Investigation of Coronary Artery Disease

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The investigation of patients suspected of suffering from coronary artery disease (CAD) is a subject of interest because heart disease is common and potentially fatal. To some extent we can predict who is going to die. Those patients with severe CAD and badly scarred ventricles have a worse prognosis than those with mild disease and normal left ventricular function[1,2]. In anatomical terms severe CAD means atheromatous narrowing of the left main stem coronary artery or disease affecting all three major branches—the circumflex, anterior descending and right.

Coronary bypass surgery, a form of treatment designed and undertaken to relieve angina, can improve survival in patients with severe CAD[3,4]. Although the Coronary Artery Surgery Study[5] casts some doubt on this belief, there are good reasons for thinking that the results of this study do not apply to practice on this side of the Atlantic; for example, those patients with left main stem lesions were excluded and 22 per cent of those participating in the randomised portion of the study had no angina.

It is obviously important to detect those patients with severe CAD and scarred ventricles. This can be achieved by left ventricular angiography and coronary arteriography but since it is impractical to undertake this investigation on everyone, various screening tests have been devised. American physicians receive regular advice on 'investigative strategies'[6–8], and respond in a predictable fashion to a clinical problem such as chronic stable angina or uncomplicated myocardial infarction. In Britain our practice is more haphazard. Many physicians admit to being confused by the panoply of cardiac investigations now available and this confusion is compounded by the uneven distribution of cardiological skills, local enthusiasms and prejudices, and, always, restricted resources. When reading the American literature we may wonder whether our colleagues are influenced by their system of remuneration; for them each investigation attracts a fee; here, each investigation denies another patient the opportunity of being investigated.

We may learn from the American experience. Two general conclusions emerge from their reviews [6–8], which are based on a wealth of original observations. First, the sensitivity and specificity of any screening test depend not just upon the diagnostic accuracy of the investigation, but also on the population studied; even a highly specific investigation will yield a number of false positive results if it is applied to disease-free individuals. Second, the greater the variety and complexity of the investigations, the better is their predictive value, but at a price that includes discomfort and inconvenience to the patient and reduplication of information. Thus the investigation of asymptomatic patients is likely to be unrewarding. False positive results will create alarm and require further investigation in order to eliminate the suspicion of heart disease. We should confine our attention to symptomatic patients; this generally means those presenting with chest pain. Among them will be some with typical cardiac pain for whom a minimum of investigation is necessary to confirm the diagnosis and advise on management. There will be others with atypical pain for whom more extensive but selective investigation will be required.

The stimulus for this review came from the recent Consensus Conference on Coronary Artery Bypass Surgery[9]. Although the conference was primarily concerned with candidates for surgical treatment, it did provide an opportunity to assess our investigative practice. The investigations can be conveniently classified as: preliminary—those which may be undertaken in general practice; intermediate—usually available in a District General Hospital (DGH); specialist—usually confined to a regional centre or teaching hospital.

Preliminary Investigations

An electrocardiogram (ECG) is invariably the first investigation requested in patients suspected of suffering from CAD. However, the ECG is normal in uncomplicated angina pectoris; moreover, the initial ECG is normal in 11 per cent of patients subsequently shown to have definite myocardial infarction[10]. Nevertheless, the ECG is worthwhile because it can give a definite diagnosis and any subsequent change may establish the diagnosis with certainty.

Some routine haematology should be performed at this stage because cardiac pain may be a presenting symptom of other diseases, e.g. anaemia. Biochemical investigations may include estimates of 'cardiac' enzymes and serum lipids. However, a word of caution must be sounded over the interpretation of cardiac enzyme estimations. An erroneous diagnosis of cardiac disease is too often entertained because an elevated creatine kinase, aspartate transaminase, or lactate dehydrogenase level was discovered, the cause of which was, respectively, an intramuscular injection, liver damage or haemolysis. Conversely, cardiac infarction may be thought to have

been excluded by a normal result when in fact cardiac damage had occurred but the blood sample had been taken too early or too late to catch the abnormal rise in enzyme level. Serum lipid estimations also have to be interpreted with caution. There is no 'normal range', but higher values are associated with a greater risk of CAD. A knowledge of the lipid levels is also essential when giving dietary advice.

Intermediate Investigations

Exercise Testing with Electrocardiography

Graded exercise on a treadmill or bicycle imposes an increasing workload on the heart which, in patients with CAD, may uncover ischaemia. Such testing is of limited value in making the diagnosis of CAD. In asymptomatic patients the false positive rate may be as high as 64 per cent if the single electrocardiographic criterion of 1 mm ST segment depression is used[11]. In the Coronary Artery Surgery Study[12] 89.4 per cent of men with a history of definite angina had CAD; the probability of detecting CAD was not significantly increased by a positive exercise test. On the other hand, 39.6 per cent of women with atypical angina had CAD but the exercise test was misleading because 46 per cent of those subsequently shown to have normal coronary arteries had a positive test.

Exercise testing may be useful in management. Important prognostic information can be obtained in symptomatic patients if multiple clinical observations are made, viz. time to onset of symptoms or duration of exercise, heart rate, blood pressure, recovery time, and the timing and nature of any electrocardiographic change. In general, early onset of angina, marked and widespread ST segment depression, slow recovery, and poor rise in blood pressure collectively indicate more severe coronary disease[13–16] and a more limited prognosis[14,17–21]. For example, McNeer and his colleagues[14], in a study of 1,472 patients, found that those able to reach stage IV of the Bruce protocol, with no significant electrocardiographic change, had a less than 1 per cent (one patient in 280) chance of left main coronary stenosis and those who reached that level of exercise with a heart rate of 160/min or more had a 99 per cent chance of surviving one year. Theroux *et al.*[19] studied 210 patients following uncomplicated myocardial infarction and found one-year mortality rates of 27 per cent in those with exercise-induced electrocardiographic ST segment changes and 2.1 per cent in those without. Dagenais *et al.*[21] showed that patients only able to reach stage I of the Bruce protocol had a five-year survival rate of 52 per cent; the comparable figures for higher workloads were stage II—73 per cent, stage III—86 per cent. Of course these studies can be criticised. Exercise testing may be poorly reproducible[22]. Many patients with the worst prognosis cannot get as far as the treadmill, let alone embark on any exercise. If testing is undertaken too late after infarction some of the high-risk patients identified by Theroux *et al.* will already have died.

The exercise test is thus of doubtful value in diagnosis and superfluous in the management of the patient with typical limiting angina because such a patient should proceed directly to coronary arteriography. However, an exercise test is valuable in those patients with CAD and mild symptoms because limited exercise tolerance and marked ST segment change should prompt referral for coronary arteriography.

Nuclear Imaging

Most DGHs possess a gamma camera and thus have the capacity for cardiac imaging, given some additional expenditure on equipment for data collection and processing. ^{99}Technetium-labelled pyrophosphate is taken up by a recent myocardial infarct. This investigation has little advantage over the usual electrocardiographic and enzyme markers of infarction and so is little used.

^{201}Thallium outlines perfused myocardium and is thus useful in detecting infarcted areas at rest, and ischaemic areas which develop on exercise. This knowledge can enhance somewhat the sensitivity of diagnosis of CAD[23,24] but cannot pick out those with more advanced coronary disease much more reliably than straightforward stress testing[25–27]. The use of thallium imaging is perhaps best reserved for those patients with atypical chest pain and a low probability of CAD in whom a negative test would obviate the need for angiography[8].

Radionuclide left ventricular angiography using ^{99}technetium and either a first-pass or gated-equilibrium technique is an excellent screening test of ventricular function. Borer *et al.*[28] were the first to show that left ventricular function deteriorated during exercise in patients with CAD. But this response is non-specific and occurs in many cardiovascular disorders, including hypertension. Nevertheless, exercise-induced abnormalities of ventricular function provide objective confirmation of cardiovascular disability. For example, in the patient with established CAD whose symptoms remain difficult to interpret, an exercise-induced deterioration in left ventricular ejection fraction (LVEF) would imply that the symptoms had an organic basis and required further treatment.

Radionuclide angiography can also identify those patients with poor left ventricular function following myocardial infarction. These patients fare badly[29–33]. The first year mortality for those survivors with poor (LVEF less than 20 per cent), moderate (LVEF 20–39 per cent) and good (LVEF greater than 40 per cent) left ventricular function was respectively 33 per cent, 19 per cent and 3 per cent in one study[33]. This information enables the physician to give a more accurate prognosis and refine his selection of those for angiography. In the future it is possible that two-dimensional echocardiography will provide similar information[34], quite apart from the value of this investigation in other forms of heart disease.

Thallium imaging of the myocardium has not gained widespread acceptance in the UK. The isotope is expensive and the information gained is often of limited value. However, radionuclide ventriculography is helpful in

identifying patients with poor left ventricular function and should be more widely used.

Specialist Investigation

In practice this means left heart catheterisation, left ventricular angiography and coronary arteriography. The investigation demands expensive equipment, involves a minimum of five trained people (doctor, two nurses, radiographer, technician) and takes about 30 minutes. The procedure is mildly unpleasant since it is performed under local anaesthesia but the distressing hot flush associated with the injection of 30–50 ml of contrast medium can be avoided by using non-ionic media. There is a small morbidity (e.g. local arterial problems, myocardial infarction, arrhythmias), and mortality; there have been two deaths in the last 2,500 cases at Papworth Hospital. Most patients are admitted to hospital, although the number of day cases is increasing.

Coronary arteriography is the gold standard in making the diagnosis of CAD. In most British centres over 90 per cent of patients thought to have CAD on clinical grounds will turn out to have obstructive lesions of their main coronary arteries. For those patients with normal coronary arteries a diagnosis of coronary spasm may be considered, but most cardiologists will return to the bedside, take the history again, and conclude that the pain had some other cause.

The extent and severity of the coronary lesions, together with the amount of damage to the left ventricle, determine the prognosis[1,2]. The information gained by arteriography is thus invaluable in management but not essential. Most patients with limiting angina despite medical treatment should undergo arteriography in order to decide about the possibility of surgical treatment. The younger and more active the patient the more likely is he to need bypass surgery to maintain his life-style. Another common example is the asymptomatic patient who has had an uncomplicated myocardial infarct. One per cent of patients investigated following a myocardial infarction will have a left main stem stenosis and 26 per cent will have disease of all three coronary vessels[35]. The remainder, nearly three-quarters of such patients, will not have severe disease. They should receive careful medical management but will not require surgery either for symptoms or for survival. A knowledge of their coronary anatomy will contribute little to their management; clinical assessment coupled with exercise testing or radionuclide angiography will identify those at high risk.

The view that some patients with CAD might not require angiography is unfashionable at present. However, those cardiologists in active clinical and investigative practice often experience difficulty in deciding how to manage a man with angina and only moderate coronary disease. Time and again the decision is most easily made in out-patients when others (nurses, junior staff, etc.) are not present and both physician and patient can talk freely on equal terms—both being dressed and seated. Only when the details of a patient's life-style, hopes, fears and ambitions are understood can a sensible decision about management be made. Coronary arteriography is the most important investigation for patients suffering from CAD but it is always an adjunct to clinical judgement.

Other specialist investigations are available. The patient may be subjected to a variety of physical stresses (dynamic or isometric exercise, atrial pacing, cold pressor) in the cardiac laboratory and these may be coupled with studies of myocardial metabolism, e.g. lactate balance. However, these are mainly research procedures. Most cardiac laboratories are busily engaged in undertaking as many coronary arteriograms as possible.

How Many Investigations?

This question may be impossible to answer but it does merit thought. Cardiologists are overwhelmed by requests for the investigation of patients with CAD, whereas general practitioners only see a few such cases annually.

Angina pectoris is usually the first manifestation of CAD. Several estimates of its prevalence have been attempted. The Whitehall study, which is exemplary and representative of its kind, found that 4.8 per cent of men aged 40–64 years admitted to symptoms suggestive of angina[36]. But this may be an over-estimate of the need for investigation because these men were not seeking help but responding to a questionnaire. Moreover, angina remits. Men who have chest pain one year may not have it the following year; in the Framingham study remission occurred for at least two years in 32 per cent of men[37].

A truer estimate of the prevalence of angina might come from studies in general practice such as that instigated by Julian in the Northern region[38]. In a population of 125,000, 336 patients were identified from practice records, sick notes, etc. The recorded rate in men aged 30–59 from those practices with the highest reporting rate was 1.6 per cent—a figure not inconsistent with the Whitehall one of 4.8 per cent if the methodological and age differences are taken into account. However, the crude figures of 336 per 125,000 give a prevalence rate of only 0.27 per cent or 2.7 per 1,000 population. The second national study of morbidity in general practice[39] found that the prevalence of angina per 1,000 population was 3.4 for men and 3.0 for women. Thus there may be some 3,000 patients with unremitting angina per million population in the UK at present. Because they are elderly or infirm, many will not require further investigation. A minority, 22 per cent in the study quoted above[38], will have angina that is severe enough to merit further action. These crude calculations suggest that 600–700 patients per million might require investigation now.

The annual incidence of new cases of angina is also unknown. The same Northern study[38] found 14 new cases of severe angina in the year before the survey, giving an annual incidence of 112 per million population. These are severe cases and it may be assumed that most would require further investigation.

Myocardial infarction is the other common manifestation of CAD. In the second general practice study the figures per 1,000 were 4.1 for men and 3.0 for women[39]. Because patients with myocardial infarction are often easier to identify than those with angina pec-

toris, further estimates of the incidence are available: for example in Edinburgh in one year 1,367 episodes in which the victim was seen by a doctor occurred in a population of approximately 500,000 persons[40]; in Oxford there were 362 cases in 375,000 persons but 140 patients died before being seen by a doctor[41]. These estimates of 2.7 and 0.6 early survivors per 1,000 population, together with the Tower Hamlets study[42] which gave an intermediate figure, suggest that there might be an additional pool of some 1,600 patients per million population who might stand to gain from further investigation of their CAD.

These imprecise estimates were discussed at the Consensus Conference[9]. Only one firm conclusion could be drawn: a minority of patients suffering from CAD can be adequately investigated given our present resources. There is a pressing need for more accurate information, not so much about the present cardiological activities of DGHs and specialist centres, which is a relatively simple task, but rather about the potential pool of CAD victims who cannot be assessed because their general practitioners know that there is no point in referring them.

Conclusion

The patient who is limited by angina pectoris despite medical treatment requires a coronary arteriogram. Patients, especially younger ones, with less severe angina should be offered arteriography if they have a 'positive' exercise test. Patients with atypical pain which defies clinical diagnosis may be reassured by intermediate investigations but will often require arteriography, especially if their livelihood is at stake.

Following uncomplicated myocardial infarction those patients who have localised damage as judged by clinical, electrocardiographic and enzymatic criteria need no further investigation. Risk stratification may be accomplished by radionuclide angiography (for those with poor left ventricular function on clinical grounds) or exercise testing (for those with good left ventricular function). Patients with refractory angina or further episodes of cardiac pain should undergo arteriography, especially if they have good left ventricular function and a positive exercise test.

This review is necessary because we lack a reliable, simple, harmless, painless and cheap method of confirming the diagnosis of CAD. In the unlikely event of such a test becoming available every hospital would still need a physician/cardiologist blessed with that elusive quality—clinical judgement.

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