Detection of acute rejection: validation of non-invasive diagnostic tests

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Detection of acute rejection is based on the identification of infiltration and cellular damage in myocardial biopsies sequentially performed after heart transplantation. Grading of rejection uses the criteria of the International Society of Heart and Lung Transplantation (ISHLT) classification. This provides a consensus framework for reporting results and for treatment of acute rejection based on histological findings. This type of widespread patient management is associated with good long-term results.

The invasive nature, discomfort to the patient, and cost of repeat biopsies have led to a search for new diagnostic tests, to provide alternative diagnostic methods for rejection. In the current issue, Abdallah et al. used both plasma tumour necrosis factor-alpha and interleukin-6. These two products of macrophage activation were used to evaluate the presence of rejection. They induced proliferation and activation of T- and B-lymphocytes and eventually exerted a deleterious effect on the graft. Endomyocardial biopsy was used as a reference method with which to compare cytokine levels. Results showed increased plasma cytokines during the first few weeks after heart transplantation and a slow reduction of serum levels thereafter. Several patients with moderate or severe rejection showed high levels of tumour necrosis factor-alpha and interleukin-6 up to one year from the operation. Higher plasma cytokine concentrations were found in patients showing cellular damage at biopsy compared with those in whom no such damage was detected. The authors rightly suggest that these products of macrophage activation could prove useful as markers for rejection.

This and other attempts to compare a new non-invasive method for the detection of rejection with endomyocardial biopsies face a crucial objection: the sensitivity of endomyocardial biopsy; in other words, how 'gold' is the standard used as a reference for acute rejection against which other methods are compared. The histological expression of allograft rejection is patchy, and in explants of patients who die as a result of refractory rejection, foci of rejection are often surrounded by large areas of apparently intact myocardial tissue. Therefore, endomyocardial biopsies of rejecting hearts may lead to sampling error. In acute myocarditis, where myocardial round-cell infiltration and damage are histologically indistinguishable from rejection, the estimated sensitivity of endomyocardial biopsy, as shown in in vivo and ex vivo studies, ranges from 0–25%. In cardiac rejection, no such studies have been performed, rendering the sensitivity of biopsy a speculative issue.

In previous studies, detection of myocardial damage through myocardial uptake of In 111-labelled monoclonal antimyosin antibodies was deemed to constitute a test of higher sensitivity than endomyocardial biopsy for the detection of rejection. Sequential use of these diagnostic antibodies after transplantation yields individual time-activity curves of rejection, information not available from any other form of human solid organ transplantation. Analysis of these curves shows the impressive variability of the phenomenon of rejection and gives some fascinating insights into this natural history in cyclosporine-treated patients. The main findings drawn from antimyosin studies are: (a) the consideration of rejection as a continuous rather than an erratic or episodic phenomenon; therefore, the term widely used of 'rejection episodes' probably does not reflect the true nature of rejection; (b) the possibility of persistence of low-grade rejection years after transplantation, in the absence of functional ventricular deterioration, and (c) the detection of a state of immunological tolerance to the graft in some patients and the great inter-individual variability of this phenomenon, both in terms of its occurrence and timing after transplantation.

The clinical implications are several. Firstly, a normal biopsy does not rule out rejection. On the other hand, after treatment of 'rejection episodes' a normal biopsy does not imply that rejection has disappeared. It might be that because rejection is less conspicuous, the sampling error is greater; this may be particularly important when assessing certain old and new anti-rejection drugs. Secondly, patients should probably be screened throughout life for
rejection; thirdly, treatment for rejection must be
tailed to each patient.

The above considerations emphasize the im-
portance of having a sensitive non-invasive diagnostic
test for rejection — both for risk stratification and
treatment — to provide a rationale for patient man-
gement. On the other hand, the precise clinical
significance of ‘false positive’ results in the new tests
for detecting rejection in relation to results of biopsies
should be ascertained before such tests are definitely
abandoned as 'non-specific'. In the paper by Abdallah
AN et al.[1] high serum tumour necrosis factor-alpha
and interleukin-6 levels detected long-term after
transplantation possibly indicate ongoing rejection.

New diagnostic developments for rejection
should focus on the significance of normal and
abnormal markers for rejection in relation to the
biopsies, but also on its evolving patterns after trans-
plantation. This could eventually lead to design algo-
rithms for elective non-invasive patient management.
However, the lack of specificity of many non-invasive
tests for detecting rejection, particularly in the early
months after transplantation (i.e. effects of myocar-
dial preservation, extracorporeal circulation or infec-
tion), provide a solid argument for not abandoning
biopsies during this period.

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Risk stratification after acute myocardial infarction in the
thrombolytic era

See page 925 for the article to which this Editorial
refers

The major determinants of prognosis after acute
myocardial infarction are the left ventricular ejection
fraction, the extent of anatomical coronary artery
disease, and the presence of spontaneous or inducible
myocardial ischaemia. High-risk exercise electrocar-
diographic stress test variables after acute myocardial
infarction include horizontal or downsloping ST-
segment depression >1.0 mm at a submaximal heart
rate or workload, failure to achieve >4 metabolic
equivalents, an exercise-induced fall in systolic blood
pressure, exercise-induced non-sustained ventricular
tachycardia and limiting angina. High-risk myo-
cardial perfusion scan variables include multiple
perfusion abnormalities in more than one coronary
vascular supply region (multivessel disease pattern),
reversible defects within the zone of infarction, abnor-
mal lung uptake of thallium-201 (201TI) and a large
defect size. The advantages of exercise or pharmaco-
logical stress perfusion imaging over exercise electro-
cardiographic testing alone for risk stratification after
acute myocardial infarction include: (1) greater sensi-
tivity for detecting residual ischaemia at submaximal
exercise heart rates, (2) better identification of multi-
vessel coronary artery disease and ischaemia remote
from a region of infarction, (3) better identification of
inducible ischaemia within the zone of infarction, and
(4) the ability to estimate infarct size.