PERIPHERAL CIRCULATION IN MAN

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PERIPHERAL CIRCULATION IN MAN

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PREFACE

The Ciba Foundation is an international centre, established as an educational and scientific charity under the laws of England. It owes its inception and support to its founder, Ciba Limited of Switzerland, but is administered exclusively by its distinguished Trustees.

As one part of the Foundation's activities, informal symposia or colloquia, strictly limited in membership, are arranged, to which leading research workers from different countries and different disciplines are invited. As the smallness of the group necessarily excludes many others active and interested in the subjects discussed, the proceedings are being published and made available throughout the world.

"*Peripheral Circulation in Man*" was the subject of a symposium arranged in succession to one held and published earlier on "*Visceral Circulation*". It was largely initiated by Prof. A. C. Burton, Prof. J. H. Dible, and Dr. O. G. Edholm, to whom the Director of the Foundation is greatly indebted for support and advice in its organisation.

The book covers the methods for studying blood flow, the changes in circulation due to exposure to cold or heat, the actions of adrenaline and noradrenaline on blood flow, the neurohistology and reflex control of the circulation and the effects of sympathectomy, the significance of cold agglutinins, and the influence of visceral activity on the peripheral circulation.

To an understanding of these problems, important workers in this field, whether anatomist, physiologist, biophysicist, pathologist, physician, surgeon, or in aviation medicine, have contributed.

It is hoped that the papers and discussions presented here will prove not only informative and stimulating, but will also give a sense of participation in this informal and friendly occasion.

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List of those participating in or attending the Symposium on "The Peripheral Circulation in Man," 11th-13th May, 1953.

G. H. Algire	Nat. Cancer Institute, Bethesda, Maryland
E. Asmussen	Gymnastikteoretiske Laboratorium, University of Copenhagen
Aziz Ahmad	Pakistan, and St. Thomas's Hospital, London
H. Barcroft	Sherrington School of Physiology, St. Thomas's Hospital, London
G. E. Burch, Jr.	Dept. of Medicine, Tulane University of Louisiana.
A. C. Burton	Dept. of Biophysics, University of Western Ontario.
L. D. Carlson	Dept. of Physiology and Biophysics, University of Washington, Seattle
K. E. Cooper	M.R.C. Laboratories, Hampstead, London
Sir H. Dale	Wellcome Trust, London
G. S. Dawes	Nuffield Inst. for Medical Research, Oxford
J. H. Dible	Dept. of Pathology, Postgraduate Medical School of London
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O. G. Edholm	M.R.C. Laboratories, Hampstead, London
U. S. von Euler	Fysiologiska Inst., Karolinska Inst., Stockholm
P. FitzGerald	Dept. of Anatomy, University College, Dublin
P. Gaskell	Sherrington School of Physiology, St. Thomas's Hospital, London, and Western Ontario
R. T. Grant	M.R.C. Clin. Research Unit, Guy's Hospital, London
A. D. M. Greenfield	Dept. of Physiology, Queen's University, Belfast
L. Guttmann	Spinal Injuries Centre, Aylesbury, Bucks
A. B. Hertzman	Dept. of Physiology, St. Louis University, Missouri
P. Howard	R.A.F. Inst. of Aviation Medicine, Farnborough, Hants
D. McK. Kerslake	R.A.F. Inst. of Aviation Medicine, Farnborough, Hants
R. B. Lynn	Dept. of Surgery, Postgraduate Medical School of London
P. Martin	Dept. of Surgery, Postgraduate Medical School of London
J. L. Nickerson	Office of Naval Attaché, U.S. Embassy, London
M. Nielsen	Zoofysiologiske Laboratorium, University of Copenhagen
J. Oudot (deceased)	Clinique Chirurgical de la Salpetrière, Paris
J. T. Shepherd	Dept. of Physiology, Queen's University, Belfast
G. Weddell	Dept. of Human Anatomy, University of Oxford
Attie Y. Werner	M.R.C. Laboratories, Hampstead, London, and University of Iowa
R. F. Whelan	Dept. of Physiology, Queen's University, Belfast
R. J. Whitney	M.R.C. Climate and Working Efficiency Unit, Oxford

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CHAIRMAN'S OPENING REMARKS

O. G. EDHOLM

THE purpose of this Symposium is to make it possible to have a more lengthy discussion than can usually be arranged at meetings of the learned societies. There is a rapidly growing activity in the field of human physiology, and particularly in studies of the peripheral circulation. It is certainly important that workers with common interests should have the opportunity of discussing their results together.

Human physiology is still regarded with some suspicion by a number of physiologists. Perhaps one reason is that research on human physiology has its own special difficulties. It is harder to work on man than on isolated pieces of tissue, for several obvious reasons. These include the necessity for strict control of the environment, and even more important for controlling the conscious subject. There are many factors which can influence the peripheral circulation in man, most of which are still poorly understood and therefore hard to control. It is not always easy to obtain subjects with the frequency and regularity that one would desire, and owing to the length of time usually necessary to carry out an experiment there is always a relatively small output of work. For these and other reasons the results of human physiological research are not always as clear cut as in animal experiments, and it must be admitted that some work has not been done as carefully as it might have been. However, work in recent years, a high proportion of which has been contributed by those present at this Symposium, has established the importance of research on the circulation in man. It has been shown that satisfactory work can be carried out on man, and the results of such work demonstrates that it is not always possible to apply the findings of animal experiments to man.

One important aspect of work on the circulation in man is that this is a most fruitful field for the collaboration of physiologists, physicians, pathologists and surgeons. It is a field in which the results of clinical work are of great importance to physiologists. Problems are revealed which would otherwise be unsuspected by the physiologists. In this Symposium there is a balance between the clinical and physiological aspects both as regards membership and papers.

It is not possible in a brief introduction to give any picture of the problems of the peripheral circulation in man, except perhaps to emphasize the extent of our ignorance. It may appear to those who are not engaged in this field that the circulatory system is relatively simple compared to many other aspects of physiology. We are in fact still unable to define with precision the laws governing blood flow in vessels and all the factors governing dilatation and constriction.

I hope we shall shed a little light on these and other aspects in the course of this Symposium.

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A CRITICAL SURVEY OF METHODS AVAILABLE FOR THE MEASUREMENT OF HUMAN PERIPHERAL BLOOD FLOW

ALAN C. BURTON

Introduction

A GREAT number and variety of methods have been devised for the measurement of blood flow in fragmented and anæsthetized animals, of which only a few are at all applicable to intact, unanæsthetized animals. Knowledge of the peripheral blood flow in the relatively undisturbed and intact animal, made possible in the human largely because of the co-operation of the subject, is so valuable that a critical survey of these few methods is very worth while. All methods that have been used have some merits, and all have disadvantages. In some cases we will never agree on these relative merits, nor should we, for any given method may be the best for one experimenter in the circumstances of his particular research, yet not as good for another worker. The methods should be regarded as complementary and not as rivals, as it is only by the knowledge of the results of all the methods, each with its own peculiarity, that we shall be able to synthesize the true picture of the peripheral circulation.

It has been the custom to classify methods of measurement as "direct" and "indirect". To do so, we must first, perhaps arbitrarily, define precisely what it is that we wish to measure which a "direct" method will give us. For the purposes of this critical survey, it is assumed that the object of our direct interest is the volume flow of blood, in ml./minute, rather than the velocity of flow, in cm./second or some related quantity. This seems a reasonable definition of aim since the major function of the circulation is to supply the metabolic needs of the tissues and the volume flow is closely related to this. Thus, by definition here, the "target variable" is the volume flow of blood. Whether or not we should express this in total amount, or per 100 ml. of tissue, or perhaps per sq.M. of surface area, is a matter too inconclusive to discuss here.

If we then decide that a method is absolutely "direct" if it yields this "target variable" without intermediate steps involving other variables, we shall have to agree that almost all available methods are "indirect", though "direct" if we had chosen some other "target variable" (such as effective thermal conductivity, amount of hæmoglobin, velocity of blood flow etc.). It seems better to abandon the classification into "direct" and "indirect" and ask three questions about each method :—

(A) What quantity or quality of tissue is directly measured by this particular method? We might call this the *intrinsic variable of the method.*

(B) What is the relation of this "intrinsic variable" to the "target variable", i.e. the volume flow of blood? What other variables are involved in this relation and thus affect the measurement? We might call this relation the "*intrinsic correlation of the method*".

(C) How greatly does the application of the method of measurement disturb the pre-existing condition of the organism ; so that though the intrinsic variable of the method is correctly reported, the undisturbed volume-flow of blood cannot be deduced? This last question is all-important to physiologists, yet it seems to be this question that is least asked. In the day of Claude Bernard it was in the minds of all biological scientists, for in his "Introduction to the Study of Experimental Medicine" he tells us of the school of thought that contended that no experiment on a living organism could be useful, because by application of the measurement, the organism was profoundly disturbed. Yet today I cannot find even a well-established term for this type of error of measurement. I would suggest we call it the "*Reactive Error in Physiology*", since it is due to the reaction of the organism to the stimulus of the application of the method of measurement. Because of this "reactive error" there is a biological "uncertainty principle" that is often of much more practical importance than that of Heisenberg in Physics (which points out that even the velocity of an electron is distorted by the act of observing it, which can only be done by introducing radiation).

Let us examine the methods available for the measurement of blood flow in man by asking these three questions, which, in the terms I have defined, are concerned with:—

(A) The nature of the "intrinsic variable" of the method.

(B) The "intrinsic correlation" of the method with the target variable, i.e. volume flow.

(C) The "reactive error" of the method.

In addition, of course, there are the other important properties of any method of measurement, such as "speed of response" or "lag", and the sensitivity to changes in the target variable (volume flow of blood). For detailed and critical discussion of each of the methods, the articles in Methods of Medical Research (1948) should be consulted.

Specific Available Methods

Direct Observation of Blood Vessels

There are growing opportunities for this in the human. The specialized capillary bed at the base of the finger nails is no longer the only area for observation. The vessels of the tongue have been used, with modern methods of microscopy and of illumination by "cold" light which will not introduce a large "reactive error". The use of fluorescence improves the contrast between tissue and blood vessels for observation.

There is a natural tendency to assume that when one actually sees the blood vessels, this must be the most certain and direct of all methods for study of the circulation. For some "target variables" it may be so, but is it so where we desire the volume flow? What is the "intrinsic variable" of the method of direct observation? My own conviction is that it is probably the velocity of movement of the erythrocytes that dominates the impressions of the observer and his judgment as to whether flow has increased or decreased. When, however, the diameter of the vessels observed changes at the same time as the velocity of the erythrocytes, the volume flow cannot be in any sense the "intrinsic variable". Volume flow is the product of the mean velocity of flow at the point of observation and the cross-sectional area there,

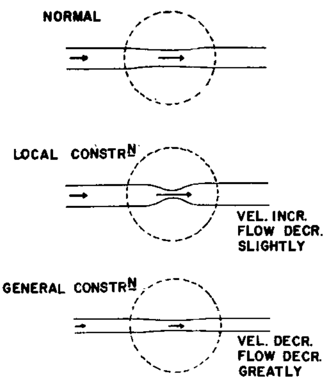

FIG. 1. Schematic diagram to illustrate the relations between velocity of flow and volume flow.

and where both change the intrinsic correlation is very complicated. For example (Fig. 1), if a narrowing of the vessels under observation occurs which is greater than elsewhere in the "line of vascular resistances", the volume flow will decrease. Yet because of the reduced cross-sectional area at this point, the velocity of flow here will increase. On the other hand, in a more severe and widespread vasoconstriction, the volume flow will decrease greatly and in this case velocity of flow also will decrease. I think this is why we find, in our undergraduate laboratory experiment on observation of flow in the web of the frog, that students are unable to decide whether the topical application of adrenaline results in an increase or a decrease in volume flow. (Most of them decide that there has been a vasodilatation.)

As far as "reactive error" is concerned, this might be considered negligible as long as the illumination, or the application of immersion oil, or the pressure of the applied apparatus, does not affect the circulation. Where a drug is used, such as adrenaline, we are of course interested in the disturbance of circulation by that drug, but here we should consider whether this disturbance is identical with the physiological disturbance by that drug. A great body of theory as to the circulation in shock has been based upon direct observation of the reaction of minute vessels to topically applied adrenaline (by Chambers, Zweifach and others). Can we be sure that the reaction of vessels would be the same to topical application as to the physiological presence of the same hormone in the perfusing blood, in view of its very rapid destruction by the enzymes in the vessel walls? Certainly, "gradients of reactivity" of different vessels found by topical application would be very different from the physiological gradients. This is a case of "reactive error of measurement" of a more complicated kind.

Circulation Time

The ingenious classical methods, using injected dyes or electrically conducting saline or substances that signal their arrival by effects on special receptors (e.g. taste or smell), have been superseded by the use of radioactive tracers, whose arrival is so easily detected by counters. With the improved techniques of arterial injection, it is now feasible to measure circulation time in a limb as well as "total circulation time".

The answer to the first of our three questions is deceptively simple. The intrinsic variable is the time, in minutes or seconds, for the injected substance to circulate from point A to point B. But we need to be cautious. A recent analysis of just what is measured has been made (Pearce, Lewis and Kaplan, 1952). Even where a "slug" of injected substance is very rapidly injected, the sharp rise of concentration of the "wave front" does not persist, and it is not the arrival of the first amount that is measured but of the first detectable amount. Thus the authors found that the injection of a 30 per cent solution of Decholin (taste as the end point) gave a circulation time 15 per cent shorter than with a 10 per cent solution. If we should decide to use the arrival of the peak of concentration instead of the least detectible amount we are in similar difficulties, because of the change in shape of the curve as the dye circulates.

As to the intrinsic correlation for the circulation time, it is most important to realize that the circulation time from point A to point B of the vascular bed is equal to the volume of the

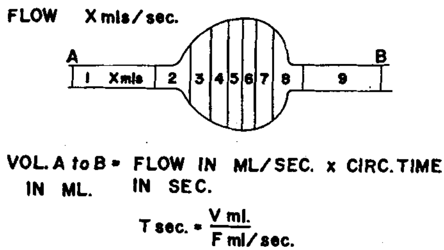

FIG. 2. Diagram to show the relation between circulation time T, volume flow F, and the volume of the vascular bed V.

vessels between A and B divided by the flow (Fig. 2). It is astonishing how this elementary fact has been ignored in the past. Since changes in flow are produced by constriction or dilation of the vessels, and also since changes in volume will result from any redistribution of pressures due to a vasomotor change, it is inevitable that both factors of the ratio for the circulation time (volume and flow) change simultaneously. In general, but not inevitably, the volume will increase as the flow increases, and thus the circulation time is remarkably insensitive as an index of flow or of vasomotor change. The intrinsic correlation is thus very poor. Indeed it is possible, during a vasoconstriction, that the volume might decrease so greatly as to offset completely the decrease of flow, and that the circulation time might actually decrease. Certainly any change in circulation time is as likely to be due to a change in volume of the vascular bed (called the "pooling effect" by Ziegler, 1951) as to change in flow. It is no wonder that few physiologists know quite what to do with circulation time after it has been measured. I know of no attempt to preserve the usefulness of the circulation time by measuring the change of volume of a limb at the same time and so calculating the change in flow. This might be a useful addition to our methods.

As to reactive error, with any method using arterial injection the possible disturbance of the *status quo*, even with small catheters, must be considered. If no local anæsthetic be used, the artery may go into spasm and the psychic effect of pain may be great. Even the anticipation of an arterial puncture can produce a very marked general vasoconstriction. On the other hand, if local anæsthetic be used, the vasomotor tone we wish to measure will be reduced to an unknown extent. In addition, there are physical reactive errors, especially with fine catheters and recording with rapid instruments, that have not been sufficiently appreciated.

Injection (dye) Dilution Methods, or the Use of the Fick Principle

As I have no experience of these, I can only point out the difficulties of them, which are well known. The chief difficulty is that of obtaining a representative venous sample, because of the collateral arrangement of the blood vessels of a limb. In acute animal experiments the collateral circulation can be occluded, but obviously this is not possible in the human limb, where Edholm and his colleagues (1951) have shown its importance. This would appear to exclude these methods for the estimation of human peripheral circulation. The same reactive errors exist as for any other method involving arterial catheterization or injection.

A disadvantage (of a different kind) of some of the Fick methods applies to the nitrous-oxide method (Kety, 1948)