Non-atheromatous ischaemic heart disease

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THE symptom of angina reports an imbalance between myocardial oxygen need and available myocardial blood flow. The overdraft may stem from *increased demand* in structural disease such as aortic stenosis, hypertrophic cardiomyopathy or thyrotoxicosis or from *reduced flow* and this is not always the result of obstructive atheroma (Table 1).

TABLE 1. Acquired non-atheromatous coronary artery disease

Embolism	Mitral stenosis (thrombus) Myxoma (tumour) Aortic stenosis (calcium) Infective endocarditis Valve prostheses
Ostial stenosis	Aortitis After valve replacement Dissection of the aorta Isolated
Coronary dissection	Marfan Pregnancy
Coronary thrombosis	Smokers Spasm
Microvascular disease	Polyarteritis Amyloid Diabetes
Iatrogenic	Coronary angiography

Myocardial ischaemia may result from congenital abnormalities in the origin or distribution of the coronary arteries. Coronary obstruction may also develop at a young age in some rare hereditary disorders such as Hurler's syndrome, homocystinuria or pseudoxanthoma elasticum. The coronary arteries may be the site of embolism; ostial stenosis may complicate luetic (or other) aortitis or coronary dissection; the small coronary arteries may be involved in certain connective tissue disorders such as polyarteritis, in amyloid heart disease or in diabetes. Finally, angina or even infarction may develop in the absence of these disorders and in the demonstrated presence of normal coronary arteries; this not so rare phenomenon has attracted increasing interest now that coronary angiography has become more generally available.

Congenital coronary anomalies

Anomalous origin of a coronary artery

This is a rare disorder. In its most usual form the left coronary artery arises from the left posterior aspect of the pulmonary artery instead of from the left coronary sinus of the aorta (Fig. 1). The artery then emerges from the pulmonary trunk and the aorta to pursue its usual course. Occasionally the anomalously arising vessel represents only one branch of the left coronary artery, the circumflex or anterior descending then arising normally. Anomalous origin of the right coronary artery has also been described but it is much rarer.

Anomalous origin of the left coronary artery results in left ventricular ischaemia or infarction, the extent of this depending on the rate of fall of pulmonary artery pressure after birth and the rapidity of

FIG. 1. Anomalous origin of left coronary artery from the pulmonary artery in a neonate. Because the pulmonary artery pressure was still high the anomalous coronary filled after contrast injection into the main pulmonary artery (anteroposterior projection).

of development of intercoronary anastomoses with possibility of blood flow between the normally arising high-pressure right coronary artery and the anomalously arising low-pressure left coronary artery. The extent of left ventricular ischaemia also depends on coronary dominance. In the presence of a heavily dominant right coronary artery, anomalous origin of the left coronary artery may be less serious.

The usual time of presentation is between 1 and 4 months of age and the mortality is high. Rarely the condition may be encountered in childhood or even in adult life. The infant presents with: (1) symptoms of myocardial ischaemia with attacks of screaming and pallor; (2) failure to thrive; or (3) heart failure.

The infant is usually well for the first week or so of life because at that time the pulmonary artery pressure is still high and the anomalous coronary is perfused at a high pressure albeit with blood of relatively low oxygen tension. Persistence of the ductus in the first few days of life may also contribute to the maintenance of left ventricular nutrition while it is open. The development of left ventricular failure may itself contribute towards an uneasy balance by delaying the normal fall in pulmonary artery pressure. It follows that by the time that the condition is recognized the left ventricle has already suffered severe, if not fatal, infarction. These infants, by definition, do not possess adequate intercoronary anastomoses, so flow down the anomalous coronary is still antegrade from the pulmonary artery and treatment is difficult. Logically it should be by reimplantation of the anomalous coronary artery into the aorta. This is done by removing it together with a cuff of pulmonary artery and implanting it either in the normal site or, more often, anastomosing it with the subclavian artery. The mortality is high because the infant is already critically ill, the left ventricle having usually already sustained irreversible damage.

The clinical signs are of heart failure often with mitral regurgitation (Noren *et al.*, 1964). The systolic murmur may be loud and the mitral reflux is attributable to papillary muscle ischaemia but may lead to the mistaken diagnosis of ventricular septal defect. The ECG is invariably abnormal and usually shows evidence of infarction or ischaemia of the left ventricle. Less often there may simply be changes of a left ventricular disorder which is not specific.

If the intercoronary anastomoses permit adequate retrograde myocardial perfusion into the left coronary artery from the right coronary artery and particularly if the territory supplied by the anomalous coronary is small then the infant may survive with no apparent problem. Both the ECG and left ventricular function may be normal or variably abnormal depending on the amount of left ventricular damage which has been sustained. Presentation in childhood

or adult life is then associated with the late development of a continuous murmur with or without symptoms and evidence of left ventricular ischaemia. Presentation at this age is attributable to excessive flow through the intercoronary anastomoses between the high-pressure right coronary circulation and the low-pressure left coronary circulation. If the run-off increases then the intercoronary anastomoses which were responsible for sustaining the left ventricular myocardium and life during infancy later on become responsible for the development of secondary ischaemia in the territory of the left coronary artery. Cardiac catheterization may reveal an oxygen step-up in the pulmonary trunk attributable to draining of blood retrograde from the aorta to the pulmonary artery through the coronary system. The right coronary artery is seen to be greatly enlarged, the left coronary artery is opacified only via the right and cannot be intubated from the aorta. At this stage the correct treatment is ligation of the left coronary at its origin from the pulmonary artery.

The third, and the rarest form of presentation, is in adult life with the development of acquired coronary artery disease in the single right coronary artery.

Coronary-cameral and arterio-venous fistulae

Sometimes a normally arising coronary artery develops a fistulous connection with one of the cavities of the heart, most commonly the right ventricle or right atrium. The connection with the low-pressure chamber slowly enlarges and a continuous murmur is often the presenting feature. Eventually myocardial ischaemia may develop.

Figure 2 shows a right coronary fistula into the right ventricle in a 20-year-old man who had been in a car accident. A continuous murmur over the cardiac apex was heard after operation for a ruptured spleen and liver and this fistula may have been traumatic rather than congenital in origin.

Rarely the onset of symptoms may be attributable to atheromatous obstruction otherwise coronary-cameral fistula more often produces no symptoms at all. Thus, a 55-year-old man presenting with angina was found to have a soft continuous murmur maximal at the right sternal edge in the third and fourth spaces. Coronary angiography revealed him to have a fistula between the sinus node branch of the right coronary artery and the right atrium but his presentation was attributable to the development of an atheromatous obstruction of the left anterior descending coronary artery. Obstruction of the latter alone may not have produced symptoms had it not been for the congenital malformation in the other coronary. Both the congenital and the acquired disorder were successfully treated surgically. The patient has lost his angina and has done well.

FIG. 2. Coronary-cameral fistula which may have been of traumatic origin (see text). The left ventricular angiogram in right anterior oblique projection shows both coronary arteries. The left coronary is normal but the right coronary artery is dilated and tortuous. There is a faint 'blush' anteriorly which in other views was shown to be caused by contrast entering the right ventricular chamber from the right coronary artery.

Congenital lengthening and tortuosity

This is an exceedingly rare congenital abnormality in which extreme tortuosity of all the coronary branches is associated with progressive myocardial ischaemia.

Elongation and tortuosity is also seen in the kinky hair syndrome (Menke's syndrome) attributable to copper deficiency.

Hereditary disorders affecting the arterial system and coronary arteries

Marfan's syndrome

Marfan's syndrome is transmitted by an autosomal dominant gene in which there is a defect in the elastic fibres of connective tissue, associated with usually increased height, skeletal abnormalities, myopia and ectopia lentis, aortic aneurysm, dissection and rupture, and valvular regurgitation. The well known habitus of Marfan's syndrome is not always present in patients who present with vascular complications (McKusick, 1972).

Hurler's syndrome (mucopolysaccharidosis I)

In this disorder (characterized by dwarfism, skeletal anomalies, a characteristic coarse facies ('gargoylism'), clouding of the cornea and low intelligence) cardiac abnormality commonly de-

velops. This may be caused by deposition of mucopolysaccharide in valve cusps leading to regurgitation or stenosis, or coronary obstruction may lead to angina or sudden death (Scheibler *et al.*, 1962).

Homocystinuria

This condition, which superficially resembles Marfan's syndrome except for the common association of mental subnormality, is characterized by arterial thromboses which can lead to angina, infarction and death.

Ehlers-Danlos syndrome

This is a heritable disorder of connective tissue characterized by hyperextensibility of the skin and a variety of visceral abnormalities which share some features of Marfan's syndrome. There are articular and ligamentous laxity, ectopia lentis and cystic medial necrosis of the aorta and other arteries leading to dissection (Beighton, 1969).

Pseudoxanthoma elasticum

This is a disorder which can be recognized clinically by changes in the skin which has a crapy texture and by the well known angioid streaks in the retina. Gastrointestinal haemorrhages, hypertension and arterial occlusions tend to develop. The first manifestation can be angina or infarction in a young person and when this occurs this disorder should be thought of and the skin and retinal changes sought. Appearance of the coronary arteries on coronary angiography is not dissimilar to that in atheromatous coronary disease and cases have been treated successfully by coronary by-pass (Bete *et al.*, 1975). The arteries show increase, fragmentation and calcification with sub-endocardial thickening rich in acid mucopolysaccharide. Medial fibrosis develops and disruption of the internal and external elastic laminae.

Acquired non-atheromatous coronary disease

Coronary embolism

Embolism to the coronary arteries is not uncommon. It is a frequent complication of infective endocarditis and of sterile thrombotic (marantic) endocarditis and is the major determinant of angina in patients with mitral stenosis. In tumours of the left atrium (usually myxoma) the presentation can be with angina or infarction due to embolism of tumour or associated thrombus into a major branch of the coronary arteries.

Calcium embolism occurs frequently in calcific aortic stenosis although it only rarely produces major infarction. Angina is one of the expected symptoms of aortic stenosis so that angina due to lodgment of particles of calcium in minor branches

FIG. 3. Acute coronary embolization during selective coronary angiography in a patient with a history of infarction but who showed no evidence of coronary atheroma or other abnormality except the iatrogenic one. The right anterior oblique view on the left shows the left coronary artery with an abrupt termination of the large calibre obtuse marginal branch of the circumflex. This cut-off appearance indicates an acute block and the patient developed an infarct. The lateral view on the right shows the stump of the blocked vessel which should have coursed down the posterolateral free wall of the left ventricle.

of the coronary branches does not alter the clinical picture nor is it usually sufficient to contribute materially to left ventricular dysfunction. The calcium can be found in the myocardium on histological examination of most fatal cases of calcific aortic stenosis.

One of the causes of death after artificial valve replacement of the aortic or mitral valve is coronary embolism and this is particularly likely to occur by direct extension of thrombus from an aortic valve prosthesis into the ostium of one of the coronary arteries, usually the left. The end of the cage of the Starr-Edwards prosthesis is one of the sites of election for thrombus deposition and from there it is only a very short distance into one of the coronary ostia.

Aortitis

In aortitis due to any cause, ostial stenosis may develop. It occurs classically in syphilitic aortitis but may also be seen in aortitis associated with ankylosing spondylitis, rheumatoid arthritis or in Reiter's syndrome, in giant cell arteritis, in oriental arteritis and aortitis (Takayasu's syndrome) and as an isolated finding. In the latter instance when there is no associated disorder to alert the physician to the possibility of ostial stenosis the condition can be missed both by the inexperienced operator at coronary angiography and by the pathologist at autopsy. Coronary ostial stenosis also develops early in hypercholesterolaemia when it is due to

atherosclerosis in the aortic root, a site of predilection and almost of xanthoma formation in this disorder. It may develop also as a consequence of turbulence after replacement of the aortic valve by a caged ball valve prosthesis (Roberts and Morrow, 1969) and also in association with supravulvar aortic stenosis.

Coronary dissection

Coronary dissection distinct from or complicating aortic dissection due to cystic medionecrosis may occur in pregnancy, in coarctation, in Marfan's syndrome and in Ehlers-Danlos syndrome.

Introgenic coronary disease

Coronary dissection or embolism can complicate the investigation of coronary angiography but in experienced hands the risk should be exceedingly low (< 1 in 1,000) (Fig. 3).

Connective tissue disorders

Coronary artery involvement in the connective tissue disorders is common. In giant cell arteritis and in polyarteritis the major coronary arteries as well as branch arteries (visible on coronary angiography) may be affected (Holsinger, Osmundson and Edwards, 1962). In suspected polyarteritis where there is evidence of cardiac involvement, coronary angiography may indeed be justified and reveal typical small aneurysms on branches of the coronary tree.

The syndrome of angina and angina-like pain with normal coronary arteries

Cardiac pain may arise from myocardial ischaemia, from pericarditis or from the aorta in dissection. It may occur in heart muscle disease (cardiomyopathy) and aortic stenosis. Angina-like pain may arise from other viscera particularly from the oesophagus. In yet other patients none of these explanations seems to apply and the source and the mechanism of their angina-like pain continues to be obscure.

Cardiomyopathy

Angina or angina-like pain is not uncommon in the primary heart muscle disorders (cardiomyopathies). In hypertrophic cardiomyopathy with or without obstruction (HOCM), angina is a major symptom in many patients and it is explicable by the overdraft created by a grossly increased muscle mass and increased internal cardiac work caused by the functional disorder in the face of normal (or even unusually large) coronary arteries. In dilated (congestive) cardiomyopathy angina occurs in about 10% of patients. These are usually patients with advanced disease in whom the association of cavity dilatation with consequent increased wall tension, the increased muscle mass and the tendency to tachycardia during exercise together account for the development of angina. Finally, in primary restrictive cardiomyopathy (usually or always due to endocardial fibrosis) cardiac pain is a common mode of presentation although its exact genesis is not well understood.

Recurrent pericardial pain

Pericarditis is apt to relapse and the pain to recur. Pericardial rubs and sizeable effusions may not be found and the patient's description of his pain may closely simulate the pain of angina. There may be no history of acute pericarditis and the syndrome may be far less flamboyant than the post-pericardiotomy syndrome or Dressler's post-myocardial infarction syndrome in which pain, fever and pericardial effusion follow cardiac surgery or myocardial infarction respectively. The pain of recurrent pericarditis tends to come in bouts separated by symptom-free intervals of days, weeks or months. During the recrudescence of symptoms the patient may either have persistent pain or pain which comes and goes over the period of a few days. It is not strictly effort related but has a pleuritic component which may make the pain seem to be worse on exercise and cause confusion if the respiratory augmentation is not determined. The ECG may show non-specific repolarization changes which, again, may be confused with those caused by ischaemia.

Aortic pain

Dissection of the aorta is frequently a cata-

strophic and rapidly fatal event. The pain is extremely severe and is in the distribution of cardiac pain but often is with radiation through to the back or down into the abdomen, these latter two components giving the clue to the source of pain. Rarely, aortic dissection may be subacute and subclinical and in these patients the pain may simulate angina. Again the pain will not be strictly effort-related.

Extra-cardiac sources of pain

Oesophageal pain caused by acid reflux ('heart-burn') is common, particularly in women, and can usually readily be differentiated from myocardial ischaemia by its burning quality and its relationship to posture occurring when the patient is lying or sitting or bending over.

The pain of achalasia can be very severe and exactly similar to that of myocardial ischaemia but again should be distinguished by its lack of relation to effort. Whereas oesophageal pain due to acid reflux can be prevented or relieved by demulcent antacids and avoidance of stooping, the pain of achalasia is not due to acid and is ill understood.

When the above conditions have been excluded there remains a considerable group of patients in whom chest pain simulating angina is the only complaint. Unlike the majority of patients with angina many of these patients are young, there is an excess of women over men, risk-related traits such as hyperlipidaemia and high blood pressure are rare but smoking is common. Sometimes the pain is atypical, lacking a strict relationship to effort, or fluctuating in severity from day to day. Physical examination, ECG and chest X-ray are all normal. Myocardial biopsy has been carried out in a group of these patients and the biopsies have been normal with no evidence of microvascular disease. Coronary sinus lactate estimation during pacing has usually not shown any evidence of lactate production nor has pain been provoked.

Therapeutic trial, antacids, glyceryl trinitrate and beta-blockers are cheaper and more relevant than wholesale prescription of barium meals and cholecystograms. After all, hiatus hernia and gall-stones are so common that finding them does not necessarily indicate that a diagnosis of the cause of pain has been achieved.

Coronary spasm

Although these patients are undoubtedly a heterogeneous group, coronary spasm now seems to be established as a real entity (Oliva, Potts and Pluss, 1973). Smoking may be an initiator of coronary spasm in a predisposed subject and may lead to coronary thrombosis through its effect also on platelet aggregation but smoking is probably not an atherogenic agent.

When Prinzmetal first described his 'inverted' angina he was referring to the paradoxical ST segment elevation which accompanied attacks of chest pain. Later he changed the name to variant angina (Prinzmetal *et al.*, 1959), which is the name still commonly used. Although Prinzmetal's original cases had atheromatous coronary artery obstruction, it has been found that the same clinical syndrome is more often associated with coronary arteries which on angiography are either normal or show only minor irregularities due to atheromatous plaquing, often without any significant narrowing of the vessels.

Variant angina differs from angina due to coronary artery obstruction in its lack of relationship to exercise (Macalpin, Kattus and Alvaro, 1973) and its failure to respond to beta-blockers. The pain associated with coronary artery obstruction is provoked by an increase in cardiac work and this is the key symptom which is far more reliable than the patient's description of how the pain feels. The clue is what brings on the pain. The pain associated with coronary spasm is virtually never exercise-provoked because exercise is a potent coronary vasodilator. The pain comes on at rest, often wakes the patient at night and may be longer lasting than the usual anginal pain. Although ST segment elevation on the ECG was first described this is probably a phenomenon which depends on the duration of the coronary spasm. Similar ST segment elevation is seen also in impending infarction before the development of the typical changes associated with myocardial necrosis. Coronary spasm of shorter duration probably produces ST segment depression but better known is the observation that variant angina may be associated with fatal ventricular arrhythmia. It is likely that prolonged coronary spasm from which the patient does not get a fatal dysrhythmia may lead to thrombosis and/or infarction. The manifestation of coronary spasm may therefore depend on its duration.

Does coronary spasm actually happen or is it a convenient fiction to explain a syndrome which we do not understand? The evidence, although largely circumstantial, is compelling. We have the better documented arterial spasm which is responsible for Raynaud's phenomenon and for migraine, and the observation that angina may frequently be provoked by cold, in individuals with obstructive coronary atheroma, or by smoking both in these people and in patients with anatomically normal coronary arteries. This angina is not provoked by effort, is well relieved by nitrates though not by beta-blockers; spontaneous coronary spasm may be seen during coronary angiography when it may be mistaken for organic coronary disease but it may be reversed by nitrates; nitrates are observed to induce dilatation even in normal 'non-spastic' coronary arteries and

workers in nitroglycerin factories may get nitrate 'withdrawal' at the week-end. There is the provocation of spasm by physical or pharmacological means such as intravenous ergonovine during coronary angiography.

The treatment of coronary spasm consists in avoiding the known provocateurs particularly smoking, the prescription of nitrates *ad libitum* and a regime of regular incremental physical exercise. Usually the clinical situation improves. Fatal ventricular fibrillation in patients with Prinzmetal's variant angina and anatomically normal coronary arteries is, however, well known so that the disorder is potentially a serious one. Beta adrenergic blocking drugs should be avoided.

Smoking

Although smoking is one of the three major risk-related traits in patients with coronary atheroma it seems that the habit engenders thrombosis rather than atherosclerosis. Smoking increases platelet stickiness, probably through stimulating fatty acid release, and nicotine may cause vascular spasm in the predisposed. The combination of spasm and increased platelet stickiness may lead to coronary thrombosis in the absence of atheroma. The enhanced risk to smokers is removed with cessation of smoking.

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