Acutely, rejection (AR) following heart transplantation (HTX) is characterized histologically by patchy or diffuse cellular infiltrates, interstitial oedema, and, if AR is more severe, by myocyte necrosis and hemorrhage. Main criterion for the usefulness of any diagnostic tool is its capability to rapidly and reliably detect AR at the latest stage when intensified immunosuppression is required. For many years, histology from endomyocardial biopsies (EMB) has remained the gold standard; no other method has been shown to consistently fulfill this requirement. All attempts to diagnose AR noninvasively by ultrasound aim at identification of its morphologic and functional consequences. Several approaches have been employed: Conventional M-mode and two-dimensional echocardiography (2D-E), pulsed Doppler (D) E and E-based tissue analysis, using either videodensitometry or 2D integrated backscatter (IB) measurements based on unprocessed radiofrequency (RF) data. More recently, Doppler Tissue Imaging (DTI) has been proposed as a diagnostic tool. This article reviews the published literature on AR diagnosis based on cardiac ultrasound and discusses practical usefulness and limitations of the various techniques.

M-MODE AND 2D-ECHOCARDIOGRAPHY

An association with AR has been reported for the following M-mode and 2D-E findings: Increased ventricular wall thickness and mass, increased myocardial echo intensity, impairment of diastolic, and, to a lesser extent, systolic left ventricular function parameters, shortening of M-mode-derived isovolumic relaxation time (IVRT), new development of, or increase in, a pericardial effusion (overview in 1). Following introduction of cyclosporin, however, survival improved at the expense of loss of sensitivity of E signs of AR, as morphologic and functional changes became more subtle. [This is confirmed by 2 more recent studies,\(^2\), in which these criteria had a high level of specificity: (84% to 87% for all AR > IB in (2), 98–100% in (3)), but a low level of sensitivity (40% to 55% in (2), 28% to 44% in (3)). Sensitivity increased with higher AR-grades (>80% in (3)); in addition, the diagnostic yield improved, when a multiparametric approach was chosen (2).] During more severe AR, absolute values often were within the normal range; 95% confidence limits were calculated from 2 AR-free studies in order to account for technical and biological variability. Only intraindividual changes exceeding these thresholds were considered indicative of AR.\(^2\) When used in this way, conventional E facilitated reliable and easy-to-perform monitoring of allograft function. Despite relatively poor sensitivity in mild AR, excellent specificity and acceptable sensitivity for significant AR justified a reduction of EMB frequency in cyclosporin-treated subjects. Sensitivity and specificity in patients treated with new immunosuppressants, which are becoming available today, remain to be evaluated.

PULSED DOPPLER ECHOCARDIOGRAPHY

Although diastolic dysfunction is a characteristic feature of AR, reported sensitivities and specificities have varied greatly when conventional DE is employed for AR surveillance. With increasing AR severity, a progressive shortening of IVRT and pressure half time, and an increase in peak early mitral flow velocity, have been observed.\(^4\) However, in a more recent study that aimed specifically at evaluating the potential of DE for the diagnosis of mild AR, we found considerable variability between consecutive AR-free examinations.\(^5\) Changes during mild AR rarely exceeded 95% confidence limits. Other authors also have reported no significant changes in diastolic filling parameters during various AR grades.\(^6\) Several factors, including methodologic aspects and differing immunosuppressive strategies\(^5\) may account for these seeming discrepancies. In addition, D false-negatives have been shown to occur during AR therapy.\(^4\) Thus, although DE monitoring can fulfill some of the objectives of a noninvasive adjunct to EMB,\(^4\) it must be kept in mind that flow across the atrioventricular valves is the net result of complex and variable influences;\(^5\) changes in diastolic filling indices may not always represent specific markers of AR.

ECHOCARDIOGRAPHIC TISSUE ANALYSIS

E-based tissue analysis aims at identification of myocardial pathology from changes of the acoustic properties of the heart muscle.\(^2\) Data obtained from orthotopic HTX recipients indicate that moderate AR alters significantly the...
magnitude of the systolic-diastolic variation of myocardial IB.\textsuperscript{7} Several animal experiments involving heterotopic HTX models used videodensitometry to show increases in end-diastolic (ED) myocardial echo intensity during AR;\textsuperscript{2} in animals maintained on standard immunosuppression similar to that used in humans, we found that moderate and severe AR altered ED echo intensity significantly, whereas mild AR was not reliably identified.\textsuperscript{8} We therefore investigated whether serial measurements of ED 2D-IB from unprocessed myocardial RF data would enhance the potential of E-based tissue analysis for detection of AR. Whereas data compression is performed by logarithmic amplification in video images, unprocessed RF-signals undergo linear amplification only. It was thus hypothesized that subtle acoustic changes, such as those associated with early AR stages, might be more readily detectable from these data.\textsuperscript{2} Based on more than 240 EMB-controlled examinations in 52 patients, we confirmed that AR is associated with an alteration of myocardial acoustic properties in humans. Increases in ED 2D-IB in serial studies, in which each subject was used as their own control, permitted reliable identification not only of moderate and severe AR (sensitivity 92%, specificity 90%), but also of mild AR (sensitivity 89%, specificity 88%). Because the 2D-IB increases were significantly more pronounced in AR grades with myocyte damage than in those without myocyte damage, a rough, noninvasive estimate of AR severity also appeared feasible. Comparison with simultaneously obtained conventional E parameters demonstrated superior sensitivity and specificity of the 2D-IB measurements and, that acoustic changes may occur independently of changes in myocardial function. The main limitation of this promising approach to AR diagnosis is its present lack of commercial availability. With development of appropriate commercial equipment, ED 2D-IB measurements may become a reliable and clinically useful tool for noninvasive serial AR surveillance.

**DOPPLER TISSUE IMAGING**

DTI is a new method for quantitative assessment of regional myocardial function that also has been tested recently for AR diagnosis. In M-mode representations of the left ventricle obtained with DTI, colors represent instantaneous myocardial velocities that may be analyzed with high temporal and spatial resolution. Using EMB as the gold standard, a recent study investigated to what extent myocardial wall velocities are affected by AR, and how such changes compare with changes in conventional E parameters.\textsuperscript{9} This preliminary report indicated that subendo- and midmyocardial velocities decrease during AR. Although the decrease was more pronounced during moderate and severe AR, wall velocities also declined significantly during mild AR. In contrast, conventional E parameters did not change significantly during mild AR. The best marker of AR was early diastolic subendocardial posterior wall velocity. When a 10% change was used as a threshold, sensitivity and specificity for the detection of mild AR were 87%, respectively.\textsuperscript{9} From these results, DTI appears to be a promising tool for AR diagnosis; it is commercially available and relatively easy to perform. However, limitations of this new technique need to be evaluated further, particularly with respect to other factors that might significantly influence DTI-derived wall velocities, such as heart rate, contractile state, and intrathoracic motion of the heart.

**LIMITATIONS**

Although numerous studies, which could be reported only in part in this brief review, provide ample evidence of the considerable diagnostic potential of ultrasound in AR diagnosis, patient echogenicity must be mentioned as the main limiting factor. Thus, for each individual, a decision must be made as to whether reliable ultrasonic monitoring is feasible. In about 5% to 10% of HTX recipients, invasive follow-up significant reduction in EMB frequency may be required due to poor image quality, if not other noninvasive tools, eg, cytoimmunological monitoring or spectral analysis of the ECG (both of limited value in the later postoperative phase) are available as a substitute.

**REFERENCES**

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