Reliability of Tissue Doppler Wall Motion Monitoring After Heart Transplantation for Replacement of Invasive Routine Screenings by Optimally Timed Cardiac Biopsies and Catheterizations

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Background—Invasive screenings at predefined time intervals for acute rejection and transplant coronary artery disease (TxCAD) are standard procedures. However, cardiac biopsies and catheterizations are distressing and risky for the patients and are also costly. We assessed the reliability of pulsed-wave tissue Doppler imaging (PW-TDI) for the timing of invasive examinations in heart recipients in an attempt to avoid unnecessary endomyocardial biopsies (EMBs) and catheterizations.

Methods and Results—PW-TDI obtained at the basal left ventricular posterior wall before 408 EMBs and 293 catheterizations was tested for its diagnostic value regarding rejection and TxCAD with the use of International Society of Heart and Lung Transplantation biopsy grading, coronary angiography, and intravascular ultrasound as standards. Early diastolic peak wall motion velocity and relaxation time showed high sensitivities for clinically relevant rejection diagnosis (90.0% and 93.3%, respectively). The negative and positive predictive values for rejection of diastolic parameter changes appeared high enough (up to 96% and 92%, respectively) to allow a reliable noninvasive PW-TDI monitoring with efficiently timed, instead of routinely scheduled, EMBs. At definite cutoff values for systolic parameters, the probability for TxCAD reached 92% to 97%. The Fisher classification functions allowed TxCAD exclusion with 80% probability.

Conclusions—Without diastolic parameter changes, acute rejection can be practically excluded, and serial PW-TDI can save patients from routine EMBs. The high specificity and negative predictive value for TxCAD of reduced systolic peak velocities and extended systolic time allow optimized timed catheterizations. Peak systolic velocity and systolic time allow diagnostic classifications that enable patients without known TxCAD but with high risk for catheterization to be spared routine angiographies. (Circulation. 2001;104[suppl I]:I-184-I-191.)

Key Words: heart diseases ▪ transplantation ▪ echocardiography ▪ rejection ▪ coronary disease

Noninvasive diagnosis of cardiac rejection and detection of transplant coronary artery disease (TxCAD) are major objectives in the management of heart allograft recipients.

Many noninvasive techniques for rejection diagnosis have been investigated, but none was found sufficiently reliable to replace endomyocardial biopsies (EMBs).1,2 However, routine biopsies are of major inconvenience to the patients and are also risky and costly. Their necessity after the first posttransplant year has already been questioned,3-5 and attempts to reduce their frequency early after surgery have also been reported.6,7 Nevertheless, rejection surveillance is based extensively on biopsies performed at predefined intervals.1

With routine annual coronary angiography for TxCAD surveillance, there are risks of major complications and also a high risk of renal failure because of chronic renal impairment due to cyclosporine. Promising results with regard to noninvasive TxCAD diagnosis were reported for stress echocardiography, electron beam CT, and positron emission tomography.8-10

Wall motion analysis by tissue Doppler imaging (TDI) can detect ventricular dysfunction earlier than is possible with conventional echocardiography.11 Its usefulness for rejection diagnosis has already been reported,12-14 but its clinical value is controversial.15 Although TDI has proved promising for the quantification of ischemia-induced myocardial dysfunction,16 its usefulness for TxCAD assessment has not yet been investigated. The high temporal and velocity range resolution provided by pulsed-wave TDI (PW-TDI) has proved also beneficial for the assessment of left ventricular (LV) global function in patients without ventricular asynergy.17,18

Therefore, we assessed the usefulness of PW-TDI for the early diagnosis of cardiac rejection and the detection of functional abnormalities due to TxCAD to test its reliability.
for the timing of posttransplant invasive follow-up examinations.

Methods

Patients and Study Design

During a study period of 18 months, 363 adult heart recipients (all patients with biatrial anastomoses) with posttransplant times of between 7 days and 13 years underwent PW-TDI before all invasive follow-up examinations.

Diagnostic EMBs were taken from patients suspected of rejection because of clinical symptoms or ECG changes. Instead of routine EMB during the early posttransplant period, we routinely performed a telemetric monitoring of the intramyocardial ECG (IMEG) from a dual-chamber pacemaker in all patients with posttransplant times <2 years. Averaged overnight QRS amplitudes (determined separately for each ventricle), heart rate, and short ECG recordings for the exclusion of arrhythmias or QRS complex deformations were analyzed by use of daily printouts.

Routine biopsies at predefined time intervals were performed only during follow-up catheterizations.

Routine coronary angiography was performed annually or at larger time intervals up to 2 years, depending on renal function and other acute or chronic diseases. Additional angiographies were performed whenever TxCAD or the aggravation of known TxCAD was suspected clinically (arrhythmias, clinical symptoms) or because of ECG and electron beam tomographic changes.

PW-TDI, performed before invasive procedures, was tested for its diagnostic value regarding rejection and TxCAD by using endomyocardial biopsies as well as coronary angiography and intravascular ultrasound as standards.

The present study was approved by the local institutional review committee. Written informed consent was obtained from patients before cardiac catheterization.

Pulsed-Wave TDI

To evaluate LV subendocardial radial and wall motion, PW-TDI was obtained in each patient from the basal posterior wall, in parasternal axis views at the level of the mitral leaflet edges.

By use of an ALOCA SSD-2200 ultrasound system, PW-TDI was obtained at end expiration simultaneously with a phonoangiogram (Figure 1). The following parameters were measured: (1) peak systolic wall motion velocity (Sm) and peak early diastolic wall motion velocity (Em), (2) systolic time (TSm, from onset of first heart sound to the peak of the systolic wave Sm), (3) early diastolic time (TEm, from onset of second heart sound to the peak of the early diastolic wave Em), and (4) systolic and early diastolic wall accelerations (Sm/TSm and Em/TEm, respectively).

As proposed by Puleo et al,4 because of the transducer angulation dependency of velocity measurements, we selected from at least 5 tracings the highest velocity above the baseline for Sm and below the baseline, during early relaxation, for Em. Time parameters were measured and averaged from 5 cardiac cycles.

PW-TDI parameters were measured online before biopsies or coronary angiographies. The examiners were blinded to the details of the present study.

The reproducibility of the measurements was tested by 2 examiners in 50 patients.

Endomyocardial Biopsies

A total of 408 EMBs of the right ventricular septum were taken from 293 patients. Biopsies were performed routinely during follow-up cardiac catheterizations and optionally whenever rejection was suspected because of IMEG changes, arrhythmias, or clinical symptoms. Rejection diagnosis was made in accordance with the International Society of Heart and Lung Transplantation (ISHLT) standardized cardiac biopsy grading.5,19

Cardiac Catheterizations

In 293 patients, after standard hemodynamic recordings, biplanar angiograms were acquired digitally and by cine film on standard biplanar angiographic x-ray equipment (INTEGRIS/LARC system Philips). Angiographic volumes and ejection fractions were evaluated by using the standard biplanar Simpson method.

Angiographic assessment of TxCAD was based on the criteria of Gao et al20 in 1988. In patients without angiographic type A, B, or C lesions, standard angiograms were followed by intracoronary ultrasound (ICUS) examinations (Endosonics device).

In the absence of angiographic type A, B, or C lesions, TxCAD was diagnosed if ICUS revealed polyfocal or diffuse intimal thickening and maximum lesions above Stanford class I.21 The absence of significant vasculopathy was diagnosed if by ICUS there was no more than a single plaque (monofocal lesion) or maximum lesion equal to Stanford class I.

Statistical Analysis

To assess the differences between individual groups, the overall significance was tested by parametric (ANOVA) and nonparametric (Kruskal-Wallis) tests. As a mean separation test, we used the Duncan multiple range test. For repeated measures, the overall significance was tested by parametric (ANOVA) and nonparametric (Wilcoxon signed rank) tests. The significance of association was assessed by contingency analysis by the $\chi^2$ test. The Fisher classification and discriminant analysis with Bayes theorem were used for classifying observations.

The results found by the same observer on different occasions (intraobserver variability) or by the 2 independent observers (inter-
Acute Rejection

Among the 408 EMBs performed throughout the study period, 195 (47.8%) were routine EMBs taken during cardiac catheterization, 181 (44.4%) were diagnostic EMBs performed in patients suspected of rejection either clinically or by IMEG recordings, and 32 (7.8%) were control EMBs performed during or after antirejection treatment. The 376 routine and diagnostic EMBs were selected as standards for PW-TDI diagnostic evaluation.

Comparing the PW-TDI pattern of heart recipients with biopsy-proven nonrejection (ISHLT grade 0) with that of patients in rejection, significant alterations were found at higher rejection grades (ISHLT grades ≥2) consisting of TEm extension and Em reduction (Figure 2A). Comparing the same patients throughout serial examinations, all the tested parameters showed significant alterations during biopsy-proven rejection, which in 76.8% of the patients was histologically mild (ISHLT grades 1A or 1B) (Figure 2B). Among the serially investigated rejection episodes, 60 (40.0%) were treated with augmented immunosuppression.

Histologically, 35 (58.3%) of these rejection episodes were classified as ISHLT grades 2, 3A, and 3B; the other 25 (41.7%) were mild cellular rejections (ISHLT grades 1A and 1B) accompanied by clinical manifestations (tachycardias, hemodynamic alterations, and clinical symptoms). During clinically manifested rejection episodes accompanied by tachycardia and blood pressure reduction, only the heart rate increase reached statistical significance (P=0.01).

The PW-TDI pattern of a patient recorded before and during a clinically manifested acute cellular rejection ISHLT grade 3A is shown in Figure 3.

Figure 4 shows the PW-TDI changes during histologically mild ISHLT grade 1A and 1B rejections, which were different in asymptomatic and symptomatic patients.

Without rejection, hemodynamically relevant tricuspid insufficiency was present in 3.5% of the investigated patients; a further 10.1% had moderate, clinically irrelevant, tricuspid regurgitation. During rejection, a hemodynamically important increase in tricuspid regurgitation was noted in 6 patients. Two patients showed mild mitral regurgitation, and 1 demonstrated moderate mitral regurgitation.

In 91.7% of the rejection episodes, the PW-TDI alterations revert completely during antirejection therapy within 65.5±24.2 hours. In 4 patients, all with posttransplant times of >5 years, the PW-TDI alterations were only partially reversible. One patient with predominantly vascular rejection...
(intensive vascular reactions, evidence of colocalization of immunoglobulin and complement in the microvasculature, and only mild cellular rejection grade 1A) died after 48 hours, despite intensive antirejection therapy. This patient showed >50% drop of Sm to 5.2 cm/s. Postmortem histology was not available.

With serial examinations, the sensitivity and negative predictive value for biopsy-proven rejection of TEm extension, Em reduction, and Em/TEm reduction was >90%. The sensitivity, specificity, and predictive values of PW-TDI parameter changes for clinically relevant, treatable rejections are shown in Table 1. Contingency analysis demonstrated a strongly significant dependence for each of the investigated PW-TDI parameters with biopsy results (for Sm, $P=9.51 \times 10^{-26}$; for TSm, $P=2.07 \times 10^{-21}$; for Sm/TSm, $P=1.68 \times 10^{-26}$; for Em, $P=5.45 \times 10^{-26}$; for TEm, $P=5.24 \times 10^{-26}$; and for Em/TEm, $P=2.18 \times 10^{-23}$).

The threshold value of 10% was selected in accordance with the reproducibility of measurements. For our examiner routinely involved in posttransplant PW-TDI, the intraob-server variability of PW-TDI parameter measurements was between $\pm 3.4\%$ and 8.5%. The interobserver variability exceeded $\pm 10\%$ only for Em measurements ($\pm 12.0\%$) and was lowest for TEm ($\pm 5.14\%$).

### Transplant Coronary Disease

TxCAD was invasively diagnosed in 214 (73%) heart recipients. Among these, 100 patients showed angiographic type A, B, or C lesions; the remainder showed ICUS-detectable polyfocal or diffuse intimal thickening and maximum lesions of Stanford class II, III, or IV.$^{21}$

Proximal stenoses of the great epicardial vessels were detected in 62 patients (29% with angiographic or ICUS-visible TxCAD). In 4 patients (2 with focal stenoses on the right coronary artery [RCA] and 2 with a left anterior descending coronary artery [LAD] stenosis), we had strong evidence of a donor-transmitted coronary disease.

The prevalence of TxCAD increased with posttransplant time. TxCAD was identified angiographically or by ICUS in 82.7% of patients with posttransplant times >3 years and in 50.6% of patients with posttransplant times <3 years. The prevalence of angiographic TxCAD alone (with or without type A lesions) was 18.6% in patients with posttransplant times <3 years and 40.6% in those transplanted >3 years before.

With TxCAD, the PW-TDI pattern showed significant changes for both systolic and diastolic parameters, but the systolic changes were more obvious. Compared with patients without the disease, even those with moderate (ICUS-visible) TxCAD showed significant differences for all systolic parameters. For Sm and Sm/TSm, there were also significant differences between angiographic and ICUS-visible TxCAD (Figure 5).

Among the diastolic parameters, only Em and Em/TEm were significantly different in patients with and without TxCAD (Figure 5).

Definite cutoff values for Sm, TSm, and Sm/TSm allow highly predictive diagnostic conclusions. Without rejection, at Sm values ≤10 cm/s, we found a 97.72% likelihood for TxCAD, whereas Sm values ≥11 cm/s can exclude angiographic TxCAD with 90.27% probability (Table 2). To improve our diagnostic decision making, we tested different mathematical models by using Sm and TSm together and obtained several functions that allowed correct diagnostic classification with similar probabilities of between 79.5% and

### Tables and Figures

#### Table 1

**Sensitivity, Specificity, and Predictive Value of PW-TDI Parameter Changes for Clinically Relevant Acute Cardiac Rejection During Serial Examinations of 161 Patients**

<table>
<thead>
<tr>
<th>PW-TDI Parameter Changes</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>Positive Predictive Value, %</th>
<th>Negative Predictive Value, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sm &gt;10% reduction</td>
<td>88.33</td>
<td>94.06</td>
<td>89.83</td>
<td>93.14</td>
</tr>
<tr>
<td>TSm &gt;10% extension</td>
<td>83.33</td>
<td>94.06</td>
<td>89.29</td>
<td>90.48</td>
</tr>
<tr>
<td>Sm/TSm &gt;10% reduction</td>
<td>86.67</td>
<td>96.04</td>
<td>92.86</td>
<td>92.38</td>
</tr>
<tr>
<td>Em &gt;10% reduction</td>
<td>91.66</td>
<td>92.08</td>
<td>87.30</td>
<td>94.85</td>
</tr>
<tr>
<td>TEm &gt;10% extension</td>
<td>93.33</td>
<td>95.05</td>
<td>91.80</td>
<td>96.00</td>
</tr>
<tr>
<td>Em/TEm &gt;10% reduction</td>
<td>91.66</td>
<td>94.06</td>
<td>90.16</td>
<td>95.00</td>
</tr>
</tbody>
</table>

Clinical relevance is defined as cellular rejections greater than or equal to ISHLT grade 2 and histologically mild rejection grades 1A and 1B in symptomatic patients.
Figure 5. Mean values of PW-TDI parameters in 293 heart recipients divided into 3 groups according to degree of coronary lesions. *ICUS-visible and angiographic TxCAD were not significantly different. †Significant differences between all 3 groups. ‡No significant differences for IVRT (P=0.2032) or TEm (P=0.2551).

80.9%. Using Fisher classification functions (F), we obtained the most suitable equations for practical use: F1 = (−63.383) + 5.324 × Sm + 0.465 × TSm, and F2 = (−59.005) + 4.639 × Sm + 0.491 × TSm.

The diagnostic decision depends on which of the 2 functions, F1 or F2, has the greater value: positive TxCAD diagnosis if F1>F2 and negative TxCAD diagnosis if F2>F1.

In patients with angiographic TxCAD without serial examinations, there were no significant differences between the PW-TDI parameters of those with or without stenoses (type A lesions) of the great epicardial vessels.

None of the PW-TDI parameters tested were correlated with LV end-diastolic pressure (LVEDP), although there were significant differences between the mean LVEDP values in patients with and without TxCAD and between those with angiographic and ICUS-visible TxCAD (P=0.0002).

The arterial pressure was not significantly different between patients with and without TxCAD, and there was no correlation between any of the PW-TDI parameters and arterial pressure. The prevalence of tricuspid regurgitation in the groups with and without TxCAD was similar.

Right bundle-branch block, found in 19.8% of our patients, was associated with significant TSm prolongation (P=0.012). As in patients without right bundle-branch block, the TSm duration was significantly longer with than without TxCAD (P=0.003). The left bundle-branch block, uncommon in our patients (4.4%), was associated with prolonged TSm (≥140 ms).

During the study period, PTCA was carried out in 20 patients. One patient died during the attempt to open a LAD acute occlusion (with consecutive anterior infarction) 24 hours after proximal LAD angioplasty and stenting. Coronary bypass surgery, performed in 4 patients, was successful in 3 of them. The fourth patient had to be retransplanted because of postoperative biventricular heart failure. The group of 12 patients who underwent RCA revascularization procedures showed a significant increase of Sm from 8.78±1.15 to 9.62±1.37 cm/s (P=0.037).

Discussion

The present study proved the reliability of PW-TDI for revealing early alterations in LV function linked to rejection and TxCAD, which allowed highly predictive diagnostic evaluations and the most appropriate timing for invasive examinations. PW-TDI is easy to perform, not time-consuming, and not expensive. In the present study, for the online PW-TDI measurements, only an additional 3.6±1.3 minutes per patient was necessary. With specific training for PW-TDI, the variability of measurements is below ±10%. Our results agree with those reported by Puleo et al., who found the reproducibility of measurements sufficiently high for clinical use.

Acute Rejection

With acute rejection, as an expression of aggravation or the new appearance of relaxation disturbances, we found significant Em and Em/TEm reductions as well as TEm extensions. Without such changes, rejection can be excluded, and biopsies become unnecessary, whereas reductions of Em and/or TEm extensions of >10% should be clarified by biopsy.

The threshold value of 10%, close to the intraobserver variability and even closer to the interobserver variability, can result in a higher frequency of false positives with, consequently, a few more unnecessary biopsies. However, this is safer for the patients than a greater number of false negatives, which would have resulted if higher threshold values were selected.

The diagnostic value of Em for cardiac rejection was recently emphasized. We proved the usefulness of diastolic wall velocity assessment for rejection diagnosis. Thus, without Em reduction, the probability of rejection of any histological grade is low (negative predictive value 88.46%). Without an Em reduction with >10%, even in symptomatic patients, the probability of acute rejection will be very low (negative predictive value 94.85%). An Em reduction >10% showed a positive predictive value of 87.30% for clinically relevant rejection episodes.

TEm has proved useful for assessing abnormal LV relaxation in heart diseases but was not investigated in heart recipients. In earlier studies that used digitized M-mode echocardiograms, we found extensions of the early relaxation time during rejection, but the clinical value of this observation was limited by time-consuming measurements. With PW-TDI, we have proved the diagnostic value of TEm for rejection. Thus, without any TEm prolongation, rejection of any histological grade appeared excludable with 94.00% probability, whereas with a prolongation >10%, the probability of a clinically relevant rejection reached 91.8%.

Systolic PW-TDI parameters were of minor value for the early detection of rejection, but for clinically relevant rejection episodes, the positive and negative predictive values of systolic changes exceeded 90%. Sudden reductions of the peak velocity Sm, without any important blood pressure increase, appeared highly predictive of rejection.

Because only 48.1% of the EMBs used as standards for PW-TDI diagnostic evaluation were routine biopsies (performed at predefined time intervals) and because the remaining 51.9% were taken from patients suspected (clinically or because of IMEG alterations) of rejection, approximately half
of the patients in whom biopsies were performed were skewed toward those most likely to be rejecting. Consequently, we had a high prevalence (39.9%) of positive results (ISHLT grades ≥1A) in the EMBs taken from our patients. The necessity of routine biopsies in asymptomatic patients has been repeatedly questioned. Screening based only on time has been substituted by more efficient strategies at our institution for several years. As a result, a selection bias as to the prior probabilities of biopsy-proven rejection could not be avoided. However, contingency analysis supports a highly significant dependence of all PW-TDI parameters with biopsy results.

In conformity with our previous observations, the PW-TDI pattern in patients without rejection varied according to the posttransplant time. After surgery, we found the most important changes, which predominantly affected the diastolic parameters. Serial examinations during the first year indicated that despite continuous diastolic function improvements, relaxation disturbances persist for at least 4 weeks. These changes in the wall motion profile could be misleading if certain cutoff values are used for rejection diagnosis. Therefore, the amount of change during serial examinations is more useful for rejection diagnosis than is the absolute value of a certain parameter.

During rejection, only 4% of our patients showed hemo-dynamically important increases in tricuspid regurgitation, and mitral regurgitation was very uncommon. Therefore, the influence of the increase of atrioventricular valve regurgitation on the general trend of PW-TDI changes during rejection was unimportant.

Because of the frequent discordance between morphological and functional alterations during rejection, the inability of PW-TDI to predict histological severity grades is not a limitation of the PW-TDI method. Moreover, it raises questions as to the infallibility of endomyocardial biopsy as a method for ascertaining the severity of rejection and the necessity for antirejection therapy. Thus, during rejection, neither clinical symptoms nor PW-TDI parameter changes were restricted to higher (≥2) ISHLT grades. In >40% of our patients treated for rejection, the therapeutic decision was primarily based on the severity of clinical symptoms that accompanied an unexpectedly low degree of cellular infiltration (ISHLT grades 1A and 1B). This group of symptomatic patients with mild cellular rejection showed a high incidence of vascular rejection components that were demonstrable histologically and/or by immunofluorescence techniques. The more severe clinical course of vascular or mixed (cellular and vascular) rejections was recently reported by Taylor et al. Transplant Coronary Disease

Although coronary angiography in combination with ICUS is the gold standard for TxCAD diagnosis, its timing by noninvasive methods could be highly beneficial. The reduced Sm and prolonged TSm during TxCAD enable PW-TDI-guided decisions for invasive coronary diagnosis. Our results indicate the necessity for invasive clarification in patients without known TxCAD who show an Sm ≥10 cm/s, because after rejection exclusion, the probability of TxCAD will be >97%. With known TxCAD, an Sm reduction >15% also needs invasive clarification, because in 90.75% of patients, it was linked to rejection or the progression of TxCAD.

By use of the Fisher classification functions, Sm and TSm allow TxCAD exclusion with 80% probability, which is sufficient for patients at high risk of catheterization to be at least temporarily spared routine angiography. With Sm and TSm ≥11 cm/s and 110 cm/s², respectively, angiographic TxCAD can be excluded, and coronary angiography becomes unnecessary.

Although Em and Em/Em were significantly reduced during angiographic TxCAD, these diastolic PW-TDI parameters showed no use for TxCAD diagnosis.

The PW-TDI parameters tested appeared unaffected by the LVEDP and, therefore, to a great extent were preload independent. The high LVEDP values in patients without TxCAD suggest that in most heart recipients the coronary disease aggravates an already preexistent diastolic dysfunction rather than primarily causing it.

We found the same PW-TDI alterations during TxCAD regardless of the presence or absence of bundle-branch block. Nevertheless, right and left bundle-branch block could impede individual diagnostic decisions because of the prolonged TSm.

Usefulness of PW-TDI for Assessment of Global LV Function

Because of diffuse morphological changes during rejection and TxCAD, ventricular dysfunction is expected to be global; therefore, a local wall motion assessment by PW-TDI with high temporal and velocity range resolution could be useful. Indeed, the diastolic wall motion velocity analysis for rejection diagnosis performed by a PW-TDI and a color TDI study showed no advantages of the high spatial resolution.
provided by color TDI. Our observations proved the diagnostic value for rejection of local diastolic parameter assessment by PW-TDI.

With angiographic TxCAD, the systolic PW-TDI parameters obtained at the posterior wall were significantly altered, but there were no significant differences between patients with or without proximal stenoses of the great epicardial vessels, although in the group with focal stenoses, 31.17% had RCA stenoses of 75% to 100%. Thus, the diffuse primarily distal vessel narrowing, known as the dominant morphological change during TxCAD, also appeared to be the major determinant of ventricular dysfunction, regardless of additional great epicardial vessel narrowing. Therefore, although PW-TDI allows only regional wall motion assessments, they reflect the functional state of large myocardial areas in patients with TxCAD. Nevertheless, our data suggest that serial PW-TDI can also reveal the progression of focal epicardial vessel stenoses. Thus, during the study period, patients developing RCA stenoses showed Sm reductions, whereas in those who underwent RCA revascularization procedures, Sm increased but did not reach normal values. Among the patients with donor-transmitted coronary lesions, only those with RCA stenoses had reduced Sm values.

In nontransplanted patients without regional wall motion disturbances, the systolic PW-TDI velocity parameters of posterior wall circumferential motion proved useful for noninvasive evaluation of global LV systolic function, and alterations in contractility were better reflected by myocardial velocity than by LV ejection fraction (LVEF) changes.

In our patients, at the basal posterior wall, Sm correlated significantly with the invasively measured LVEF ($P=0.001$, $r=0.537$). Nevertheless, unlike LVEF, significant Sm, TSm, and Sm/TSm alterations had already occurred during early TxCAD; therefore, PW-TDI parameters were more useful than the LVEF for the early detection of systolic dysfunction during TxCAD.

Limitations of the Study
We did not include corrections of parameters to the heart rate. Although the heart rate increased significantly ($P=0.03$) during rejection, TEm was significantly prolonged despite a shortened diastole. Thus, a correction to the heart rate would further emphasize the rejection-induced relaxation disturbance and could further improve the diagnostic value of PW-TDI, but it would also be time consuming.

Our biopsy strategy produces higher prevalence of rejection in our sample. Therefore, our positive predictive value is higher and our negative predictive value is lower than it should be in a sample with lower prevalence of rejection. However, the $\chi^2$ statistics showed the highly significant dependence of all PW-TDI parameters with biopsy. The high negative predictive values of PW-TDI parameters, which will be even higher in a sample with lower prevalence of rejection, allow a reliable exclusion of rejection in the absence of PW-TDI alterations. Our higher positive predictive values of PW-TDI alterations will result in a few more unnecessary biopsies, which is, however, preferable to the incomparably higher number of unnecessary biopsies performed during routine invasive screenings.

In accordance with Rickenbacher et al., we classified the posttransplant anatomic abnormalities of coronary arteries into angiographic TxCAD and ICUS-visible TxCAD. It is well known that early after transplantation a minor part of coronary lesions may be imported and is sometimes hardly distinguishable from posttransplant developed TxCAD. In the present study, most discrepancies between invasive coronary diagnosis and PW-TDI occurred within the first posttransplant year and could, therefore, be partially attributed to the imperfect standard.

The low number of serial angiographies performed during the study period limits our statements on the usefulness of PW-TDI for the timing of follow-up catheterizations. However, our data suggest that serial catheterizations would bring further support for PW-TDI as a potential tool for the timing of follow-up angiographies.

Conclusions
Our results validate the radial wall motion assessment by PW-TDI as being particularly suited for the early detection of LV functional alterations linked to rejection and TxCAD.

The reliable PW-TDI diagnosis of relaxation disturbances, which is highly predictive for rejection, questions the necessity of routine biopsies. Serial PW-TDI examinations can save most patients from routine biopsies. The functional alterations revealed by PW-TDI during biopsy proven rejection are more closely related to clinical manifestations than to the histological severity grade.

The detection of altered systolic PW-TDI parameters in nonrejecting patients, which is highly predictive for TxCAD, could allow optimal timing for cardiac catheterizations. Thus, serial multiparametric PW-TDI evaluations for rejection and TxCAD follow-up, which are easy to perform and not time-consuming, could spare patients unnecessary and very distressing routine invasive examinations.

References


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