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Measuring left ventricular function after heart transplantation via digitization of M-mode echocardiograms

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Abstract The aim of the study was to assess the usefulness of M-mode echocardiography for noninvasive diagnosis of cardiac rejection. For this purpose, 292 M-mode images of 26 heart transplant recipients were analyzed. The echocardiographic images were digitized into an image analysis system. The curves of left ventricular diameter changes were obtained and its first differential calculated. A total of 23 parameters were measured. The most important parameters were: peak velocity of systolic diameter change, peak velocity of diastolic diameter change, time to peak velocity of systolic diameter change, time to peak velocity of diastolic diameter change (TPEAK-D), isovolumetric relaxation time (IVRT), rapid filling time (RFT), shortening fraction (SF), and mean velocity of circumferential fiber shortening (MVCF). The echocardiographic parameters were compared to biopsy results. In 18 patients, 23 biopsy-proven moderate rejections occurred. When rejection occurred, IVRT decreased 23% ± 6% ($P<0.05$), SF decreased 13% ± 14% ($P<0.05$), MVCF decreased 18% ± 18% ($P<0.05$), and TPEAK-D increased 27% ± 27% ($P<0.05$). We concluded that the analysis of digitized M-mode images can identify heart transplant rejection.

Key words Heart transplantation Echocardiography · Rejection

Introduction

Cardiac transplantation has become an accepted procedure for treating patients with end-stage heart disease. Endomyocardial biopsy was the only reliable method for detecting cardiac rejection and assessing its treatment. The aim of this study was to assess the viability of M-mode echocardiography for noninvasive diagnosis of cardiac rejection.

Methods

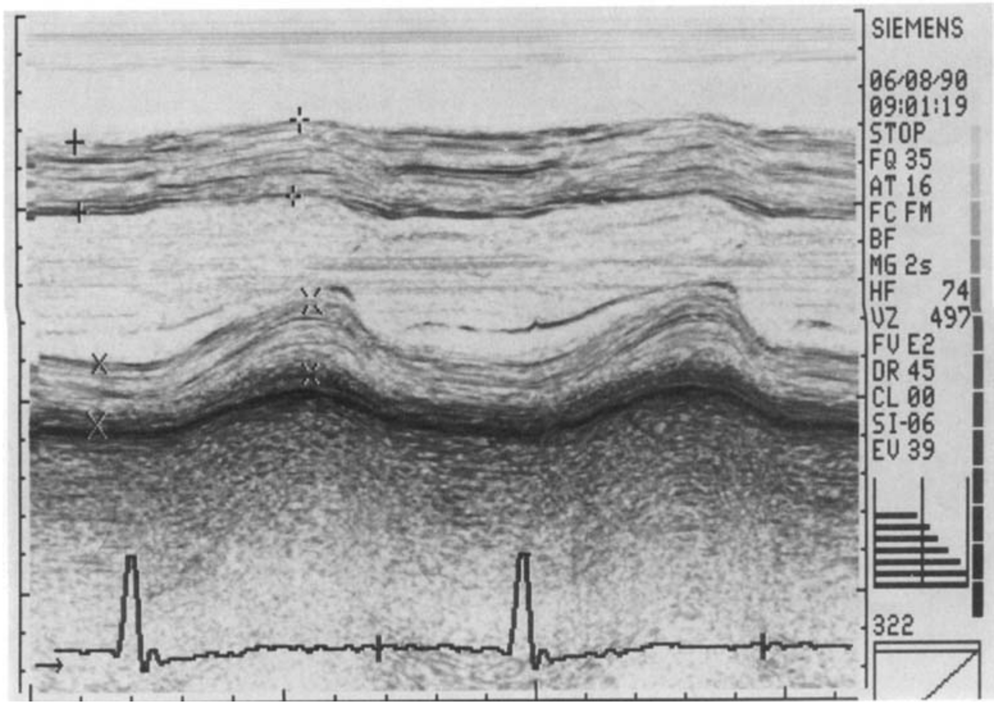
Patients

The study group consisted of 26 heart transplant recipients. Mean patient age was 45±15 years. The follow-up period was 6±3 months. The first 2 weeks postoperatively were excluded because myocardial dysfunction has been reported early after heart transplantation.

Endomyocardial biopsy

At least five specimens of right ventricular endomyocardial tissue were obtained in each biopsy and graded according to the Hanover

Fig. 1 M-mode echocardiogram



classification [1] as positive if moderate rejection (A 3a or A 3b) was observed and as negative if no (A 0) or mild (A 1 or A 2) rejection was present. Eight patients had no rejection episodes during the study. A total of 179 biopsy results from 18 patients were available for comparison of the groups, including 84 indicating no (39) or mild (45) rejection, and 87, moderate rejection.

Standardized echocardiographic examination

A total of 292 M-mode echocardiograms were obtained within 24 h of endomyocardial biopsy. M-mode tracings (Fig. 1) of three cardiac cycles were printed on paper at a recording rate of 100 mm/s peper speed.

Date acquisition

The M-mode echocardiograms were digitized by using a digitizing table of the "Kontron Cardio-80" image analysis system. The curves of left ventricular diameter change (Fig. 2, upper curve), its first differential (Fig. 2; lower curve), and the parameters of diastolic and systolic function were calculated using the computer analysis system.

A total of 23 parameters were evaluated. To reduce the amount of parameters, we excluded all parameters with a P value of greater than 10%. Thus, we included the most important parameters, listed below:

1. Peak velocity of systolic diameter change
2. Peak velocity of diastolic diameter change
3. Time to peak velocity of systolic diameter change
4. Time to peak velocity of diastolic diameter change (TPEAK-D)
5. Isovolumetric relaxation time (IVRT)

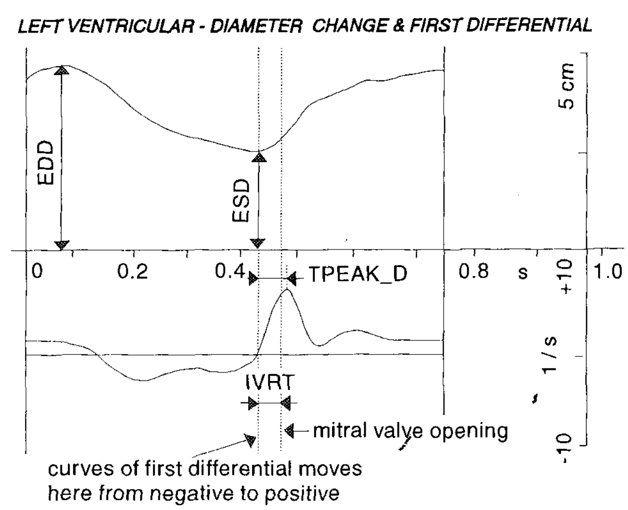


Fig. 2 Immediate change in diameter and its first differential

6. Rapid filling time (RFT)
7. Left ventricular ejection time
8. Shortening fraction (SF)
9. Mean velocity of circumferential fiber shortening (MVCF)
10. Thickness of septum and posterior wall
11. Enddiastolic and endsystolic diameter

Table 1 shows the four parameters that were found to be of greatest significance.

Table 1 Method of determining significant parameters (*EDD* end-diastolic diameter, see Fig. 2, *ESD* endsystolic diameter, see Fig. 2, *LVET* mean of three aortic valve M-Mode tracings)

Parameter	Method of determination
Isovolumetric relaxation time (IVRT)	See Fig. 2
Shortening fraction (SF)	(EDD-ESD)/EDD
Mean velocity of circumferential fiber shortening (MVCF)	SF/LVET
Time to peak velocity of diastolic diameter change (TPEAK-D)	See Fig. 2

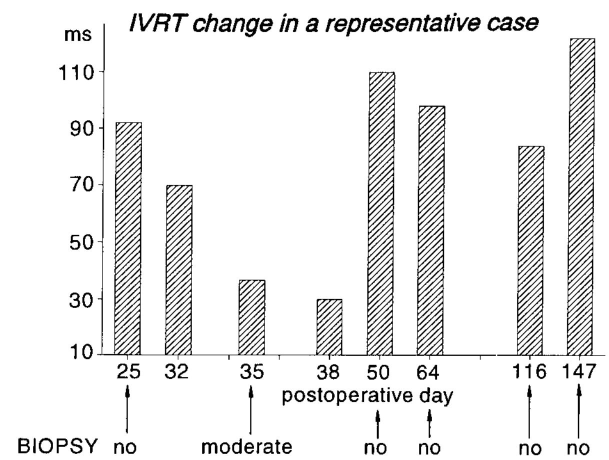


Fig. 3 Change (in %) between biopsy-proven IVRT of each patient during nonrejection and during episodes of rejection

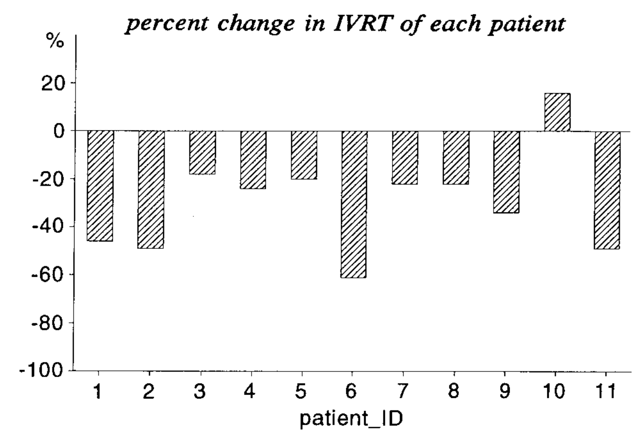


Fig. 4 Change in IVRT parameter during rejection in a representative case. The *arrows* represent the respective biopsy results

Statistics

The results are presented as averages of the intra-individual percentage change (and its standard deviation) between episodes with and without rejection. Group comparison was made using the Wilcoxon test for matched pairs. Differences were considered significant if P was less than 0.05.

Results

Table 2 shows the results of those parameters that were found to be of greatest significance. IVRT and TPEAK-D decreased in biopsy result A3a (therapy not required) as well as in biopsy result A3b (therapy required). The systolic parameters (SF and MVCF) first began to change

Table 2 Significant results

Parameter	Biopsy classification		
	A3a and A3b together	A3a	A3b
IVRT	Decreased ($n=11$) 30% ± 21% ($P < 0.006$)	Decreased ($n=6$) 23% ± 6% ($P < 0.05$)	Decreased ($n=5$) 38% ± 30% ($P < 0,05$)
SF	Insignificant ($n=13$)	Insignificant ($n=7$)	Decreased ($n=6$) 13% ± 14% ($P < 0.05$)
MVCF	Insignificant ($n=10$)	Insignificant ($n=6$)	Decreased ($n=4$) 18% ± 18% ($P < 0.05$)
TPEAK-D	Increased ($n=13$) 27% ± 26% ($P < 0.05$)	Increased ($n=7$) 27% ± 27% ($P < 0.05$)	Increased ($n=6$) 28% ± 24% ($P < 0,05$)
Other parameters	Statistically insignificant		

as rejection became more advanced (A3b). All other parameters exhibited no significant changes.

Figure 3 illustrates the parameter IVRT in an intraindividual comparison between episodes with and without rejection. In one patient, the IVRT increased during an episode of rejection while biopsy indicated rejection. This episode was clinically inconspicuous and did not indicate the need for rejection treatment.

Figure 4 shows an individual example of how the parameter IVRT decreased with the onset of rejection and subsequently increased. The arrows indicate the respective biopsy results. As a point of reference, Fig. 4 includes the IVRT values 3 days before and 3 days after an episode of rejection.

Discussion

The early detection of rejection is of vital importance for human cardiac allograft recipients. In the last 10 years many attempts have been made to find a sensitive, noninvasive method to serve as a useful adjunct to endomyocardial biopsy, and further, to decrease the frequency of biopsy. Echocardiography is an ideal method for monitoring patients after cardiac transplantation. It can be performed quickly both as a bedside method during the isolation phase and just as effectively in an outpatient unit during follow-up. Since cyclosporin A was introduced into immunosuppressive therapy for heart transplant recipients, echocardiographically measured increases in wall thickness that are associated with rejection have decreased. Paulsen et al. [6] first demonstrated that echocardiographie-derived indexes of diastolic function are abnormal in patients with acute allograft cardiac rejection. Subsequently, Valentine et al. [7] and Desruennes et al. [3] have demonstrated that Doppler indexes of diastolic function are prolonged in rejecting patients.

This study showed that moderate rejection was associated with a significant change in early diastolic parameters. The shortening IVRT associated with the rejection episode confirms previous reports [2–4, 7]. The TPEAK-D was increased during rejection. This result is comparable with the findings of Angermann et al. They have reported that maximum systolic and immediate diastolic area changes are achieved later during rejection. Park et al. [5] have described a rejection-related prolongation of the parameter time-constant Te, a parameter of maximal velocity of posterior wall endocardium backward-motion that is comparable to TPEAK-D. The shortening of IVRT was consistent with premature mitral valve opening due to increased pulmonary artery wedge pressure as has been postulated by Valantine et al. [8]. The significant decrease in TPEAK-D during rejection undoubtedly reflected a decreased compliance because of impairment in passive properties of destensibility secondary to diffuse interstitial edema and cellular infiltrate. These alterations may prolong the early diastolic relaxation secondary to an increased stiffness of the elastic elements.

MVCF and SF were also decreased during rejection but these alterations occurred later then our two parameters of the early diastolic function. The mechanism of impaired systolic function may be similar to those of the diastolic impact; however, the contractile elements were affected later than the elastic components. The majority of investigators have not found significant rejection-related changes in systolic function. Valantine et al. [8] have suggested a cumulative immune-mediated ventricular dysfunction as a restrictive pattern. However, a decline in systolic function, even in the absence of change in diastolic function, is considered an indication for close surveillance and earlier endomyocardial biopsy [4].

Conclusions

1. Heart rejection correlated with changes in early diastolic function. Systolic function may also be useful in augmenting the identification of rejection
2. Analysis of digitized M-mode images is a useful tool for detecting heart transplant rejection.
3. Reliable diagnosis of rejection via digitized M-mode images requires intraindividual observation.

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