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EXPERIMENTAL STUDIES ON THE MYOCARDIAL COLLATERAL CIRCULATION

(Abridged)

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I want to talk about the measurement of collateral flow that Dr. Fulton has so clearly demonstrated. It is not possible to assess this after myocardial infarction in man, and as at present collateral vasculature of the dog resembles that of man we have used this animal to study collateral flow rates immediately following infarction, the changes which accompany recovery, and the effects of drugs and sympathetic blockade.

The infarcts are produced in two ways – anterior by ligating the anterior descending coronary artery at operation, and posterior by wedging a catheter in a large branch of the circumflex artery. The latter is inserted via the left carotid artery. In either case moderate sized infarcts result, with the expected electrocardiographic and enzyme changes, and an overall mortality of about 20 per cent collateral flow is determined by the clearance of radioactive xenon 133 injected into the vessels of the infarct via a fine catheter, and measured with an external scintillation counter.

Before producing infarction, we usually measure the normal myocardial blood flow by the same method – measuring the clearance of xenon 133 injected in solution through a catheter, which does not interfere with normal flow, lying in the mouth of the left coronary artery. In a normal heart the radioactive xenon diffuses rapidly through the myocardium and is then gradually removed over the next two to three minutes.

With the aid of a computer the clearance can be measured in several ways, the clearance rate (K) calculated, and the myocardial blood flow derived in ml/mm/gram. By contrast, in an infarct 3 days old clearance may take as long as 20 minutes, because of the low rate of collateral flow. Estimates of collateral flow immediately after infarction have varied from negligible to adequate, and the current continental and Russian view, recently supported in the Lancet, has been of interest to us. It is suggested that collateral flow after infarction is at first adequate, but then falls to zero within a few hours as a result of harmful sympathetic vasoconstrictor reflexes which may be reversible. If this were so, there would be important therapeutic implications.

In both types of infarcts in our study we found that immediate collateral flow was established at about a quarter to a third of normal myocardial blood flow. There is usually a slight rise in collateral flow in the first hour and then a slow fall to the original level, but there is no evidence that it ever falls to zero. Occasionally this fluctuation is very marked. In one instance, the collateral flow was initially quite low, then rose to the highest we recorded, and finally fell until death from ventricular fibrillation after 5 hours. We have no idea what causes these fluctuations which are unrelated to blood pressure.

We have now recorded collateral flow just before or after resuscitation from ventricular fibrilliation on five occasions, and found that it was always very low, ranging from ·05 to ·15 ml/min/gram of infarct. This is about —15 per cent of the normal value for the heart, a rate which is obviously dangerously inadequate. Two of these animals were successfully resuscitated with subsequent improvement in clearance.

We have examined the effects of general and local sympathetic blockade as well as surgical sympathectomy without demonstrating any beneficial effect on collateral flow, but it does increase slowly on successive days after recovery from myocardial infarction. There is usually little change over the first 3 days, but then it begins to rise and by about the 8th day reaches approximately ⅔ of the normal value. However this does not always happen. After an initial high level of collateral flow, the rate may fall and this may be followed by the death of the animal.

There are of course marked individual variations, but the usually inadequate early collateral flow is established through the fine interarteriolar anastomoses which we know do exist in the

normal heart of both dog and man, and the subsequent increase by the 4th day is due to progressive enlargement of some of these channels. After 10 days, there are often quite large anastomoses around the obstruction in the artery, around the apex in the septum. How responsive is this collateral vasolature during recovery? We are perhaps most interested in the capacity for vasodilation, and for this reason we tested dipyridome, the most active coronary dilator drug at present available. Under its influence, collateral flow increases, only slightly at first, but substantially more as the infarct ages. This response though considerable remains less than in normal myocardium. Our results show that collateral channels are almost maximally dilated in the first hours of infarction, but the greater increments in collateral flow caused on subsequent days indicate that the collateral vessels are then no longer fully vasodilated.

We have also found that collateral flow varies with the systemic blood pressure so that reductions in flow accompany the hypotension of shock and large doses of barbiturate. Conversely the use of pressor drugs is accompanied by an increase in collateral flow. The action of nitrites in angina is likely to remain controversial until we can decide where in the myocardium angina rises, and until we can measure blood flow at this focus. Meanwhile it may be unwise to dismiss the possibility that nitrites act in part by increasing flow.

In fact our studies support the alternative view that an important function of glyceryl trinitrate is to reduce the myocardial oxygen requirement, even though there is a transient initial increase in exteonal cardiac work. This increased efficiency of energy utilization is not a specific effect of the drug but the normal consequence of increasing cardiac output at the same time as a fall in blood pressure takes place. What of the effect on flow? In the normal heart it is easy to demonstrate a biphasic action on myocardial blood flow. The initial increase is, however, transient and would easily be missed in studies in patients, which are harder to control.

When we measured the effect of glyceryl trinitrate on blood flow to the ischaemic myocardium we found an increase of collateral flow in 4 out of 6 animals given the drug 6 hours after infarction. The increase was slight, transient and less than in normal animals, but nevertheless occurred in the most unfavourable setting that could be devised. In those animals that responded the mean increase was 25 per cent.

We were fortunate to come across a natural occurrence in one dog which closely resembled the situation in a patient with ischaemic heart disease and previous infarction. Though spontaneous myocardial infarction in dogs is rare, this animal had a large anterior infarct showing fibrosis and new vessel formation. The anterior descending artery was sclerotic and much narrowed. In this animal we were able to measure collateral flow to an ischaemic zone with an old infarct and recent (induced) coronary obstruction. Not surprisingly the flow rates were a good deal higher than in the other dogs. They were in fact sufficient to prevent further infarction, and it is of particular interest that glyceryl trinitrate and diperidamole increased the collateral flow.

Most studies of the glyceryl trinitrate in patients have been started too late to detect any vasodilator effect, which animal studies show to be over within 3 minutes of giving the drug. But with appropriate timing an increase in myocardial blood flow may be found even in patients with angina. In one such, a single tablet of glyceryl trinitrate taken sublingually increased the myocardial flow rate from ·61 to ·70 ml/min/gram.

Conclusion:

In experimental myocardial infarction collateral blood flow is immediately established at a rate of about one quarter of the normal resting value. It usually rises to a maximum after 2 hours, but is then liable to a slight and gradual reduction. Occasionally, for reasons not at present apparent, large fluctuations occur. Neurone blockade has no effect either in preventing infarction or in increasing collateral flow.

At any time during the early days after infarction, flow may fall below the potentially dangerous level of about ·15 ml/min/gram of infarct (15 per cent of the normal resting value) when ventricular fibrillation may occur.

On average, collateral flow begins to increase spontaneously after 4 days, and normal levels may be attained 10 days after infarction. For a few hours the collateral vessels are only slightly responsive to vasodilator drugs, presumably because they are already maximally dilated, but they begin to respond some days before the spontaneous rise in collateral flow.

Finally, though glyceryl trinitrate has other effects, perhaps of greater importance, it may cause a modest increase in collateral flow to the ischaemic myocardium.