The pathology of myocardial ischaemia

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To understand the pathology of myocardial ischaemia detailed knowledge of the anatomy and physiology of the coronary arterial tree is required. The anatomy of the major coronary arteries running on the epicardial surface of the heart has been common knowledge for years. The equally important micro-anatomy of vessels within the myocardium has been neglected along with the physiology of intramyocardial blood flow.

Coronary artery anatomy

The anatomy of the major coronary arteries is so well known that it does not need lengthy consideration apart from emphasizing a few salient points. Each major arterial branch supplies its own segment of the left ventricular muscle from epicardium to endocardium. There is little functional anastomotic or collateral blood flow between major branches in the *normal* heart and thus the coronary vessels are often referred to as 'end arteries'.

The left anterior descending coronary artery constantly supplies 50-60 per cent of the total left ventricular muscle mass, including the anterior wall and the anterior two-thirds of the interventricular (I-V) septum. As a general rule the left circumflex artery supplies the lateral wall and the right coronary artery the posterior wall of the left ventricle including the posterior third of the I-V septum. These two arteries are, however, inverse in size with a spectrum of which the two extremes are a left circumflex supplying the lateral and posterior walls of both ventricles and a right coronary artery supplying the whole posterior wall and the lateral aspect of the left ventricle in addition to the whole right ventricle. In the former case (extreme left dominance) the right coronary is represented only by the tiny conus artery to the right ventricular outflow tract and in the latter (extreme right dominance) the left circumflex artery is absent. Every intermediate variation occurs. Generally the terms right (70 per cent of individuals) or left (30 per cent of individuals) dominance are used to indicate whether the right or left circumflex artery gives rise to the posterior descending coronary artery. Within each group so defined there is, how-

ever, a wide range of the actual mass of left ventricular muscle supplied by a particular artery.

While there is no functional communication between the major epicardial arteries in normal hearts, collateral flow rapidly develops in pathological conditions. The usual stimulus for the appearance of collateral vessels is probably a pressure differential between areas supplied by different major arterial branches (Gensini and Da Costa, 1969; Sheldon, 1969). The cause in virtually all instances is atheroma in one of the arteries in question, but some evidence suggests collateral flow also develops in severe hypertrophy of the left ventricle without arterial disease. Collateral vessels are recognized with ease in coronary arteriograms taken in life, or at necropsy, by their characteristic corkscrew course. This appearance probably results from an incomplete medial muscle layer in such vessels. The speed with which collateral vessels appear makes it certain that they exist as anatomical structures in all human hearts, but remain 'unused' unless required. Clinical experience indicates that there is considerable individual variation in the degree to which collateral blood flow develops.

The micro-anatomy of the intramyocardial arteries received little attention until the detailed work of Farrer-Brown (1968). He has shown that the epicardial arteries send arborizing branches into the myocardium as far as the endocardium with a second system of unbranching straight vessels passing directly to the trabeculae carneae and centre of the papillary muscles (fig 1). A subendocardial plexus of vessels probably receives flow from both systems, but only in the ischaemic scarred myocardium serves an important function in collateral flow.

Physiology of coronary arterial blood flow

The major epicardial arteries fill in ventricular systole and have a pressure trace similar to that of the aortic root; in contrast intramyocardial flow other than the immediate subepicardial zone is entirely diastolic. Flow into the depths of the myocardium is dependent on the pressure gradient between the epicardium (X) and the endocardium

Fig. 1 Diagrammatic representation of intramyocardial arterial supply. X represents the epicardial surface, Y the endocardial. The papillary muscle receives its own supply without branches to the remainder of the myocardium.

Fig. 2 Comparison of aortic root pressure (p) which is virtually identical to pressure in the epicardial arteries and LV cavity pressure (LVp). Intramyocardial flow only occurs in diastole and is proportional to the shaded area between X and Y.

Fig. 3 Venn diagram of the clinical features of ischaemic heart disease (after Rose, 1972).

(Y) in figure 1. Consideration of the aortic root pressure trace represented by X and the left ventricular cavity pressure trace represented by Y shows that only in diastole can such a gradient exist (fig 2). Coronary flow is proportional to the shaded area between the two pressure traces in diastole as illustrated in figure 2. This area can be easily reduced by many factors (Hoffman and Buckberg, 1975), the most important of which are rapid heart rate shortening diastole, lowered aortic systolic pressure, or elevated diastolic pressure in the left ventricle. The micro-anatomy and physiology of intramyocardial blood flow are such that all factors reducing overall coronary perfusion will, particularly if the small intramyocardial vessels are at maximum vasodilatation, have a maximal effect on the sub-endocardial zone, including the centre of the papillary muscles. The vulnerability of the subendocardial zone is exemplified by the occurrence of transient subendocardial ischaemia, demonstrable on ECG, with maximum exercise even in young, fit athletes (Barnard *et al*, 1973).

Clinical expression of myocardial ischaemia

Three major symptom complexes occur in myocardial ischaemia: angina, myocardial infarction and sudden death. The three overlap to a considerable degree (fig 3) (Rose, 1972), but the pathology can be considered separately with profit.

ANGINA

In general the patient with stable angina has a well preserved and even morphologically normal left ventricular muscle but with significant coronary artery disease in the form of one or more areas of severe stenosis (Roberts, 1976). Angina results from a temporary failure of an adequate blood supply being provided to one area of the myocardium for a work load increased by exercise. Occasionally angina may be precipitated by rate or rhythm change or emotion. When the work load is reduced below a critical level, blood supply is again adequate and pain vanishes within a few minutes. The work load at which any individual with stable angina develops pain is remarkably constant after correction for variation in heart rates (Robinson, 1967). While it can be demonstrated that the great majority of patients with stable angina have significant coronary atherosclerosis, the exact pathophysiology within the arterial tree is obscure. The critical degree of stenosis at one point necessary to produce angina is uncertain. Experiments *in vitro* of flow in isolated arteries suggest that only severe stenosis with reduction of the lumen of 80 per cent or more significantly reduces flow (May *et al*, 1963). Clinical

experience suggests that multiple areas of stenosis in series may be as significant as a single area of greater stenosis. Abnormal flow patterns are thought to be important in the pathogenesis of the pain. Where a series of branches open between areas of stenosis which fix flow at a low level, exercise may so increase blood flow in the proximal branches that pressure falls to a level at which no flow occurs in the distal branches (Soloff, 1972). Clinical study of patients with angina by coronary arteriography, as well as postmortem studies, allow grading of cases of angina into those with single, double or triple major vessel stenosis. The majority of patients with angina have severe stenosis in more than one major vessel (Zoll *et al*, 1951; Roberts, 1976) and histological examination frequently indicates that such areas were once total occlusions in which recanalization has occurred.

While the great majority of patients with angina can be subsequently proven to have coronary artery disease, a small minority do not. Such patients usually have abnormal left ventricular function with, most commonly, severe myocardial hypertrophy (Vlodaver *et al*, 1972). In aortic stenosis perfusion pressure in the major epicardial arteries is reduced at the same time as left ventricular wall thickness is increased and end diastolic cavity pressure raised. Angina is a

common presenting symptom indicating subendocardial ischaemia. Hypertension may be associated with angina, provoked by the same mechanism. Aortic regurgitation, mitral regurgitation and congestive cardiomyopathy all reduce overall coronary perfusion and occasionally may be associated with angina. Angina is a common presenting symptom of hypertrophic obstructive cardiomyopathy (Frank and Braunwald, 1968). After elimination of those cases of angina due to coronary artery disease and abnormal ventricular haemodynamics, a tiny but identifiable group remains where no cause is ever shown. Current hypotheses for this fascinating tiny group of patients include some abnormality of oxygen transport at cell level and the usual risk factors for coronary artery disease are strikingly absent (Herman, 1971).

MYOCARDIAL INFARCTION

The occurrence of myocardial necrosis is usually taken to indicate total deprivation of blood supply to an area of cardiac muscle for an appreciable period of time. The period need be as little as seven to 10 minutes as judged by experimental work in animals. While at first sight the pathology in man is straightforward, considerable controversy exists over some

Fig. 4 Diagrammatic representation of the various forms of myocardial necrosis. Type A are segmental or regional infarcts and type B diffuse subendocardial necrosis or circumferential infarcts.

Fig 5a

Fig. 5 Fresh myocardial slices stained by Nitro BT method with added succinate substrate. Myocardial necrosis remains unstained. Normal myocardium is dark blue.

a Small antero-lateral regional or segmental infarct (arrows) involving full thickness (transmural) of left ventricle. Occlusion due to recent thrombus of left circumflex artery.

b Large postero-septal regional transmural infarct involving whole interventricular septum. Recent occlusion of main right coronary artery and old occlusion left anterior descending artery.

Fig 5b

aspects. Much of the difficulty arises from failure to appreciate that several patterns of myocardial necrosis occur in man whose causes at a pathophysiological level are very different and the terminology used is very confused. The demonstration of the shape and topography of areas of necrosis is best made by the various modifications of the Nitro BT staining method, using fresh slices of myo-

cardium (Nachlas and Shnitka, 1963). By this technique normal muscle stains dark blue; the areas of necrosis remain pale. The method reflects loss of substrate and enzyme activity in the dead muscle.

Two basic macroscopic patterns of myocardial necrosis can be recognized. A single segment or quadrant or region of the ventricular circumference may be involved, that is anterior, lateral, posterior or

Fig. 6 Diffuse subendocardial necrosis (laminar infarction) involving the whole circumference of the left ventricle and also areas of the right ventricle. Death 48 hours after left ventricular bypass and aortic valve replacement (Nitro BT with substrate).

septal (fig 4A). Such necrosis may be full thickness, ie, transmural (fig 5), or involve only the subendocardial zone. A quite distinct second basic form of necrosis (fig 4B) involves the whole circumference of the subendocardial zone, scattered foci up to 1.2 cm in diameter and the centres of the papillary muscles (figs 4, 6). This type is probably best known as diffuse subendocardial necrosis but is also referred to as laminar or circumferential infarction. Combinations of transmural regional infarction with diffuse subendocardial necrosis are, however, now becoming more common (fig 4), confusing the distinction even further.

The terminology is confusing and has created confusion. Current practice at St George's Hospital is to draw the infarct on sketches of the heart, rather than to indulge in confusing semantics in the necropsy report.

The pathophysiology of the two basic types, ie, transmural regional and diffuse subendocardial necrosis, is quite different. The former results from severe reduction and most often total cessation of blood flow in one major epicardial artery, the latter from an overall fall in coronary perfusion with abnormality in distribution of blood within the myocardium.

Regional or segmental infarction

This is the type most frequently seen in the necropsy room and is the classic myocardial infarct for which ECG criteria are well defined and accurate localization to the segment of ventricle involved is possible by the clinician even before necropsy. While there is general agreement that the epicardial artery supplying that area of myocardium is severely affected by

atheroma, the details are highly controversial. Some authorities, particularly in the United States and Italy, consider severe stenosis alone may precipitate infarction (Roberts and Buja, 1972; Baroldi, 1965); others consider total occlusion by a mixture of thrombus and atheromatous debris is the precipitating event, a view most widely held in Britain (Davies *et al*, 1976), but also by some workers in the United States (Chapman, 1974). A further extension of the first view is to regard coronary thrombi, when present, as secondary and merely a consequence of stasis following infarction (Roberts, 1974).

Opinion over the presence or absence of occlusive thrombi in acute regional infarction has undergone a series of extreme swings during this century. The variation is so great that it cannot be explained by other than differences in definition, selection or interpretation and not in actual pathology. The two extremes (Burchell, 1974) are represented by an incidence of occlusive thrombi in the regional artery of less than 50 per cent to virtually 100 per cent (Chandler, 1974).

Personally, I have always found occlusive thrombi to be present in genuine regional infarcts (Davies *et al*, 1976). Reasons for lower figures for occlusive thrombi may lie in poor dissecting technique, inclusion of all forms of myocardial necrosis, both regional and laminar, inclusion of sudden deaths without acute infarction being present and simply a different philosophy on the part of the prosector. The controversy, however, is futile; no one would disagree that acute regional infarction results from a failure of regional blood flow in one main coronary artery branch whatever the mechanism. Even those who deny the role of occlusive thrombi admit that incorporation of mural thrombus is largely respon-

sible for areas of stenosis increasing to a point at which flow almost ceases (Roberts, 1973).

The regional or segmental subendocardial infarction may be considered as a variant in which the subendocardial zone, always most vulnerable, has undergone necrosis with collaterals just enabling subepicardial flow to be maintained. This type of infarct is uncommonly seen in the necropsy room and adequate pathological study is difficult. The lesion is certainly more commonly diagnosed in life by ECG criteria than it is seen in cases in the necropsy room.

The infinite variation in size and site of a transmural infarct is explicable by different sites of arterial occlusion, anatomical variations of the major arteries and by different degrees of collateral development. The preponderance of infarcts involving the anterior-septal segment is associated with the high incidence of disease in the left anterior descending artery and its relative importance in supplying up to 60 per cent of the ventricle. Posterior and lateral infarcts follow anterior lesions in the approximate ratio of 8.5:1 (Davies *et al*, 1976).

Diffuse subendocardial necrosis

This type of myocardial necrosis in the pure form is less commonly seen. Clear recognition that the pathophysiology was a failure of overall coronary flow to a level at which the subendocardial zone was not perfused came from open heart surgery. In patients placed on left heart bypass, a characteristic sequence of a stormy postoperative period culminating in death from left ventricular failure with diffuse subendocardial necrosis seen at necropsy was recognized. The major coronary arteries were anatomically normal and relatively disease free, but common clinical features were impaired ventricular performance before operation, lengthy periods on bypass, severe ventricular hypertrophy and prolonged ventricular fibrillation during the operation (Najafi *et al*, 1969; Buckberg *et al*, 1972). Subsequent improvement of technique to maintain coronary

Fig. 7 Aortic stenosis with sudden death. No significant coronary artery disease. Muscle necrosis involves the inner layer of the left ventricle and particularly the centres of papillary muscles and trabeculae (Nitro BT with substrate).

perfusion during arrest at operation has greatly reduced the complication, but Hoffman and Buckberg (1975) were stimulated to define clearly the factors which influence subendocardial perfusion. Some factors which reduce subendocardial perfusion even with anatomically normal epicardial vessels are listed in table. Severe triple vessel stenosis reducing overall perfusion in the epicardial arteries is often an important potentiating factor or may be a primary cause of diffuse subendocardial necrosis in its own right (Davies *et al*, 1976). Patients with longstanding angina toward the end of the clinical course may develop steadily increasing pain which is associated with diffuse subendocardial necrosis at necropsy. Mitral regurgitation often develops in this terminal phase from papillary muscle damage and a vicious circle of a dilating left ventricle with more muscle necrosis occurs. The actual event starting this cycle, however, is difficult to pinpoint.

The most frequent valve lesion associated with diffuse subendocardial necrosis is severe aortic stenosis where left ventricular failure has occurred. In this situation, aortic root pressure falls to very low levels associated with very high end-diastolic pressure within the left ventricle. At the same time the myocardial wall thickness is increased and developed tension in the endocardial zone much increased. These factors all make it seem certain that at times subendocardial flow can cease in severe aortic stenosis

1 Anatomical	
Diffuse coronary atherosclerosis	Triple vessel disease Peripheral extension atheroma to small vessels
2 Pathophysiological	
Fall diastolic aortic root pressure	Aortic valve disease, shock
Rise LV end diastolic pressure	LV failure, mitral regurgitation
Short diastole	Rapid rate
3 Altered left ventricular shape	
Thick LV wall	
Dilated LV cavity	

Table Factors associated with an overall fall in myocardial perfusion maximal in subendocardial zone

Fig. 8 Male with many years of angina and hypertension. Terminal 14 days severe left ventricular failure. Triple vessel coronary atherosclerosis. Two episodes of different age segmental infarction on posterior-lateral wall (A and B). Widespread subendocardial and focal 1 cm areas of necrosis in remainder of left ventricle.

(fig 7). The clinical effects include a high incidence of sudden death, progressive left ventricular failure and mitral incompetence developing as a consequence of papillary muscle necrosis. End-stage aortic stenosis is often associated with considerable degrees of subendocardial fibrosis (Moller *et al*, 1966).

Mixed infarction patterns

Increasing numbers of patients managed in intensive care units have meant longer survival of patients with regional infarcts large enough to diminish seriously left ventricular performance and produce the clinical syndrome of shock. In such cases a combination of transmural regional infarction with superimposed diffuse subendocardial necrosis may occur (fig 8). This pattern is in fact the most common form of diffuse subendocardial necrosis encountered by the hospital pathologist in routine practice. Factors tending to promote the superimposition of diffuse subendocardial necrosis or regional infarction include severe left ventricular failure, shock, severe stenosis in all three vessels, coexistent mitral regurgitation, peripheral extension of atheroma into small arteries as in diabetes or myxoedema, previous old infarcts and left ventricular hypertrophy.

Sudden death

It is indisputable that patients suffering from angina with or without a history of previous infarction and patients without previous overt clinical symptoms can die suddenly of ischaemic heart disease (Myers and Dewar, 1975); the number who do so is very large (Paul, 1974). It is therefore surprising (Camps, 1969) that neither the exact pathology nor the pathophysiology of the terminal event is known.

A proportion of cases are patients in whom an acute transmural regional infarct would have developed had they survived longer; death has occurred in the first 12 hours before it is easy to demonstrate the area of infarction. The coronary artery pathology is identical with that in acute regional infarction in that occlusive thrombi are found in a major epicardial artery. Opinions of the incidence of such thrombi in sudden death range from 20 per cent to 90 per cent but agreement on 50-60 per cent would be accepted by many people working in the field; few would deny that a significant proportion of cases do not have histological evidence of any recent acute event in the coronary arteries (Friedman *et al*, 1973; Liberthson *et al*, 1974).

Death must be presumed to be due to an electrophysiological aberration and some evidence exists for ventricular electrical instability in patients with coronary artery stenosis (Chiang *et al*, 1969; Lown and Wolf, 1971; *British Medical Journal*, 1973). If this view of the event is accepted, the question arises as to how much coronary artery stenosis must be present for sudden death to occur. No answer to this question is available, but most cases do have double- or triple-vessel disease in a degree equivalent to patients with angina. A minority have only single-vessel disease and inevitably the suspicion must arise in such cases that death was due to a cause other than coronary artery disease. It is an astonishing fact that we do not as yet know the minimal degree of coronary artery stenosis which can be associated with sudden death.

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