainty from change in resistance to flow. However, when the arteriovenous pressure difference and blood composition remain constant, differences in flow can be initiated only by changes in vessel caliber. Changes in peripheral resistance are normally initiated by alterations in vessel radius. The relationship between the pressure inside and outside the vessels (distending or transmural pressure) and vessel radius is determined by the properties of the blood vessel wall. These properties are referred to as vessel tone or stiffness, and can be altered by nervous, humoral and local factors. In studies on the circulation of the human limb in which the conditions can be altered in one limb, the corresponding limb can be used as a control. Under these conditions, both limbs are subjected to the

same perfusion pressure, and it can be assumed with confidence that the changes in flow on the experimental side are due to active changes in vessel caliber.

Although the arterioles are the major source of the peripheral resistance, other vessels contribute to a variable degree. As no observations have been made in the human that are comparable to those of Haddy et al. (1961) in the dog regarding the relative importance of the different segments of the vascular bed in causing changes in resistance under different conditions, it is often expedient just to state that the caliber of vessels responsible for resistance to flow has changed.

Since much less is known of the reactions of the capacity vessels, the reactions of these vessels to various stimuli are discussed as a unit in Section Two, Chapter 12, rather than in the individual chapters dealing with the effects of various stimuli on the resistance vessels.

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SECTION ONE

Nervous Control of Blood Vessels