The Myocardial Collateral Circulation

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When a large coronary artery becomes blocked, immediate restoration of flow depends on the collateral vasculature. Small collateral vessels dilate at once to offer an alternative blood supply, but in the normal heart their capacity is usually insufficient to prevent necrosis and infarction. Subsequently, they undergo rapid enlargement and with a gradual, often incomplete, recannulation of the obstructed artery the blood supply to the surviving myocardium is restored. When the coronary artery obstruction develops gradually, the collateral circulation may increase at such a rate and to such an extent that the myocardium functions normally despite multiple arterial blocks.

There is nothing new in the idea of interarterial anastomoses in the coronary circulation, though their existence has been denied from time to time. They were postulated by Richard Lower in 1869, and others, including Thebesius and Morgagni, agreed with his views. Their existence has been challenged by Hyrtl in 1885, by Cohnheim and von Schultness-Rechberg in 1881, and most recently by Schlesinger in 1938. However, the presence of anastomoses in the coronary circulation is now an established fact as a result of the work of Spalteholz in 1907, Gross in 1921, and the more recent studies of James in 1961, and Fulton in 1965.

SPECIES VARIATION

There is much variation between and some variation within species concerning the abundance of these anastomotic connexions in the normal heart. They have been found to be more frequent in the dog than in man, and more frequent in man than in the pig or sheep. Opinions have varied to some extent with the technique for injecting the fine arterial connexions, but regardless of their relative abundance, in all the species that have been studied, the collateral circulation has proved insufficient to

prevent infarction after sudden coronary arterial obstruction, a fact that depends not only on the size of the collateral vessels but also on the high metabolic activity of the myocardium.

In human hearts it is now apparent that collateral vessels up to 200μ in diameter can be repeatedly demonstrated by modern injection techniques. These occur between branches of the same coronary artery, named intracoronary, and between branches of the right and left vessels, named intercoronary. Fulton (1965), in particular, has demonstrated the anastomoses that exist in most regions of the normal human heart. These arteriolar links are larger and more abundant in the deeper layers of the ventricular wall, mainly in the septum and the subendocardial vascular plexus of the left ventricle. Epicardial anastomoses are few in the normal human heart though some are usually present at the apex, and there are some connexions with mediastinal vessels from the atrial walls, which may be of potential importance. Normally, such collaterals are functionally inadequate, but in the presence of chronic ischaemic heart disease, they may enlarge greatly and may carry the bulk of the myocardial blood supply.

COLLATERAL FLOW MEASUREMENT

Is it possible to measure this collateral flow? In man this cannot be done. Indeed, measurement of normal myocardial blood flow in the human heart is still difficult, requiring either coronary sinus catheterization, using the nitrous oxide method, or coronary artery catheterization, using the radio-xenon clearance technique. It can be seen, therefore, that opportunities to measure myocardial blood flow in the normal or diseased heart of man are restricted, and that it is not yet possible to measure collateral flow rates in patients with myocardial infarction.

In the experimental animal, however, methods are available for the assessment of collateral flow, though this presents several problems. Firstly, collateral blood is delivered through a multitude of

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small vessels of varied size so that flow meters cannot be used. Secondly, the distribution of collateral blood within the ischaemic zone is uneven and may perhaps vary: some parts have no flow and become necrotic, whereas other parts have flow rates which differ from place to place. We must therefore attempt to describe and measure flow in a region of myocardium, the minute supply vessels of which are inaccessible, and which is unevenly and sometimes but partially perfused.

Determination of the peripheral coronary pressure (beyond the coronary arterial obstruction) was one of the earlier ways of assessing the collateral circulation. This pressure, at first low, rises towards the coronary perfusion pressure as the collaterals enlarge. It can be shown, however, that systolic peripheral pressure is mainly determined by a pressure wave directly transmitted from the ventricle, and thus cannot be an index of collateral flow. Some workers, such as Schaper (1967), have used the diastolic peripheral coronary pressure for this purpose, but we do not find a good correlation between these pressures and collateral flow measured in other ways. Moreover, general experience has shown it is usually erroneous to attempt to correlate pressure directly with flow.

Retrograde flow from the distal end of an obstructed artery through a tube inserted beyond the block has also been used for some time as a measure of collateral flow in experimental myocardial infarction (Gregg, 1950). Such blood proves to be arterial in composition and is undoubtedly derived from collateral vessels. Though it has been stated that retrograde flow may overestimate true collateral flow, it has been found in fact that retrograde flow measurements are lower than those of collateral flow rates determined by other means. Moreover, when retrograde flow is compared with collateral flow measured by radioxenon clearance, isotope washout is sometimes found to continue at a reduced rate during back bleeding.

Retrograde flow in diastole depends on the distribution of anastomotic blood flow according to the relative resistances of the collecting tube and of the arterioles within the infarct, but in systole ventricular contraction causes a pressure wave which greatly increases resistance within the infarct and augments retrograde flow. It follows that the relation between retrograde flow measurement and the collateral flow rate is complicated and imprecise.

Clearance methods are more acceptable in some ways. With a radioactive tracer such as rubidium-86 the uptake of isotope by the ischaemic myocardium may be compared with the normal (Levy, Imperial, and Zieske, 1961). There is the disadvantage of only a single comparison, since the

myocardium must be sectioned for the determinations. Similar clearance methods using heavy water have been developed, and the clearance principle has also been used in a method of embolization with radioactive glass microspheres.

Another method of collateral flow measurement by heat clearance requires a needle flow probe inserted into the myocardium (Grayson and Mendel, 1961). This uses the principle of internal calorimetry, whereby heat loss from a thermocouple at the needle tip is an index of tissue blood flow. This has the advantage of permitting flow measurement over some hours at several sites in the heart, but there is the risk that the probe itself may cause focal alteration in tissue flow in regions where the collateral supply is poor.

The radioxenon clearance method has some other advantages (Rees and Redding, 1967). Once the infarct is caused, no further disturbance results from the flow measurements. Isotope in solution is injected into the vessels of the infarct through a fine catheter brought out to the surface, and its clearance rate is measured with an external scintillation counter. A modification permits infarction to be caused by wedging a catheter down the coronary artery. By this means infarction can be produced, and collateral flow rates measured, without thoracotomy and without disturbing the heart, its vessels, or nerves, in any other way. It is thus possible to measure collateral flow rates repeatedly in the intact animal and to study the changes in collateral flow over hours or days as desired. The method distributes radioxenon throughout the ischaemic zone so that its clearance rate is determined by the over-all collateral flow, in contrast to the focal measurements of the flow probe method. There is the disadvantage that fast and slow components of clearance can usually be shown, changes in each of which are always in the same direction. Since the slower component is usually ignored, it follows that the clearance rates which are obtained slightly overestimate the mean over-all collateral flow.

EARLY COLLATERAL FLOW RATES

Using these clearance methods, there have been several reports of collateral flow soon after obstruction of a large coronary artery in the dog. Flow rates about 25 per cent of the normal myocardial blood flow are usual, but with a wide range from 10–75 per cent. Flow is unevenly distributed and with rare exceptions is insufficient to prevent infarction.

There is some disagreement over the changes in the next few hours. Some have found distal coronary pressure, retrograde flow, and isotope clearance are not much changed as the infarct develops.

Rees and Redding (1968) found radioxenon clearance to be maintained for 6 or more hours. Despite some individual variation collateral flow never fell to zero, and there was usually the opposite tendency for flow rates to rise initially only to fall later to their previous level. Those animals with the lowest collateral flow rates were liable to develop ventricular fibrillation. Grayson *et al.* (1968), using a flow probe method, postulated a vasospastic process after coronary artery occlusion whereby collateral flow falls progressively towards zero. They found that this could be reversed, and that infarction could be prevented by adrenergic neurone blockade. This claim could not be substantiated using another method of collateral flow measurement, when evidence was adduced that the collateral vasculature was near fully dilated in the early hours after infarction, and that some vasodilatation also occurred in the arterioles within the infarcted region (Redding and Rees, 1968). Whether a vasospastic element may sometimes be of importance in the development of myocardial infarction therefore remains uncertain.

There are also interesting changes in flow in the coronary arteries adjacent to the infarct. Flow is usually found to be increased after occlusion of a major coronary artery, but only partly because it supplies the collateral blood. We have compared myocardial blood flow in muscle adjacent to the infarct with that in more distant muscle, and find flow in the immediate vicinity of the infarct to be greater than elsewhere, supporting the suggestion of Driscoll and Eckstein (1967) that this is a response to an increase in local metabolic activity. It seems likely that vascular resistance in the remaining vessels can be adjusted appropriately after occlusion of a large coronary artery and that the calibre of the collateral, adjacent, and distant coronary arterioles varies independently according to local needs.

LATER CHANGES IN COLLATERAL FLOW

Studies over longer periods have shown that serial daily measurements of collateral flow rates are usually unchanged for about 3 days. After this a progressive rise in flow begins, continuing into the normal range by about the tenth day. This development appears to be delayed in older dogs, but in contrast is accelerated in young pigs, in which collateral flow rates in the first few hours are only one-half those of the older dogs. This increase in collateral flow after a few days has been shown to coincide with enlargement of the interarteriolar anastomoses.

There have been attempts to increase this collateral supply, but for many hours after coronary

obstruction the collateral vasculature is widely dilated in response to ischaemia, so that the response to vasodilator drugs is slight, and far less than occurs in the normal myocardium. Indeed it has even been suggested that powerful vasodilator drugs may reduce collateral flow at this stage. After 24 hours, however, a progressive rise in collateral flow results from their administration, and it is of interest that this increased responsiveness precedes the natural increase in collateral flow. This implies that some growth of collateral vessels occurs rapidly, and that the extreme early vasodilatation of collaterals in acute myocardial infarction is not long maintained. It is not yet known what are the effects of powerful vasodilators in patients with acute myocardial infarction. If the same time relationships apply, they would not be of much benefit in the early hours when mortality is greatest, though some effect on collateral flow might be expected later.

It is of interest that collateral vessel growth can be stimulated in the hearts of animals without coronary disease by anaemia, and it has also been shown that anaemia has this effect in man (Zoll, Wessler, and Schlesinger, 1951). Recently it has been suggested that powerful coronary vasodilator drugs may stimulate collateral vessel growth in the hearts of normal animals and thus might ameliorate the effects of subsequent coronary artery obstruction (Schaper, Xhonneux, and Jageneau, 1965).

How do these different stimuli, anaemia, vasodilator drugs, and the most potent of all, ischaemia, promote collateral vessel growth? The common feature is prolonged vasodilatation, and Schaper (1967) has shown that the resultant increase in tangential stress leads to cell division within the vessel wall. This permits further vasodilatation, and depending on the strength of the stimulus, a progressive growth of collateral vessels. The interesting question is whether collateral vessel growth, promoted in this way by vasodilator drugs, can be confirmed in other species and whether it offers any practical benefit to man.

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