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Value of Doppler echocardiography in the detection of low-grade rejections after cardiac transplantation

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Abstract Modifications of the diastolic parameters pressure half-time (PHT) and isovolumic relaxation time (IVRT), recorded using cardiac Doppler echocardiography (CDE), were studied in 23 heart transplant recipients and compared to the results of 345 endomyocardial biopsies (EMB) performed on the same day. Two different protocols, analyzing respectively (1) a decrease of 20 % or more in IVRT and/or PHT with respect to the mean and (2) a decrease of 20 % or more in IVRT and/or PHT with respect to its preceding value, were used to evaluate the efficiency of CDE in diagnosing mild and moderate rejections. When a mild rejection was detected by EMB, a statistically significant decrease was found in the average CDE parameter values of the patient population. However, these variations were weak and did not differ from the spontaneous variations observed in each patient in the absence of rejection. Thus, it is not surprising that the sensitivity of CDE in the detection of mild rejections was very low (45 %) using the most sensitive protocol (variations of the parameters from their preceding value). We conclude that CDE alone does not seem to be sufficient to perform the noninvasive diagnosis of low-grade rejections and must be complemented by other noninvasive methods.

Key words Heart transplantation, rejection, echocardiography · Rejection, heart transplantation, echocardiography · Echocardiography, heart transplantation, rejection

Introduction

Cardiac Doppler-echocardiography (CDE) has proved to be an efficient and sensitive tool in the assessment of acute cardiac rejection of moderate severity in cyclosporin-treated patients [2, 7, 17]. Today, it is well accepted that significant reductions in pressure half-time (PHT) and isovolumic relaxation time (IVRT) are correlated with moderate transplant rejections and that constitute high sensitivity diagnostic indices [4]. However, few studies [12] have been performed so far to evaluate the sensitivity of these CDE indices in the detection of low-grade cardiac rejections [1, 13]. While most studies agree that patients who experience a moderate rejection should be treated immediately, the early treatment of mild rejection still remains controversial [3, 8, 11], although some authors [10, 11] have seen a spontaneous progression to the moderate grade of rejection in 30 % of untreated patients with mild rejection.

In this study, we have evaluated the value of CDE in the detection of mild and moderate rejections occurring in heart transplant recipients.

Patients and methods

Patients and treatments

We examined 23 heart transplant recipients (22 men and 1 woman, ranging in age from 20 to 68 years, mean 49 years) over a period of 2.5 years. Seventeen of them were treated with cyclosporine (4–10 mg/kg per day), together with prednisolone (0.5–1 mg/kg per day) and azathioprine (0.1–0.2 mg/kg per day). Six patients received double therapy, consisting of cyclosporine (4–10 mg/kg per day) plus prednisolone (0.5–1 mg/kg per day) or azathioprine (0.1–0.2 mg/kg per day).

When mild acute cardiac rejection occurred in the 1st year after transplantation, cyclosporine doses were adapted in order to increase the plasma level of the drug by 30% over a period of 7 days. All patients exhibiting moderate rejections were given an additional 100 mg/day of oral prednisolone for 5 days. In order to monitor the effects of the immunosuppressive treatment, CDE and biopsy examinations were carried out again 7–10 days after the beginning of the adapted immunosuppressive therapy.

Endomyocardial biopsy (EMB)

All patients were simultaneously monitored by EMB and CDE (performed on the same day) weekly during the 1st month, every 15 days during the next 3 months, and then every month for the following 9 months. After the 1st year, CDE was performed every month while an EMB was performed every 3 months. In addition, an EMB was taken when the CDE parameter or clinical state suggested a possible rejection. All EMB were analyzed by the same pathologist without knowledge of the CDE or clinical results. Rejections were graded according to the criteria of the International Society for Heart and Lung Transplantation (ISHLT) [1]. "Mild" rejections corresponded to grades 1 A and 1 B of the ISLHT classification. "Moderate" rejections corresponded to grades 2 and 3 A of this classification [13].

Echocardiogram and Doppler echocardiography

M-mode, two-dimensional, echocardiographic studies were conducted on a Hewlett-Packard SONOS 1000 system equipped with a 2.5 MHz tranducer. Initially, left ventricle chamber size, wall thickness, and systolic function were measured. Pressure half-time (PHT), isovolumic relaxation time (IVRT), and early peak mitral flow velocity (M1) were calculated when recipient atrial contraction occurred in diastole or in early systole [2, 4] (Fig. 1). Each index was obtained by averaging ten consecutive measurements. CDE was performed without knowledge of the biopsy results.

Data analysis and statistics

Each CDE value was compared to the EMB result. The mean and standard deviation of each CDE variable were calculated for each histological grade of rejection. Comparison of means was performed using an unpaired Student's t-test since each measurement was considered to be independent, as previously described in similar statistical treatments [16, 17]. Statistical analysis was performed on means calculated from pooled values (all examinations done in all patients) or on means calculated from individual values (all examinations done in each patient).

In order to assess the value of CDE in the detection of low-grade (mild and moderate) cardiac transplant rejection, we performed a retrospective study beginning on the 60th day after transplantation in order to eliminate any interference with hemodynamic changes (remodeled pulmonary vasculature) and inflammatory processes (pericardial effusion).

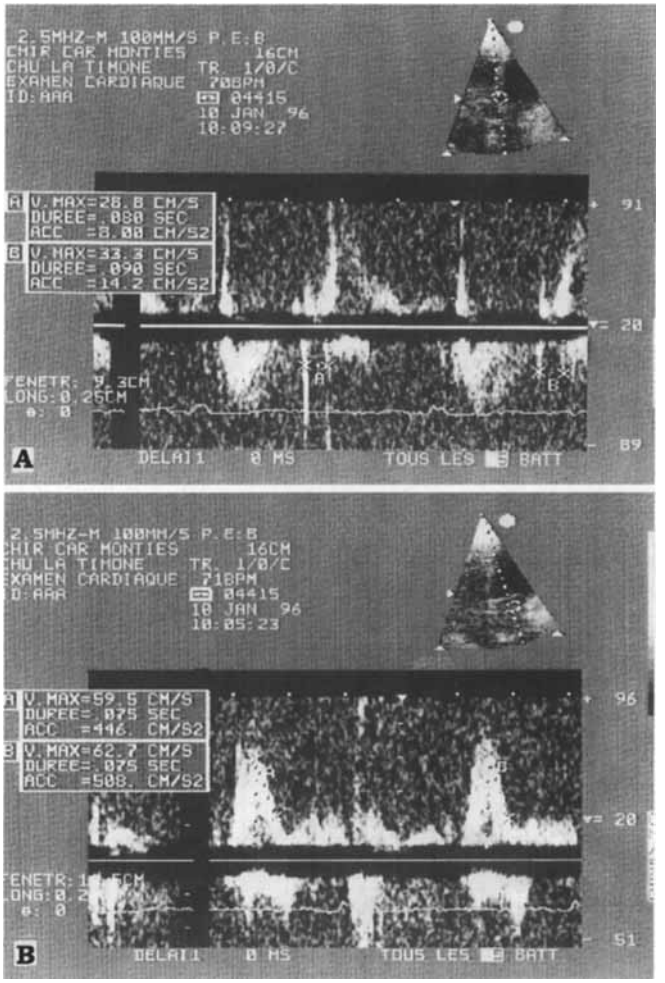


Fig. 1 A, B Two-dimensional echocardiogram showing the determination of **A** isovolumic relaxation time (IVRT): interval between aortic valve closure and mitral valve opening and **B** pressure half-time (PHT): time of half decay of the transmitral pressure gradient. Results are given in ms

In a first protocol (A), the individual physiological variations were calculated with respect to CDE values obtained when EMB displayed no signs of rejection. Each patient was characterized by his/her own reference values and individual variations were expressed as mean ± standard deviation for each parameter. A decrease of 20% or more in IVRT and/or PHT from the individual mean was considered as an echographic sign of rejection and was compared to the contemporaneous biopsy result. In a second protocol (B), a decrease of 20% or more in IVRT and/or PHT from its preceding value was considered as an echographic sign of rejection and, as for protocol A, was compared to the contemporaneous biopsy. The two protocols are summarized in Figs. 4 A and 5 A.

At the end of each protocol, the sensitivity and specificity of CDE were calculated by comparison to the EMB, which is considered the gold standard.

Results

In this study, 345 EMB and CDE examinations were analyzed in 23 heart transplant recipients over a period of 8–48 months, depending on the patient. Normal myocardial tissue (without rejection) was found in 261 EMB. Mild rejections were detected in 73 EMB and moderate rejections in 11 EMB (occurring only in nine patients). No severe rejection was observed. Three patients did not present any signs of rejection after the 60th day following transplantation.

Table 1 displays the mean IVRT and PHT pooled values recorded at the time of all the 345 biopsies performed in the absence or presence of transplant rejection (whatever the histological grade). Table 2 shows that both mild and moderate rejections induced a statistically significant decrease in the CDE parameter pooled values, respectively –6 % and –16 % for the IVRT and –6 % and –15 % for the PHT. In Table 2, the average pooled values are compared only to the values recorded during the CDE examination preceding the rejection episode (normal EMB). We found no significant difference in the fractional shortening pooled values when mild or moderate rejections were detected.

Figures 2 and 3 display the evolution of average IVRT and PHT values calculated for each patient presenting episodes of rejection. When a moderate rejection was detected by EMB, the individual variations were about 15 %–20 % of the last value of the CDE diastolic parameters recorded in the absence of rejection.

Table 1 Average pooled values of parameters describing the diastolic function (IVRT and PHT) calculated for all heart transplant recipients in the absence or presence of rejection

	No rejection ($n = 261$)		Occurrence of a rejection ($n = 84$)
IVRT (ms)	102 (± 10)	$P < 0.05$	94 (± 13)
PHT (ms)	53 (± 3)	$P < 0.05$	49 (± 7)

When a mild rejection was detected by EMB, the individual variations were only about 6 % of the previous value of the CDE diastolic parameters obtained in the absence of rejection. In 12 % (for PHT) to 18 % (for IVRT) of the rejection cases, we detected a paradoxical increase in PHT or IVRT values (as described previously in [6]).

Figures 4 and 5 illustrate how the two protocols modulate the efficiency of CDE in the detection of the low histological grade rejection. Protocol B increases the sensitivity of the diastolic CDE parameters to rejection by about 20 % with respect to protocol A. The specificity of echocardiography is not significantly affected by protocol B (89 % vs 93 %). However, the specificity of CDE in detecting mild or moderate rejections has no clear meaning because CDE has only to alert the clinician about the likelihood of the occurrence of a rejection, which has to be confirmed later on using EMB.

Discussion

Some authors [4, 6, 17] have reported a decrease of 20 % in IVRT and PHT values during acute rejection. These indices constitute signs of a restrictive syndrome during rejection, whereas parameters describing the ventricular contractility remain unaffected. The diastolic indices are considered to have a good sensitivity with regard to the diagnosis of rejections with a low histological grade when conditions that influence the left ventricular compliance are similar. The results of our study are in partial agreement with these observations since we detected a significant reduction in the IVRT and PHT values in moderate rejections (ISHLT grades 2 and 3A; Figs. 2, 3; Table 2) and since the sensitivity is similar to that obtained by both Valantine et al. [16, 17] and Desruennes et al. [4]. However, in our study, we detected only a few moderate rejections, and so we cannot estimate changes in PHT and IVRT that would occur in a sufficiently large statistical population.

The use of CDE in the detection of the lower grade mild (ISHLT grades 1 A and 1 B) rejections is not as satisfactory as in moderate rejections. We were able to detect slight global changes in the average pooled values

Table 2 Average pooled values of parameters describing the diastolic function (IVRT and PHT) calculated when a "mild" or "moderate" rejection occurs. These average pooled values are compared to the values recorded during the CDE examination preceding the rejection episode (normal EMB)

	Before mild rejection ($n = 73$)		Mild rejection ($n = 73$)	Before moderate rejection ($n = 11$)		Moderate rejection ($n = 11$)
IVRT (ms)	102 (± 10)	$P < 0.05$	96 (± 11)	101 (± 7)	$P < 0.005$	85 (± 13)
PHT (ms)	52 (± 4)	$P < 0.05$	49 (± 5)	53 (± 2)	$P < 0.005$	45 (± 6)

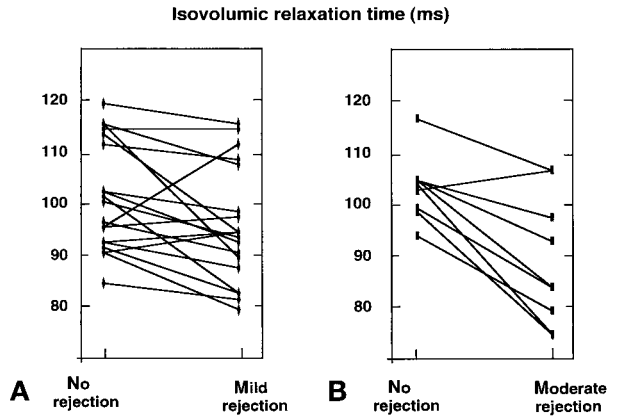


Fig. 2 A, B Evolution of isovolumic relaxation time (IVRT) values recorded in each patient during the examinations performed just before and during a **A** mild and **B** moderate rejection episode. Each point represents the mean of all IVRT values recorded in one patient before and during all rejection episodes that occurred during the study

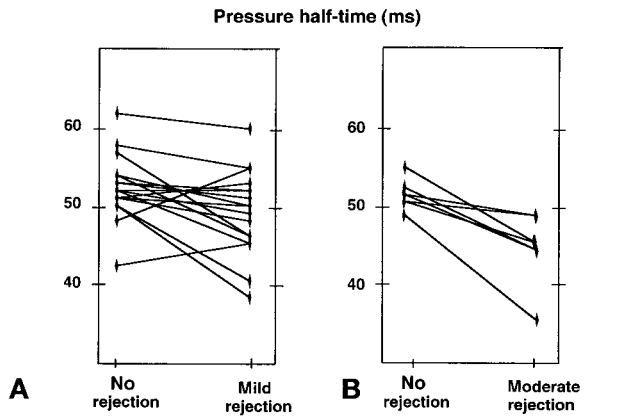
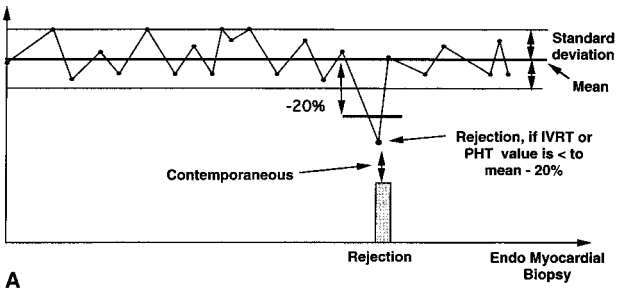


Fig. 3 A, B Evolution of the mean pressure half-time (PHT) recorded in each patient during the examinations performed just before and during a **A** mild and **B** moderate rejection episode. As in Fig. 2, each point represents the mean of all PHT values recorded in one patient before and during all rejection episodes that occurred during the study. In this figure, one patient presenting a moderate rejection was eliminated as an outlier in relation to an aberrant value of the PHT



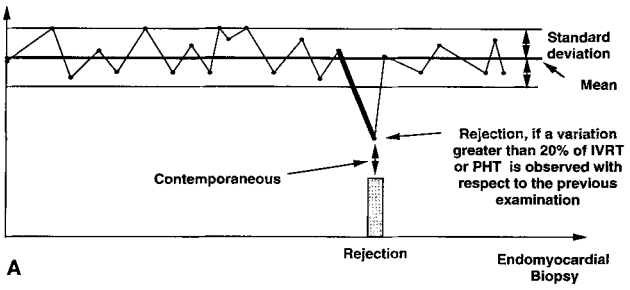
	TP	FN	SE %	SP%
Mild + Moderate n=(84)	26	58	31	93
Mild (n=73)	20	53	26	-
Moderate (n= 11)	6	5	64	-

B

Fig. 4 A, B Evaluation of sensitivity and specificity of cardiac Doppler echocardiography (CDE) in the detection of low-grade rejections using protocol A: **A** scheme summarizing the protocol; **B** table of sensitivities and specificities (*TP* true positive, *FN* false-negative, *SE* sensitivity, *SP* specificity)

of the two indices (–6 %), but these changes are not sufficient to diagnose a mild rejection in each patient because they correspond to the amplitude of the experimental error. In addition, the analysis of "CDE response" for each patient during a mild rejection episode (Fig. 2, 3) confirms that the mean of pooled values calculated in a population of graft recipients is not adequate to evaluate the efficiency of CDE in the diagnosis of mild rejection. In most patients with mild rejection, a slight decrease in the diastolic indices can be detected. In some patients, we found a paradoxical increase in the CDE diastolic indices. In other patients no variation was detected. These results emphasize the strong inter-individual differences in the variations of the diastolic cardiac behavior that explain the small modifications in the mean CDE parameter values when all results from all patients are analyzed together. The observed changes in CDE parameters are statistically significant only because a comparison between groups is made. These comparisons do not represent the effective clinical situation, in which the heterogeneity of the responses presented by each patient is the rule.

Protocols A and B are supposed to represent a clinical situation. The questions that arise are: first, how many rejections can be diagnosed by CDE and, second, what is the best strategy to increase the sensitivity of CDE? A comparison of Figs. 4 and 5 would clearly favor protocol B, which takes into account not only interindividual variations but also the intraindividual longitudinal variations that occur in each patient and depend on multiple factors, such as treatment observance, diet, administration of other drugs, intercurrent pathologies, psychism, spontaneous evolution of transplant physiology, etc. When the average value of CDE parameters calculated in the absence of rejection serves as the reference value, the sensitivity of CDE is low: only 26 % of mild rejections are detected (Fig. 4). When CDE parameters are longitudinally compared to those obtained during the preceding examination, the sensitivity of the CDE to detect a mild rejection is increased to 45 % (Fig. 5). Although Dawkins et al. [2] suggested that a de-



A

	TP	FN	SE %	SP%
Mild + moderate (n=84)	41	43	49	89
Mild (n=73)	32	41	45	-
Moderate (n= 11)	9	2	82	-

B

Fig. 5 A, B Evaluation of sensitivity and specificity of cardiac Doppler echocardiography (CDE) in the detection of low-grade rejections using protocol B: **A** scheme summarizing the protocol; **B** table of sensitivities and specificities (*TP* true-positive, *FN* false-negative, *SE* sensitivity, *SP* specificity)

crease of 10 % in IVRT was a good criterion of rejection, other studies have emphasized the importance of the spontaneous intraindividual variability of all indices [5, 17, 19] in the absence of any rejection. Our study demonstrates the effective impact of this variability in limiting the efficiency and reliability of CDE in the detection of the weakest rejections and confirms the results of Mannaerts et al. [12].

The detection of low-grade rejection may appear useless when one considers that most authors [1, 5, 8, 11, 19] advocate any modifications of the treatment in the presence of mild rejections. Lloveras et al. [1] demonstrated that mild rejection persists 10 days after its initial discovery in 51 % of patients when no specific treatment is initiated. Imakita et al. [9] and Kobashigawa et al. [10] demonstrated a spontaneous transformation of mild rejection into moderate rejection in about 30 % of patients in the absence of specific treatment. However, the main argument for an early diagnosis of the lowest grade rejections is that treatment of these rejections leads to a transient and moderate increase in blood cyclosporin levels, blocking the evolution of mild rejection to more severe grades without increasing the occurrence of infectious and renal complications [3]. Consequently, the use of methylprednilosone antilymphocyte sera and their related consequences can be reduced together. The particular attention paid to the resolution of low-grade rejection in our patients seems to have had positive consequences since no high-grade rejections have been diagnosed in our cohort. Long-term benefits (survival rates, quality of life, etc.) of this strategy are currently under evaluation. Finally, the formation of transplant atheroma is probably the most prevailing concern for clinicians in heart transplantation. As yet, its pathophysiology has not been completely elucidated, and conflicting data exist on the role of acute rejections in the establishment of cardiac allograft vasculopathy [14].

Consequently, in agreement with Yeoh et al. [20], we think that, when possible, low-grade rejections must be diagnosed and treated. As demonstrated in this study, CDE alone is not sufficient to detect or to rule out the diagnosis of rejection, but it does have a role to play among other noninvasive procedures for diagnosing early cardiac rejections. We have therefore developed a combined protocol using CDE and high-resolution magnetic resonance spectroscopy of plasma in order to increase the detection of low-grade rejections [15, 18]. A combination of noninvasive and inexpensive strategies, which allow for a fine tuning of the immunosuppressive treatments in function of the immunological and cardiac state, might be the best choice to increase both the quality of life and life expectancy in heart transplant recipients.

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