



Coronary Blood Flow and Myocardial Metabolism in Angina Pectoris

Richard Gorlin

Abstract

It is interesting to note on this centenary celebration that we still are uncertain about the nature of anginal pain; we discuss the nitrites, we carry out experiments, yielding new data, and yet we are still really not quite sure how these agents act. I think it is desirable to review with humility some of Lauder Brunton's ideas about the actions of these drugs. At a major national meeting in America just one year ago, the observation was made that the blood pressure rises before pain occurs in attacks of spontaneous angina pectoris. Unfortunately the speaker failed to appreciate that Sir Lauder Brunton had suggested the use of amyl nitrite for this very reason, namely high blood pressure with angina. He thought that nitrites might reduce the pain of angina pectoris by lowering the pressure.

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CORONARY BLOOD FLOW AND MYOCARDIAL METABOLISM IN ANGINA PECTORIS

(Abridged)

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It is interesting to note on this centenary celebration that we still are uncertain about the nature of anginal pain; we discuss the nitrites, we carry out experiments, yielding new data, and yet we are still really not quite sure how these agents act. I think it is desirable to review with humility some of Lauder Brunton's ideas about the actions of these drugs. At a major national meeting in America just one year ago, the observation was made that the blood pressure rises before pain occurs in attacks of spontaneous angina pectoris. Unfortunately the speaker failed to appreciate that Sir Lauder Brunton had suggested the use of amyl nitrite for this very reason, namely high blood pressure with angina. He thought that nitrites might reduce the pain of angina pectoris by lowering the pressure.

I would like to discuss some aspects of angina and myocardial ischaemia and present briefly our thoughts about the actions of nitroglycerine on the coronary circulation and the myocardium.

Anginal pain may arise not only as a function of deficient blood supply to a particular region of the heart, but also as a function of the distribution of collaterals supplying the same area from other coronary arteries. The situation is further complicated by the fact that the resistance blood vessels can constrict or dilate under various local influences and thereby alter the flow to a potentially ischaemic zone. Another complicating factor is the bombardment of an affected area by various efferent stimuli originating within the central nervous system. This can increase the force and speed of muscle contraction (so-called inotropic actions), and elevate the heart rate, thus increasing cardiac activity and so that energy requirements outstrip the blood supply of a potentially ischaemic zone. Then there are motor pathways which affect the arterioles of the coronary system and may cause them to react with either constriction or dilation, irrespective of the local effects of hypoxia. Finally – on the question

of the pain stimulus itself – we must always remember that a chemical reaction occurs in the presence of ischaemia which may produce various peptide substances (kallikrein and plasma-kinins). These have the ability to stimulate unmyelinated nerve fibres which may or may not be present in any given zone of the heart, depending on the degree of previous nerve damage and the patient's inherent nerve supply. Once these receptors are stimulated the impulse goes back to the central nervous system, but there are many slips between the cup and the lip. This pain can be augmented by impulses arising in other systems of the body or dampened if there has been some change in interpretation within the cerebral cortex. So all of these features must enter into our discussion of angina pectoris, irrespective of the objective assessment of myocardial ischaemia.

One way to learn something about the nature of myocardial ischaemia is to study cardiac metabolism. To do so, it is necessary to place a catheter in the coronary sinus. This is a simple and safe procedure, if done under proper conditions, by which blood samples can be obtained from various veins which course over the left ventricle. The metabolic exchanges of various substrates by the heart can then be studied by analysis of both arterial and coronary venous samples. The normal metabolism of the heart is essentially oxidative but when there is inadequate oxygen supply, the heart switches to glycolytic metabolism, with the result that lactic acid is generated as an end product and ultimately diffuses out into the blood stream. Thus, lactic acid concentration in the coronary sinus in excess of levels in the arterial blood is evidence of myocardial ischaemia. In normal subjects the heart extracts lactate and uses it as a fuel both at rest and during most stresses but ischaemic hearts can do this only at rest – when the oxygen supply is still adequate. In a patient who has coronary heart disease with greater than 75 per

cent obstructions in one or all three arteries, there is usually lactic acid extraction by the heart at rest. But, when cardiac activity is stimulated, the lactate concentration rises so that coronary venous concentration becomes higher than the arterial. When nitroglycerine is given, it relieves anginal pain, improves oxygen supply and burns off lactic acid production. On the other hand, isiprenaline stresses the ischemic heart and increases lactic acid production.

In some marginal attacks we have recorded coronary vasoconstriction totally inappropriate to the situation. The first spontaneous observation of this phenomenon showed a normal coronary flow of 116 cc per minute per 100 grammes of muscle, which fell to 78 cc at the time of an anginal attack. Another patient had no pain, a blood pressure of 150/78, a pulse rate of 54, and a coronary flow of 71 cc, when the recording began. The patient then became hypertensive (180/110) and developed pain; the coronary flow *fell* to 51 cc. Nitroglycerine was given, the patient obtained relief of pain, the blood pressure fell to 130/73, the pulse rate dropped and the coronary flow *increased* to 88 cc per 100 grammes per minute. This phenomenon of a reduction in coronary flow associated with hypertension and coronary vasoconstriction has now been seen in three patients, each of whom developed a spontaneous attack of angina. Each also gave a prior history of apparently unprovoked attacks of anginal pain. These findings show that there is such an entity as coronary vasoconstriction, and that nitroglycerine appears to be effective in attenuating such an attack by tending to normalize the blood pressure and by augmenting coronary blood flow.

Bernstein and his collaborators at the Johns Hopkins Medical School have attempted to measure the effect of nitroglycerine on coronary blood flow alone. Finding that the blood pressure tended to fall after nitroglycerine administration, they gave it directly into the coronary artery so that systemic circulation would be unaffected by its peripheral dilator actions. Under these circumstances, different from how the drug is taken, they were able to demonstrate that coronary flow is augmented, that nitroglycerine is a coronary vasodilator in both normal subjects and angina patients. But is this its most important action? Several workers have found evidence of a beneficial and somewhat selective effect to augment collateral blood flow by collateral vessel dilation

and we have been able to confirm this by means of selective coronary angiography and radio-krypton studies of coronary flow.

Summary

It is our belief that nitroglycerine has actions on the coronary vasculature as follows. Coronary flow is increased by arteriolar dilation which is particularly important in the presence of induced vasoconstriction. There is also a profound effect to increase blood flow via the collateral circulation. As a result, blood is shunted towards the post-obstructive and poorly perfused areas of the myocardium.