Editorials

Which test for detecting accelerated coronary artery disease in the heart transplant patient?

See page 692 for the article to which this Editorial refers

The paper by Barbir et al. in the present issue\(^1\) specifically deals with a very important but still unresolved issue: how to detect reliably accelerated coronary artery disease in the heart transplant patient? Ninety-one consecutive patients, while hospitalized for their annual systematic coronary arteriography, underwent several non-invasive tests: exercise electrocardiography, rest and exercise radionuclide ventriculography, and echocardiography. The assessment of coronary stenoses was done visually, and not quantitatively. Over a mean 21 years follow-up, 31 events occurred in 18 patients: five cardiac-related deaths, 17 myocardial infarctions and/or heart failures, eight percutaneous transluminal coronary angioplasties and one coronary artery bypass grafting. Only two variables were predictors of lower event-free survival: an echocardiographic left ventricular ejection fraction <60%, and the presence of at least one coronary stenosis (both >25% and >50%). These two tests provide different information, since they are both statistically significant predictors of cardiac events in the multivariate analysis: the odds ratio of cardiac events with luminal narrowing >25% (vs <25%) is 14 (\(P=0.01\)), the odds ratio of cardiac events with echocardiographic left ventricular ejection fraction >60% (vs <60%) is 0.2 (\(P=0.005\)). Barbir et al.\(^1\) rightly say that one limitation of their study is the small number of events, and that their findings must be validated in other settings.

Over time, heart transplantation has become a well-established treatment of terminal congestive heart failure. Better diagnosis and treatment of rejection have led to an improvement in survival rates. Since then, accelerated coronary artery disease has become the main complication and the first cause of morbidity and mortality after heart transplant. In spite of the introduction of cyclosporin, the incidence of accelerated coronary artery disease has not changed dramatically, and it remains high: 5–18% at 1 year, 25% at 2 years, and 36–50% of 5 years.

Accelerated coronary artery disease raises several issues. Its pathogenesis is still unknown. It is probably multifactorial, and includes immunological factors, infective factors (role of cytomegalovirus infection), and metabolic factors (increased platelet aggregation). Except for dyslipidaemias, classical risk factors for coronary artery disease do not seem to play a role. Its diagnosis is difficult at the early stage because of the denervation of the heart, and diagnosis is often carried out when complications have occurred — heart failure, arrhythmias, myocardial infarction, or sudden death.

All this has led to the study of the predictive value of several cardiac tests. The sensitivity of exercise testing is poor, because of frequent very submaximal exercise, basal ECG abnormalities, and difficult interpretation due to axis deviation — findings corroborated by the present study. Thallium scanning\(^2\) and ambulatory ECG monitoring\(^3\) also have poor sensitivity. At echocardiography, the only predictive factor is decreased left ventricular ejection fraction. But the progressive decrease of left ventricular ejection fraction over successive echocardiographies seems better than one simple cut-off value, as found in Barbir's study\(^1\). Caution is required in the interpretation and in the routine use of this result since the 60% cut-off has been determined by preliminary examination of the data, and not by theoretical clinical considerations. In a previous study, Barbir et al. found that coronary calcifications detected by ultra-fast CT scanning were a marker of accelerated coronary artery disease, but they did not include this test in the present study on cardiac events. Two tests seem to perform well: stress echocardiography\(^4\) and intracoronary ultrasound\(^5\). But there is no definite answer for non-invasive tests, and most heart transplant centres perform routine coronary arteriography since it is still the best test, although this 'gold standard' does not perform perfectly. In the study by Uretsky et al.\(^6\), 28% of the patients who had cardiac events had no angiographic evidence of coronary artery disease.

The importance of coronary stenoses is usually underestimated, compared with anatomical findings. This may be why a >25% narrowing is a better predictor of cardiac events than the >50% narrowing in Barbir's study. Although the influences of a 25% to
50% narrowing has not been tested in the present study, such a 'mild' degree of stenosis has probably an independent predictive value: the odds ratio of cardiac events with luminal narrowing >25% (vs <25%) is 20, whereas the odds ratio of cardiac events with luminal narrowing >50% (vs <50%) is 3-5.

Barbir et al. do not discuss their contradictory findings: why is a left ventricular ejection fraction less than 60% at echocardiography a strong predictor of cardiac events, whereas it is not so with the same cut-off at radionuclide angiography? The authors do not give the correlation between the two techniques in their institution. Radionuclide angiography usually gives lower values than echocardiography. The most probable explanation for this discrepancy is that radionuclide angiography is usually performed at 70° and 45° anterior oblique projections. These projections are unsuitable for heart transplant recipients as the new heart is in a different position to that of the non-transplanted patient (the apex is more posterior).

Finally, there is the therapeutic issue. Preliminary findings with diltiazem and pravastatin need to be confirmed. Because of their anatomical characteristics and diffuseness, coronary lesions in the heart transplant patient are often not amenable to revascularization (percutaneous transluminal coronary angioplasty, or coronary artery bypass grafting), and the only possibility is re-transplantation.

We have made progress in knowledge about accelerated coronary artery disease, but a lot remains unknown, and there is considerable work in front of us.

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References