Radio-isotopes and regional blood flow

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The study of regional blood flow is a matter of increasing importance to the cardiologist. Its interruption within the coronary vessels is his main clinical problem, and leads to obscure changes elsewhere in regional flow. Though it has been possible for some time to measure cardiac output in man, there have not previously been satisfactory clinical methods for tissue flow measurement. Recent techniques with radio-isotopes which can be used in man are therefore of interest, and this editorial reviews generally the theory underlying their use and their application in the past few years.

The great advantage of radio-isotopes is that they may be measured easily in the body using an external detector, and the main development of recent years has been the increasing use of highly diffusible gamma emitters for such measurement.

Blood flow can be determined by observing the rate of disappearance of isotope from the site at which it is injected, and it is customary to replot such disappearance slopes logarithmically. The decay constant k is obtained from the half-disappearance time, and, using the Fick principle, flow is given by $F = k\lambda$, where λ is the partition coefficient between the tissue and blood. This method of residue detection assumes that a constant ratio exists between specific activity in the tissue and the capillary bed, that equilibration is rapid, and that concentration gradients within the tissue do not occur.

If the tissue is evenly perfused, the disappearance slope follows a single exponential curve, a simple state that applies to the heart and testis. Most tissues, however, including brain, kidney, liver, and skin, are unevenly perfused, and compartmental analysis is then applied to the decay slopes on semi-logarithmic paper. By a process of deconvolution or 'curve peeling', various compartments are obtained whose flow rates and

relative size may be determined, but it should be remembered that the identification of separate compartments in this way does not necessarily confer physiological significance.

Zierler (1965) has recently suggested an alternative approach by considering the ratio of height to the area beneath the curve, rather than its slope, using the formula

$$F = \frac{H}{A} \text{ ml./g./min.}$$

where H is peak value and A is area.

It is not necessary to assume that the tissue is homogeneous or that blood and tissues are in equilibrium at all times. However, Lassen (1967) considers that Zierler's method can be applied only in the case of exponential clearance where mean flow from area analysis is the same as that from the slope analysis, and he believes that in a multicompartmental system, analysis of the initial slope gives mean flow rate.

It has also been pointed out that residue detection with an external counter is basically the same as outflow detection by the Kety-Schmidt method. For both we may write the same formula, $F = \frac{H}{A}$ ml./g./min., but for outflow detection H is initial venous concentration and A is the area between the arterial and venous concentration slopes. Both methods in fact measure mean transit time.

It is now believed that freely diffusible tracers such as ^{133}Xe are most suitable for clearance methods. Being lipophilic they diffuse across the whole cell membrane, and for many tissues it has been shown that their clearance is flow limited. On the other hand, diffusion of hydrophilic ions such as sodium is apparently restricted to a small fraction of the capillary surface, and in tissues with high flow rates their clearance may be limited by diffusion and cannot then be used as an index of flow.

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The isotope may be given as a single shot into the artery or the tissue, or by prolonged arterial saturation, and it is assumed that this causes no disturbance, that labelling occurs in proportion to the volumes of flow distribution, and that recirculation is negligible. For most tissues it is valid to derive mean flow from the initial slope, and to perform compartmental analysis, but the use of the area beneath the curve is dubious.

The Fick principle has recently been applied in its original form using various isotopes, including labelled microspheres and macro-aggregated albumin, the venous concentration of which is zero. Flow can also be measured with non-diffusible indicators using the dye-dilution principle, or the development by Oldendorf and Kitano (1965) whereby mean circulation time is derived from the interval between maximum rate of appearance and disappearance of isotope.

These are the ideas on flow which have been developed in recent years and are now being put to practical use, principally in residue detection using Xenon. Considering the various tissues in turn, there have been some 1200 relevant publications in the past few years so that this review will necessarily be selective, and will deal mainly with brain, heart, and muscle.

Brain

Blood flow through the brain has been studied most, and there is now much evidence validating the residue detection method, with ^{133}Xe or ^{85}Kr injected into the carotid artery, both for mean flow and two compartments representing grey and white matter.

The rebreathing method (Mallett and Veall, 1963) has the great advantage of avoiding the risks of carotid arterial puncture, since radioactivity of the head is counted during desaturation after breathing isotope. Unfortunately, simple analysis gives results which underestimate flow by about 20 per cent since these curves are distorted by extracranial activity and appreciable recirculation. Recently, it has been shown how this may be corrected by deconvoluting end-expiratory activity and the slow component due to extracranial flow using a computer.

In practice, the rebreathing method allows repeated determinations when required, whereas the injection method allows more accurate measurements whenever the carotid artery is accessible for angiographic or surgical procedures.

A recent development has been the use of multiple highly collimated detectors ranged

over the hemisphere allowing perfusion to be compared in 16 or more adjacent regions of the brain. This is inevitably something of a compromise, but acceptable collimation can be achieved without the need for a massive dose of ^{133}Xe .

In patients it has been shown that a reduction in flow occurs in cerebrovascular disease, and that in arterio-sclerotic dementia the relative size of the fast compartment is reduced. In patients with dementia, differences in perfusion can be shown between those in whom the disease is primary and those in whom it is vascular in origin. Unilateral lesions are associated with underperfusion of the opposite hemisphere, and a reduction in flow has been found in migraine and to a lesser extent in myxoedema (O'Brien and Harris, 1968). It is interesting to learn that in patients undergoing internal carotid ligation a reduction in flow rate of no more than 25 per cent leads to hemiparesis (Jennett, Harper, and Gillespie, 1966).

With regional studies, flow rates slightly higher than average have been found in precentral grey matter and in the region of the internal capsule, and rise in parietal flow has been reported during mental arithmetic. It seems that some caution is needed before regional differences are attributed to disease. In a study of patients with strokes, it was found that most of them showed focal hyperaemia, with loss of normal vasomotor regulation. It has, therefore, been suggested that the injured brain in apoplexy is overperfused (Høedt-Rasmussen *et al.*, 1967), but before accepting this, we must wait until focal measurements, restricted to the infarct, can be made.

Heart

Turning to the heart, the most accurate isotopic method for general use is residue detection using ^{133}Xe , the validity of which has been shown over a wide flow range. From the normal ventricle a uniform clearance constant is obtained on exponential analysis for more than 90 per cent of the clearance. Unfortunately, coronary arterial catheterization is required for accurate curves so that opportunities for measurements in man are restricted. However, no differences in resting flow have been detected between normal patients and these with ischaemic heart disease, and the latter have been shown to retain their capacity for coronary vasodilatation.

The method has been used more experimentally in studies of the intact heart and circulation, and it has been shown that various

regions of the left ventricle are equally perfused over a wide pressure range, in contrast to the lower perfusion of the right (Rees and Redding, 1969). Despite this regional homogeneity, local injection of isotopes and embolization with radioactive microspheres reveal small and varying changes in perfusion at different depths within the ventricular wall (Moir and DeBra, 1967; Brandi, Fam, and McGregor, 1968). The local injection technique has been applied to some patients at operation, and by this means regions of underperfusion were found in most of those with ischaemic heart disease (Sullivan *et al.*, 1967).

Experimentally, collateral flow can be measured by the injection of ^{133}Xe into the arterial system of an infarct beyond the block, and the changes during recovery can be studied. It is thus possible in the intact animal to compare collateral flow, flow in normal muscle at the edge of an infarct, and more distant flow (Rees and Redding, 1969). These methods give precise local measurements of the sort we would like to have in patients, but the application of these techniques to human disease states is at present beyond us, and it is doubtful if we yet have a simple method for measuring mean myocardial blood flow in man. Some years ago, it was suggested (Sevelius and Johnson, 1959) that a peak representing coronary flow could be separated from the record of isotope passing through the heart using a praecordial counter, but this has proved impossible.

Since rubidium is taken up by the heart it has been suggested that this uptake, detected externally, will measure coronary flow. A recent development has been the use of ^{84}Rb and a pair of counters on the front and back of the chest. Since this isotope is a positron emitter, precise collimation of a cylinder enclosing the heart is possible using a coincidence counting system. Unfortunately, rubidium diffuses slowly, and its extraction fraction by the heart falls as flow increases. Thus, it has been found that its clearance underestimates coronary flow by one-quarter to one-half, depending on the flow rate, and is inaccurate for quantitative measurement (Moir, 1966).

Thus we lack a simple and accurate method for measuring flow rates through the heart, and even if a suitable isotope were available, external measurement of the variable perfusion of the ischaemic heart would be a most complex task with present techniques. Since ischaemia is the urgent problem it is likely that scanning methods and selective

uptake by ischaemic muscle will be more rewarding. For instance, both chlormerodrin and brommercuroscan, labelled with ^{203}Hg are selectively taken up by infarcts and appear as hot areas on heart scans in experimental studies (Málek *et al.*, 1967).

Skeletal muscle

Recent progress in muscle flow owes much to the work of Lassen and his colleagues who have shown differences in clearance between lipophilic and hydrophilic tracers at higher flow rates, indicating the need for rapidly diffusible isotopes. Their accuracy by local or arterial injection has been shown by comparison with directly metered flow, plethysmography, and indicator dilution. It seems likely that there is uniform distribution of flow, but it appears that diffusion equilibrium is not maintained after the initial part of the washout because of counter-current exchange through vessel walls, which partly explains the slow tail of the desaturation curve (Sejrsen and Tønnesen, 1968).

There have been many recent studies of lower limb flow in peripheral vascular disease. It is possible to compare flow rates at various sites and to examine the effects of exercise using small detectors strapped to the leg. Resting perfusion in those with peripheral vascular disease is little different from normal, but maximum flow in response to exercise, or the injection of histamine mixed with the isotope, is reduced and there is prolonged and excessive post-exercise hyperaemia. These results correlate well with function, and an increase in collateral flow has been shown with induced systemic hypertension for the treatment of gangrene (Lassen *et al.*, 1968).

Lung

Measurement of lung perfusion with radioactive gases has recently been reviewed by West (1967) and will not be discussed further. For general use the micro-embolization method with labelled macro-aggregated albumin and lung scanning (Wagner and Tow, 1967) has become popular because of its simplicity, and there have been recent reports of regional variations in perfusion in a variety of diseases from carcinoma to pulmonary embolism. Though not strictly a measurement of flow, but of its interruption, the detection of venous thrombosis might be mentioned since the introduction of fibrinogen labelled with ^{125}I has led to an important advance. When given intravenously, the marker with a half-life of 60 days accumulates in any thrombus that forms, which may thus be detected by scanning over the legs.

The natural history of venous thrombosis can be studied over many days, and the test helps to decide the effectiveness of thrombolytic treatment (Kakkar *et al.*, 1969).

Kidney

In the kidney renal blood flow by inert gas clearance correlates well with results by flowmeter, and cortical and medullary perfusion may be obtained, as in the brain. However, this has found limited clinical application, though viability of renal transplants has been correlated with flow rates immediately after surgery, and measurements in a few patients with tumours have shown reductions in flow (Lewis *et al.*, 1967; Cosgrove, Evans, and Raphael, 1968).

Liver

In the liver external counting has allowed separate determination of flow rates by the hepatic arterial and portal venous routes in the intact animal. It has been shown that these differ, and that blood may not take a common pathway through the organ (Rees, Redding, and Ashfield, 1964). There have not been many clinical applications but hepatic perfusion rates measured at laparotomy were found to be reduced in a few patients with cirrhosis and increased in regenerating liver. Local clearance after injection of ^{133}Xe at laparotomy has also been measured in patients with metastases, and it was found that occlusion of the hepatic artery reduced perfusion of the tumour much more than that of normal liver (Gelin, Lewis, and Nilsson, 1968).

Spleen

Similarly splenic blood flow has been measured in patients by selective injection of inert gas in saline into the splenic artery, and the fast component of a complex washout slope was shown to represent splenic flow (Williams *et al.*, 1968). An interesting method for splenic blood flow in patients with massive splenomegaly utilizes the atraumatic re-breathing method (Garnett *et al.*, 1969). Splenic activity is recorded externally and the washout slope is corrected for expired air activity as in the brain. It was found that perfusion rates were in the normal range, but because of enormous enlargement this represented total splenic flows as high as 4 l./min.

Similar radio-isotope methods have been usefully applied to various other tissues, but the cardiologist will remain most interested in those parts most prone to ischaemic disease. There is much to be gained from the

refinement of methods for flow measurement within selected ischaemic regions, and from the combined study of cardiac output and regional flow in disturbed circulatory states.

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