Assessment of Microcirculatory Remodeling With Intracoronary Flow Velocity and Pressure Measurements

Validation With Endomyocardial Sampling in Cardiac Allografts

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Background—Intracoronary physiology techniques have been validated extensively for the assessment of epicardial stenoses but not for the lone study of coronary microcirculation. We performed a comparison between 4 intracoronary physiological indices with the actual structural microcirculatory changes documented in transplanted hearts.

Methods and Results—In 17 cardiac allograft patients without coronary stenoses, ECG, intracoronary Doppler flow velocity, and aortic pressure were digitally recorded before and during maximal hyperemia with a dedicated system. Postprocessing of data yielded 4 indices of microcirculatory status: coronary flow velocity reserve (2.13 ± 0.88 mm Hg · cm⁻¹ · s⁻¹), instantaneous hyperemic diastolic velocity pressure slope (1.65 ± 0.88 mm Hg · cm⁻¹ · s⁻¹), and coronary resistance reserve (2.36 ± 0.65). Quantitative morphometry was performed in endomyocardial biopsies during the same hospital intake; arteriolar obliteration (76.57 ± 6.95%) and density (2.00 ± 1.22 arterioles per 1 mm²) and capillary density (645 ± 179 capillaries per 1 mm²) were measured. Univariate regression analysis between intracoronary measurements and histological findings revealed that instantaneous hyperemic diastolic velocity-pressure slope correlated with arteriolar obliteration (r = 0.58, P = 0.014) and capillary density (r = 0.60, P = 0.012). Statistical adjustment revealed an independent contribution of arteriolar obliteration (β = 0.61, P = 0.0009) and capillary density (β = 0.60, P = 0.0008) to instantaneous hyperemic diastolic velocity-pressure slope values, resulting in an excellent predictive model (r = 0.84, P = 0.0002). Coronary resistance index correlated only with capillary density (r = 0.70, P = 0.019). Relative indices (coronary flow velocity reserve and coronary resistance reserve) did not correlate significantly with arteriolar obliteration, capillary density, or arteriolar density.

Conclusions—Intracoronary indices derived from pressure and flow, particularly instantaneous hyperemic diastolic velocity-pressure slope, appear to be superior to coronary flow velocity reserve in detecting structural microcirculatory changes. Both arteriolar obliteration and capillary rarefaction seem to influence microcirculatory hemodynamics independently. (Circulation. 2009;120:1561-1568.)

Key Words: blood flow ▪ capillaries ▪ microcirculation ▪ physiology ▪ transplantation

Structural coronary microcirculation abnormalities are important prognostic determinants in different clinical settings, including acute coronary syndromes, diabetic coronary disease, hypertrophic cardiomyopathy, and transplant cardiac allograft vasculopathy. However, in clinical practice, its detection is hampered by the lack of well-validated methods. Intracoronary physiological techniques have been advocated, and several indices for the assessment of changes in the microcirculatory bed have been proposed. Although most authors have used the concept of coronary flow velocity reserve (CFVR) as the theoretical framework to study microcirculation invasively, this approach has 2 limitations: The cutoff value for clinical use of CFVR has been derived from patients with epicardial stenoses, and being a relative measure, CFVR is highly dependent on baseline reference values, which frequently are unrealistic. In an attempt to overcome the latter problem, some authors have proposed indices based on the combination of pressure and flow velocity measurements, which can provide estimates of vascular resistance in the epicardial and microcirculatory compartments of coronary circulation.

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The present work aims to shed light on these aspects and, as a primary objective, to compare CFVR and several indices derived from pressure–flow velocity with the actual histolog-
Physiological Indices of Microvascular Status

Postanalysis of Data and Calculation of Physiological Indices of Microvascular Status

Methods

Subjects

Twenty-one heart transplantation patients scheduled for routine follow-up cardiac catheterization and endomyocardial biopsy whose coronary arteries were angiographically free of stenoses were initially included in this study. None of them had contraindications for intravenous administration of adenosine. The study was approved by the ethics committee of our institution, and all participants provided informed consent. Demographic data, including age, sex, and cardiovascular risk factors, were recorded.

Catheterization Procedure and Acquisition of Intracoronary Physiology Data

The study was performed as part of scheduled diagnostic cardiac catheterization. A right femoral artery approach was used. Left cardiac catheterization was carried out, after which coronary angiography was performed. After administration of 5000 IU unfractionated heparin and 200 μg intracoronary nitroglycerine in the right and left coronary arteries, baseline coronary angiograms were obtained in several angiographic views. Aortic pressure was obtained from a 6F guiding catheter without side holes connected to a pressure transducer (B/Braun, Braun, Melsunger, Germany) and to a computerized polygraph (Horizon 9000, Mennen Medical Inc, Tel Aviv, Israel). Coronary blood flow velocity measurements were performed in the mid segment of the left anterior descending coronary artery with a 0.014-in intracoronary Doppler guidewire connected to the corresponding interface (FloWire and FlowMap, Cardiometric, Rancho Cordova, Calif). Measurements were obtained 3 to 5 minutes after intracoronary administration of nitroglycerine, first at baseline and then during maximal hyperemia. Given the propensity of the denervated transplanted hearts to develop atherosclerotic block during adenosine administration, sustained intravenous adenosine infusion was avoided to induce maximal hyperemia, so 60-μg intracoronary adenosine boluses were used instead. Continuous digital acquisition and storage of ECG, aortic pressure, and instantaneous intracoronary peak flow velocity were performed with a 12-bit-resolution analog-to-digital converter (DL-200 PGL, DataQ Instruments, Inc, Akron, Ohio) controlled by dedicated software (WinDaq 200, DataQ Instruments, Inc) linked to the FloMap console and the polygraph. Sampling rate was 114 Hz per channel. Left ventricular end-diastolic pressure was measured with a pigtail 6F catheter.

The following indices were calculated: CFVR, defined as the ratio between average peak velocities (V_{ave}) measured during hyperemia and at baseline (V_{ave heteremia}/V_{ave baseline}); hyperemic coronary resistance index (CRI), defined as the ratio between mean aortic pressure (P_a) and average peak velocity during maximal hyperemia (P_a/V_{ave hyperemia}); and coronary resistance reserve (CRR), defined as the ratio between the coronary resistance indices measured at baseline and during maximal hyperemia. The formulation used by Krams et al., which incorporates left ventricular end-diastolic pressure (LVEDP) in an attempt to introduce the effect of extravascular compression on coronary resistance, was used. Thus, CRR was calculated as follows: (P_a−LVEDP)/V_{ave baseline}/(P_a−LVEDP)/V_{ave hyperemia}. We also calculated instantaneous hyperemic diastolic velocity-pressure slope (IHDVPS), which is equivalent to hyperemic diastolic conductance. IHDVPS is defined as the slope of the pressure–flow velocity relationship during end systole and diastole under maximal hyperemia. The diastolic pressure and flow velocity measurements were identified using a reference the highest flow velocity (beginning of mid-diastole) and the sharp decrease in diastolic velocity at the end of diastole. By applying linear regression analysis to the selected data, we obtained the slope of the regression line (hyperemic diastolic coronary conductance, expressed in cm·s⁻¹·mmHg⁻¹; Figure 1). Linearity of the flow velocity–pressure relationship in the studied interval was described through the use of the r² regression coefficient.
Endomyocardial Biopsy and Histological Assessment of Microvascular Status

Endomyocardial biopsies were obtained with 7F biopsy forceps (Cordis Corp, Miami, Fla) during the same hospitalization. The methodology followed was the same as described by Kram et al.\textsuperscript{1,4} The tissue was fixed with paraformaldehyde and immersed in 10% buffered formalin. Hematoxylin staining was used to identify and analyze intramyocardial small arteries. Arterioles were identified on the basis of the presence of a layer of media and a diameter <100 \( \mu \)m. The number of arterioles per 1 mm\(^2\) was measured. Capillaries were identified with specific antibodies against endothelium (CD34, Dako, Glostrup, Denmark). Quantitative morphometric analysis of the histological sections was performed with a Leica Q500 MC micromorphomorphometry workstation (Leica Inc, Bannockburn, Ill). The density of capillaries (capillaries per 1 mm\(^2\)) was assessed using 5 cross sections per patient (1000 capillaries). The arteriolar lumen-intima and adventitia-media borders, which defined the lumen and wall thickness regions, were traced manually in 5 arterioles per patient with the morphometry system. The corresponding areas obtained, luminal area (LA) and total arteriolar area (TAA), respectively, were calculated automatically. An arteriolar obliteration index (AOI), analog to the percent area stenosis index used to describe vessel narrowing in epicardial vessels, was calculated from the following formula: \( \text{AOI} = \left[ 1 - \frac{\text{LA}}{\text{TAA}} \right] \times 100 \). Only round arteriolar sections without side branches were used to estimate arteriolar obliteration.

To have a histological reference for the technique used, control endomyocardial biopsies were obtained from 8 nontransplanted subjects: 4 patients with constrictive pericarditis and 4 who died as a result of a noncardiac illness. Mean age of the subjects in the control group was 64 \( \pm \)12 years. None of the patients in the control group had a prior history of hypertension, diabetes mellitus, ischemic heart disease, or cardiomyopathy. As in the heart transplantation group, biopsies were obtained from the septum of the right ventricle and subjected to the same process described above.

Quantitative Coronary Angiography

Vessel size was measured with an automated edge detection quantitative angiography system (QCA-CMS Medical Imaging Systems, Leiden, the Netherlands). The filmed catheter tip was used as a scaling device.

Statistical Analysis

A commercially available statistical package (StatView) was used for data analysis. Mean, SD, and percentages were obtained. Student \( t \) test was used to compare mean values. Linear regression analysis was performed to assess univariate relationships between continuous variables. Bivariate linear regression analysis was used to perform statistical adjustments to both arteriolar and capillary components of microcirculation. A value of \( P<0.05 \) was considered statistically significant.

Results

Adequate physiological tracings were obtained in 17 of the 21 patients recruited for the study. These patients are referred to as our study population. Mean age was 50 \( \pm \)14 years, and 12 (71%) were male. The reasons for transplantation were idiopathic dilated cardiomyopathy in 12 patients, ischemic heart disease in 3, restrictive cardiomyopathy in 1, and cardiac allograft vasculopathy in 1. Mean donor age was 33 \( \pm \)10 years. The mean time from transplantation to enrollment was 23 \( \pm \)28 months (range, 1 to 82 months). Six patients (35%) had diabetes mellitus, 9 (53%) had hypercholesterolemia, 13 (76%) had hypertension, and 1 (6%) had smoked since transplantation. Treatment included immunosuppression in 17 patients (100%), angiotensin-converting enzyme inhibitors in 9 (52%), lipid-lowering drugs in 10 (59%), and antiplatelet therapy in 3 (18%). Thirteen patients (76%) were asymptomatic at the time of the study, 3 presented with shortness of breath, and 1 had recent episodes of syncope. All patients successfully completed the study according to the protocol described without complications.

Physiological Data

Physiological measurements were performed in left anterior descending coronary arteries free of stenosis and with a mean diameter in its proximal segment of 4.13 \( \pm \)0.62 mm. All patients were in sinus rhythm, with a baseline heart rate of 88 \( \pm \)14 bpm. Table 1 shows the values corresponding to the 4 indices of microcirculatory function measured. The linearity of the mid- and end-diastolic relationship between pressure and flow velocity measurements was demonstrated by an \( r^2 \) coefficient of 0.88 \( \pm \)0.06. No statistically significant influence of hypertension, diabetes mellitus, or dyslipidemia was noted on any of the 4 indices evaluated.

Histological Analysis

An average of 4 biopsies were obtained in each patient. Morphometric analysis of the retrieved myocardial tissue in the transplanted patients revealed significant changes in the microvascular bed, revealing a variable degree of microcirculatory remodeling. Arteriolar density was similar in transplant biopsies (2.00 \( \pm \)1.22 arterioles per 1 mm\(^2\)) than in control subjects (2.50 \( \pm \)0.75 arterioles per 1 mm\(^2\); \( P=NS \)). The arteriolar obliteration index was significantly higher (76.57 \( \pm \)6.95% versus 59.66 \( \pm \)6.65%; \( P<0.0001 \); Figure 2) and capillary density was significantly lower (645 \( \pm \)179 versus 1101 \( \pm \)322 capillaries per 1 mm\(^2\); \( P<0.0001 \)) in transplant biopsies than in control subjects (Figure 3). No significant relationship between the degree of arteriolar obliteration and capillary density was found. No association was found between hypertension, diabetes mellitus, or dyslipidemia and arteriolar density, arteriolar obliteration, or capillary density. No evidence of rejection was found in 13 patients. In 4 patients, rejection grade 2R or lower was documented. Capillary density and arteriolar obliteration did not correlate with degree of rejection, donor age, or time elapsed since transplantation.

Relationship Between Physiological Indices and Structural Changes in Microcirculation

Univariate regression analysis comparing the 4 physiological indices and arteriolar density, arteriolar obliteration, and

<table>
<thead>
<tr>
<th>Table 1. Microcirculatory Function Indices</th>
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<tr>
<td>Baseline APV, cm/s</td>
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<tr>
<td>Hyperemic APV, cm/s</td>
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<tr>
<td>CFVR</td>
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<tr>
<td>Mean aortic pressure, mm Hg</td>
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<td>CRI, mm Hg · cm(^{-1}) · s(^{-1})</td>
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<td>LVEDP, mm Hg</td>
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<td>Baseline resistance, mm Hg · cm(^{-1}) · s(^{-1})</td>
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<td>Hyperemic resistance, mm Hg · cm(^{-1}) · s(^{-1})</td>
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<td>CRR</td>
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<td>HDVPS, mm Hg · cm(^{-1}) · s(^{-1})</td>
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APV indicates average peak velocity; LVEDP, left ventricular end-diastolic pressure.
capillary rarefaction was performed. No significant relationship was found between arteriolar density and HHDVPS ($r=0.33$, $P=0.19$), CRI ($r=0.004$, $P=0.99$), CFVR ($r=0.07$, $P=0.78$), or CRR ($r=0.02$, $P=0.93$). Regression analysis between arteriolar obliteration, capillary rarefaction, and the 4 physiological indices is shown in Figure 4. A statistically significant relationship with both capillary density and arteriolar obliteration was fulfilled only by HHDVPS. CRI correlated only with capillary density, whereas CFVR and CRR did not correlate with any of the histological variables.

To gain further insight into the combined contribution of arteriolar obliteration and capillary density, bivariate regression analysis was performed to assess the correlation between histological and physiological variables under conditions of statistical adjustment. Table 2 shows the results of this analysis. The index showing the best correlation with structural changes in the microcirculation was HHDVPS ($r=0.84$, $P=0.0002$); both capillary density and arteriolar obliteration were independent predictors of HHDVPS. CRI also demonstrated a significant relationship with the degree of underlying microcirculatory abnormalities assessed in the study, with a significant contribution of capillary density and a strong trend toward an independent contribution of arteriolar obliteration. On the other hand, CFVR and CRR did not reach statistical significance in this regard.

**Patient Follow-Up**

Follow up was performed $25\pm8$ months (12 to 40 months) after invasive assessment of coronary microcirculation. During follow-up, 1 patient died suddenly, and 5 patients developed heart failure that required hospitalization. Patients with events had significantly higher coronary resistance at the time of study.
inclusion, as reflected by the lower values of IHDVPS and higher CRI (Figure 5). CFVR and CRR did not differ significantly (Figure 4). Likewise, no statistically significant differences were found between patients with and without cardiac events with regard to the initial left ventricular ejection fraction (69%±8% in the events group versus 74%±6% in the group without events) and time from transplantation (28±32 versus 20±26 months). A strong trend toward a more severe arteriolar obliteration was found in patients who developed events (80.90±5.10 versus 74.21±6.86; P = 0.054), whereas capillary density was not significantly different (589±219 versus 675±157 capillaries per 1 mm² in the group with events versus group without events, respectively).

**Discussion**

In the present study, the value of several intracoronary physiology indices to detect changes in coronary microcirculation was explored in cardiac allografts. The main conclusions also are theoretically applicable to nontransplantation patients in whom structural changes in coronary microcirculation are suspected. As a secondary objective, the influence of microvascular physiology and histopathological findings on the outcome of the transplanted patients included in the study was investigated. The main findings are the following. First, both arteriolar obliteration and capillary rarefaction have an independent influence on microcirculatory hemodynamics. Second, the indices that best reflected the influence of both abnormalities were IHDVPS and, to a lesser degree, CRI; a higher microvascular resistance, corresponding to higher CRI and lower IHDVPS values, was documented in patients who later developed cardiac events during follow-up. Finally, relative indices of microvascular function such as CFVR and CRR failed to show a significant relationship with histological abnormalities in the microcirculation; these indices did not predict the development of cardiac disease during follow-up. Because the complexity of the study precluded the inclusion of a large number of patients, our findings should be considered hypothesis generating and are discussed in the following paragraphs.

**Assessment of Microcirculatory Remodeling With Intracoronary Physiology Indices Based on Coronary Flow Velocity and Pressure**

Although intracoronary physiology techniques have been proposed for the separate assessment of epicardial and microvascular aspects of coronary circulation, most authors have focused on the former, specifically in the evaluation of coronary stenoses.8 Diagnostic cutoff values for these techniques have been established for the detection of hemodynamically significant stenoses with noninvasive tests of myocardial ischemia used as a reference.8 Unlike these works, and because our research focused on the assessment of coronary microcirculation, none of the patients included in the present study presented with epicardial stenoses, and histological quantification of microvascular remodeling was performed. This approach provides a robust reference for intracoronary physiology measurements, although its complexity probably explains why it has been applied by only a few authors and in small populations.14,16

The first aspect that deserves attention is the poor performance of CFVR in detecting microcirculatory remodeling.
present in endomyocardial biopsies. Although CFVR is by far the most frequently used approach to evaluate coronary microcirculation, the reliability of the index is hampered by its dependence on baseline flow velocity, a variable that can be altered substantially by hemodynamic parameters, age, diabetes mellitus, left ventricular mass, and even diffuse atherosclerosis. Denervation and enhanced sympathetic tone may also influence baseline flow velocity measurements in cardiac allografts. Heart rate and baseline coronary blood flow velocity parameters in our population were higher than those reported in a cohort of patients with nonobstructed left anterior descending coronary arteries, providing a partial explanation of why the relative indices in the cardiac allografts of our patients such as CFVR and CRR did not correlate with histopathological measurements, although absolute or nonrelative indices of hyperemic microcirculatory resistance such as CRI or IHDVPS did. These differences between denervated and nondenervated hearts might also explain why a significant inverse relationship between coronary flow reserve and capillary density could be documented in a cohort of nontransplanted patients with heart failure despite the similar population size.

From a more general perspective, one of the main messages of the present work is that direct estimation of microvascular resistance might be more reliable than relative approaches that are dependent on baseline measurements. Several authors have previously reported on the intrinsic reliability and reproducibility of nonrelative microcirculatory resistance obtained with a combination of flow and pressure measurements, a pressure/flow intercept of 0/0 would be assumed; consequently, measurements performed under conditions with critical closing pressures >0 would be altered. Therefore, IHDVPS should provide a more reliable estimation than resistance indices based on time-averaged values like CRI or thermodilution-derived resistance indices.

Another finding of the present study is that capillary rarefaction can become an independent contributor to impaired microcirculatory hemodynamics. It is assumed that, in the absence of coronary stenoses, arterioles account for >50% of total baseline microvascular resistance, whereas the capillary network causes little resistance as a result of the high number of capillaries laid in parallel in normal myocardium. Most of the studies on microcirculatory remodeling have focused in obliterate arteriolar changes that might increase its resistance or blunt its regulatory capability, in this regard, we also found that in our patients arteriolar obliteration (not arteriolar density) contributed to altered microcirculatory abnormalities. However, a decrease in capillary density to the levels documented in our patients (mean capillary density in the allografts was nearly half of that in nontransplanted control hearts) may have a significant impact on total microcirculatory resistance, particularly during hyperemia, when capillary density and recruitment become a bottleneck to coronary flow. Unfortunately, there is virtually no information on the phenomenon of capillary rarefaction in human myocardium, and its presence in noncardiac vascular beds has been used as a surrogate of coronary microcirculatory changes in the context of arterial hypertension and syndrome X. To the best of our knowledge, this is the first demonstration in vivo that both capillary rarefaction and arteriolar obliteration contribute independently to microcirculatory hemodynamic disturbances.

Figure 5. Comparison of the values of the 4 indices of microcirculatory function in patients with (shaded boxes) and without (white boxes) cardiovascular events during follow-up (FU).
Microcirculatory Remodeling in Cardiac Allografts

Cardiac allograft microvasculopathy affects >40% of cardiac transplant recipients within the first posttransplantation year and is associated with poor survival and freedom from cardiac events independently of epicardial vasculopathy. In this specific disease, attention has been focused on arteriolar obliteration, which has been related to immunosuppressive treatment and hypertension. Because of its prognostic importance, it has been proposed that coronary microcirculation should be assessed in future trials on prevention of transplant vasculopathy as an important marker of treatment efficacy. As stated, capillary rarefaction appeared to be an independent contributor to the impairment of coronary hemodynamics in the cardiac allografts studied. Whether the documented capillary rarefaction is specific of transplant vasculopathy or is common to other conditions deserves further attention, particularly in light of a recent study by Tsagalou et al that has documented its occurrence in patients with heart failure and altered CFVR. Although coronary microcirculation in heart transplantation patients has been functionally studied by most authors using CFVR, our results suggest that this is not the method of choice for the assessment of microvasculopathy in cardiac allografts, providing an explanation of controversial findings with CFVR in these patients. So far, 2 studies have evaluated cardiac allograft microcirculation using techniques other than CFVR: Klaus al using CRI (same methodology as in our work) and Fearon et al using a thermolitation-derived resistance index. However, a comparison with the histological substrate was not performed in either of these studies.

Our finding that heart transplant recipients who develop cardiac events during follow-up had higher coronary resistance at the time of study inclusion, as reflected by the lower IHDVPS and higher CRI, is of concern. However, because this was not the primary objective of the study, the prognostic relevance of the physiological indices described in cardiac transplant recipients should be interpreted with caution. The information might prove useful, however, in the formulation of future studies addressing prognosis as its main objective.

Limitations

Calculation of IHDVPS is rather complex in the absence of commercially available systems for its measurement. In 4 of the 21 patients initially included in the study, the quality of signals recorded was altered by noise to a degree in which calculation of IHDVPS was unreliable (r2 of the flow velocity–pressure relationship < 0.80) and thus had to be excluded. It is foreseeable that further refinement of the technique (eg, signal filtering) might improve its performance. Biopsy sampling constitutes an inherent limitation to the approach followed in our study, although it might be expected that transplant graft microvasculopathy would occur following a homogeneous distribution in the myocardium. Pressure fixation cannot be performed in endomyocardial biopsies; therefore, arteriolar shrinkage or capillary collapse may have occurred. Although immunostaining with CD34 has been used in works similar to ours, the possibility that this technique might cause underestimation of the absolute number of capillaries per 1 mm2 should be kept in mind. Because such underestimation would be expected to occur to a similar degree in both allograft and control biopsies, this should not affect our conclusions about the presence of microcirculatory remodeling in allograft biopsies. Correspondence between physiological measurements and myocardial sampling was attempted by performing measurements in the left anterior descending coronary artery, which is responsible for most of the coronary support to the interventricular septum, the site of endomyocardial biopsy sampling. For safety reasons, maximal hyperemia was achieved with intravenous boluses of adenosine and not with intravenous infusion, which might cause complete atrioventricular block in denervated transplanted hearts. A higher dose of adenosine per bolus (60 μg) than that routinely used (20 μg) in the intracoronary route was chosen in an attempt to ensure maximal reduction of microvascular resistance. Diastolic ventricular function was not assessed in this study. Simultaneous measurement of left ventricular diastolic pressures, which might have helped us ascertain the influence of extravascular compression on CRI, was not performed to minimize risks and to reduce the complexity of the study. Because there was a wide range of time from transplantation, and not being an objective of the study, the possibility that microcirculatory remodeling in cardiac allografts is a time-related phenomenon cannot be excluded.

Conclusion

Our study provides valuable information about the most useful method to evaluate microcirculation and suggests that its assessment could be of importance in determining the evolution of heart transplant recipients.

Disclosures

None.

References

Structural changes of coronary microcirculation occur in a significant number of diseases. These include common disease processes such as systemic arterial hypertension and diabetes mellitus, among many others. Having an adequate method to detect microcirculatory involvement in these pathologies is important not only to perform an accurate diagnosis, but also to establish the impact on patient outcome and to measure the effect of treatment strategies. Although the most frequent indication to perform coronary microcirculation assessment of the physiological significance of coronary stenosis in humans. Circulation. 1994;90:1215–1224.


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