Dilated Cardiomyopathy

Regional Coronary Flow and Contractile Reserve in Patients With Idiopathic Dilated Cardiomyopathy

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OBJECTIVES
The purpose of this study was to assess regional coronary flow and contractile reserve in patients with idiopathic dilated cardiomyopathy (IDCM).

BACKGROUND
Although IDCM has been associated with alterations in coronary blood flow and contractile reserve, little is known about their regional distribution and correlation.

METHODS
Fourteen patients with IDCM and 11 control subjects underwent coronary flow velocity (APV) measurements in the left anterior descending (LAD), left circumflex (LCx), and right coronary (RCA) arteries at baseline (b) and at maximal hyperemia (h). Coronary flow reserve (CFR) was defined as h-APV/b-APV. Wall thickening was assessed in 16 segments (7 assigned to LAD, 5 to LCx, and 4 to RCA) both at rest and under peak stress during low-dose dobutamine echocardiography. Regional contractile reserve was defined as the percentage difference in wall motion score index between rest and stress in each vascular territory.

RESULTS
Although there were no significant differences in b-APV, patients with IDCM had significantly lower h-APV than controls in all three vascular territories and reduced CFR (LAD: 2.79 ± 0.43 vs. 3.48 ± 0.51, p < 0.05; LCx: 2.71 ± 0.39 vs. 3.36 ± 0.65, p < 0.05; and RCA: 3.43 ± 0.55 vs. 4.02 ± 0.73, p < 0.05). There was also a significant correlation between CFR and the corresponding contractile reserve in the vascular territory of the LAD (r = 0.75, p = 0.002) and the LCx (r = 0.64, p = 0.014).

CONCLUSIONS
Patients with IDCM have alterations in regional coronary flow and reduced CFR. Furthermore, the correlation between regional CFR and the corresponding contractile reserve indicates that microvascular dysfunction may have a pathophysiologic role in the evolution of the disease. (J Am Coll Cardiol 2004;44:2027–32) © 2004 by the American College of Cardiology Foundation

Dilated cardiomyopathy is a syndrome characterized by cardiac enlargement and impaired systolic function of one or both ventricles. Idiopathic dilated cardiomyopathy (IDCM) represents the final common expression of primary myocardial damage produced by a variety of as yet undefined myocardial insults, producing areas of interstitial and perivascular fibrosis, particularly of the left ventricle (LV).

It has been assumed that myocardial ischemia does not play a role, because a prerequisite for the diagnosis of IDCM is the absence of significant coronary artery disease. However, previous studies have shown not only that coronary blood flow abnormalities occur even in the early stages of the disease (1,2), but also that myocardial ischemia attributable to coronary microvascular dysfunction may have an independent role in the progression of the disease. Although conflicting data exist concerning alterations of global coronary flow and their regional distribution (3–10), there is a general agreement that coronary flow reserve (CFR) is impaired in IDCM and may correlate with prognosis (11).

Meanwhile, abnormal contractile responses during dobutamine echocardiography have been observed in these patients (12), and contractile reserve has also been associated with their prognosis (13–16). Thus, if any correlation between CFR and contractile reserve can be confirmed, then the microvascular dysfunction hypothesis, in which ischemia and systolic dysfunction constitute a vicious circle with a central role in the disease process, would be strongly supported. Accordingly, the purpose of this study was to assess and correlate regional distribution of coronary flow and contractile reserve in patients with IDCM.

METHODS

Patients. The study included 16 patients with IDCM who consented to undergo functional assessment of coronary circulation following the completion of programmed routine cardiac catheterization and stress echocardiography within one week.

The diagnosis of IDCM was based on an LV ejection fraction ≤45%, LV end-diastolic diameter >55 mm, or LV end-systolic diameter >45 mm and the absence of stenotic lesions on coronary angiography. All patients had to be in sinus rhythm with no or mild to moderate symptoms of heart failure (New York Heart Association functional class
I, II, or III) over the past six months and stable under oral treatment.

The following patient groups were excluded: patients with congenital, valvular, or hypertensive heart disease; hypertrophic cardiomyopathy; myocarditis; and patients with previous myocardial infarction, diabetes mellitus, or thyroid disease. We also excluded patients with alcohol abuse and chronic systemic disease or cor-pulmonale.

All cardioactive medications were continued except beta-blockers, which were discontinued at least three days before the study period.

Control group. Eleven patients who had coronary angiography for clinical indications with coronary arteries free of stenotic lesions and left ventricular ejection fraction >55% consented to have Doppler guide wire measurement of CFR. The same exclusion criteria were also applied to this group. All cardioactive medications were continued except beta-blockers, which were discontinued at least three days before the study.

All patients and controls gave their written informed consent to participation in the study. The study protocol was approved by the hospital's ethics committee.

Echocardiography. Echocardiography was performed in all patients using a Hewlett-Packard Sonos 2500 echocardiograph device (Andover, Massachusetts) with a 2- to 2.5-MHz wide-angle phased-array transducer. Measurements were obtained following the recommendations of the American Society of Echocardiography (17).

The LV end-diastolic and -systolic diameters were measured from the M-mode trace obtained from the parasternal long-axis view. The LV volumes were measured from the apical two-dimensional echocardiogram and ejection fraction was calculated using a modified Simpson’s rule algorithm.

After baseline-rest echocardiography had been performed, low-dose dobutamine echocardiography was begun using a mechanical infusion pump. The initial dose was 5 μg/kg/min for 5 min and was then increased to 10 μg/kg/min for 5 more minutes. Four standard views of the LV were obtained for each acquisition: parasternal long-axis, short-axis at papillary muscle level, and apical four- and two-chamber views.

The LV was divided into 16 segments (18), and of these 7 were assigned to the left anterior descending coronary artery (LAD), 5 to the left circumflex (LCx), and 4 to the right coronary artery (RCA) or to LCx, whichever was the dominant artery.

For each segment, systolic wall thickening was scored qualitatively by consensus of two experienced observers who were unaware of other patient data: 1 = normal, 2 = hypokinetic, 3 = akinetic, and 4 = dyskinetic.

Regional wall motion score index (WMSI) was defined as the sum of scores of the segments assigned to each vascular territory divided by the number of assigned segments. Regional WMSI was calculated at rest and peak stress. Regional contractile reserve was defined as the percentage difference of regional WMSI between rest and stress.

Coronary angiography. All patients underwent selective coronary angiography using 6-F standard catheters and conventional views. On completion of diagnostic cardiac catheterization, the video record of the procedure was reviewed. Only patients whose coronary arteries were angiographically normal were enrolled in the study.

Coronary flow velocity measurements. Immediately following coronary angiography the left and right coronary arteries (in random order) were selectively engaged with a diagnostic catheter. Intracoronary nitroglycerin (200 μg) was given every 15 min of the procedure to prevent catheter-induced coronary artery spasm and to avoid changes in coronary artery diameter. A 0.014-inch (0.036-cm), 15-MHz Doppler guide wire (Jometrics FloWire, Jomed, Volcano Therapeutics, Rancho Cordova, California) was advanced through the catheter to the proximal portion of all three coronary arteries. Frequency analysis of the Doppler signals was carried out in real time by fast Fourier transform using a velocimeter (Jometrics FloMap, Jomed).

Once baseline flow-velocity data had been obtained, a bolus injection of intracoronal adenosine, 18 mg for the left and 12 mg for the RCA, was given to obtain data during hyperemia. To confirm that maximal hyperemia had been achieved, coronary blood flow velocity was recorded during administration of an additional larger dose of adenosine (4 mg larger than the initial dose). This was repeated until a plateau in flow velocity was reached.

In each artery, all measurements were made at a constant heart rate of 100 beats/min, for both patients and controls subjects, in order to exclude the influence of variant heart rate. This was accomplished by right atrial appendage pacing via a temporary pacing lead.

Time-averaged peak coronary flow velocity (APV) was measured for each vessel. Coronary flow reserve was determined as the ratio of APV at maximal hyperemia to APV at baseline. Pretreatment and method of measurements were as previously described (19).

Statistical analysis. Continuous data are summarized as mean values ± SD. Repeated measures analysis of variance (ANOVA) with one within factor at two levels (baseline, maximal hyperemia) and one between factor also at two levels (IDCM patients, control subjects) was used to assess main and interaction effects on APV. All other parameters were compared between the two groups with independent
Table 1. Regional Stress Echocardiography Parameters Measured in Patients With Idiopathic Dilated Cardiomyopathy

<table>
<thead>
<tr>
<th></th>
<th>LAD</th>
<th>LCx</th>
<th>RCA</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>r-WMSI</td>
<td>2.01 ± 0.27</td>
<td>2.10 ± 0.29</td>
<td>2.15 ± 0.34</td>
<td>NS</td>
</tr>
<tr>
<td>s-WMSI</td>
<td>1.47 ± 0.29</td>
<td>1.43 ± 0.28</td>
<td>1.42 ± 0.46</td>
<td>NS</td>
</tr>
<tr>
<td>δ-WMSI (%)</td>
<td>27.7 ± 10.4</td>
<td>32.1 ± 8.6</td>
<td>34.5 ± 17.3</td>
<td>NS</td>
</tr>
</tbody>
</table>

LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; NS = nonsignificant; δ-WMSI = contractile reserve; r-WMSI = wall motion score index at rest; RCA = right coronary artery; s-WMSI = wall motion score index at peak stress.

RESULTS

Of the 16 patients initially included in the study, two had poor-quality recordings; these patients were excluded from the final analysis. For the remaining 14 patients (10 men), the mean age was 52.9 ± 12.1 years.

In the control group, which included eight men, the mean age was 53.1 ± 8.4 years. Six of them had non-typical chest pain syndrome with a negative or nondiagnostic exercise electrocardiogram. The remaining five were asymptomatic and had cardiac catheterization for episodes of nonsustained ventricular tachycardia.

There were no significant differences between patients and controls concerning age, gender, or systolic (122 ± 17 mm Hg vs. 126 ± 11 mm Hg) and diastolic (69 ± 9 mm Hg vs. 74 ± 8 mm Hg) blood pressures.

The mean LV ejection fraction was 33 ± 7% in patients with IDCM and 66 ± 5% in the controls (p < 0.05), and the LV end-diastolic pressure was 14.9 ± 4.3 mm Hg and 8.2 ± 2.5 mm Hg, respectively (p < 0.05).

Stress echocardiography. In patients with IDCM the LV end-systolic diameter was 49.9 ± 7.5 mm, the end-diastolic diameter 62.6 ± 5.2 mm, the end-systolic volume 107.9 ± 30.8 cm³, and the end-diastolic volume 160.6 ± 42.4 cm³.

Patients with IDCM had increased WMSI at rest, and they exhibited a significant improvement after low-dose dobutamine echocardiography in all three vascular territories (Table 1).

Table 2. Left Anterior Descending, Left Circumflex, and Right Coronary Artery Doppler Flow Velocity Measurements in Patients With Idiopathic Dilated Cardiomyopathy and in Controls

<table>
<thead>
<tr>
<th></th>
<th>LAD</th>
<th>LCx</th>
<th>RCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>h-APV (cm/s)</td>
<td>19.6 ± 4.4</td>
<td>17.8 ± 4.7</td>
<td>15.5 ± 4.9</td>
</tr>
<tr>
<td>h-APV (cm/s)</td>
<td>54.5 ± 14.9</td>
<td>47.8 ± 12.9</td>
<td>51.8 ± 14.2</td>
</tr>
<tr>
<td>CFR</td>
<td>2.79 ± 0.43</td>
<td>3.48 ± 0.51*</td>
<td>3.43 ± 0.55*</td>
</tr>
</tbody>
</table>

h-APV = time averaged peak coronary flow velocity at baseline; CFR = coronary flow reserve; h-APV = time averaged peak coronary flow velocity at maximal hyperemia; IDCM = idiopathic dilated cardiomyopathy; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; RCA = right coronary artery.

Regional contractile reserve was 27.7 ± 10.4% in the LAD vascular territory, 32.1 ± 8.6% in the LCx vascular territory, and 34.5 ± 17.3% in the RCA vascular territory (Table 1). There were no statistically significant differences in regional contractile reserve among the three vascular territories.

Coronary flow velocity measurements. The Doppler parameters recorded at baseline and at maximum hyperemia are given in Table 2. LAD. Although there were no significant differences in APV between patients and controls at baseline, there was a significant group effect (p = 0.026) during maximal hyperemia. There was also a significant drug effect (p < 0.001) and interaction (p = 0.003).

Left anterior CFR was significantly lower in patients with IDCM than in controls (2.79 ± 0.43 vs. 3.48 ± 0.51, p < 0.05).

In patients with IDCM, LAD CFR showed a significant correlation with the corresponding contractile reserve (r = 0.75, p = 0.002) (Fig. 1) and a negative correlation with LV end-diastolic pressure (r = −0.72, p = 0.004) (Fig. 2).

LCX CFR. Although there were no significant differences in APV between patients and controls at baseline, there was a significant group effect (p = 0.028) during maximal hyperemia. There was also a significant drug effect (p < 0.001)
Right coronary artery CFR was significantly lower in patients with IDCM than in controls (3.43 ± 0.55 vs. 4.02 ± 0.73, p < 0.05). In patients with IDCM, RCA CFR showed no significant correlation with the corresponding contractile reserve and LV end-diastolic pressure.

**DISCUSSION**

This study is the first to assess coronary blood flow in all three vascular territories and compare the results with the corresponding regional contractile reserve in patients with IDCM. Our main findings were as follows: 1) there was no significant difference in baseline regional coronary flow between patients with IDCM and controls; 2) regional coronary flow at maximal hyperemia and CFR was significantly lower in patients with IDCM than in controls, indicating microvascular dysfunction; and 3) regional CFR was correlated with the corresponding contractile reserve and LV end-diastolic pressure in the LAD and LCx vascular territories.

**Coronary flow in IDCM.** Myocardial blood flow abnormalities, despite the presence of angiographically normal coronary arteries, have been documented in patients with heart failure caused by IDCM. In particular, a reduction in myocardial blood flow in response to either metabolic (2) or pharmacologic vasodilating stimuli (2–11) has been reported, consistent with our findings.

Although coronary blood flow abnormalities were initially attributed to extravascular mechanisms (7,20) as the result of LV dysfunction, more recently structural and/or functional alterations of the small coronary vessels (microcirculation), associated with the disease process, have been implicated in their pathogenesis.

The microcirculation (defined as vessels <200 μm in diameter) not only consists of a channel of passive networks but also is an active site of blood flow control. This is achieved by arterioles that have smooth muscles with a strong and immediate myogenic response (autoregulation). At rest (baseline), the capability for blood flow regulation is high, as 60% of total myocardial vascular resistance is offered by arterioles (21,22). However, when hyperemia is induced, smooth-muscle vasodilation results in dilation of the arterioles and venules with no change in the capillaries. The total myocardial vascular resistance decreases and capillary resistances now comprise 75% of the total myocardial vascular resistance. Thus, capillaries offer the most resistance to coronary blood flow during hyperemia and provide a ceiling to hyperemic blood flow (21,22). Consequently, conditions that are associated with lesser capillaries (either anatomically or functionally) are associated with reduced CFR despite the absence of coronary stenosis.

Because IDCM is associated with areas of interstitial and perivascular fibrosis (23,24), functional and/or structural changes in microcirculation could be expected and explain our findings of normal coronary flow at baseline and...
Pathophysiologic role of coronary flow abnormalities in IDCM. The previously mentioned abnormalities in endothelium-independent coronary flow regulation, in conjunction with the abnormal microvascular endothelial function that is frequently observed in these patients (9,10,25), lead to decreased hyperemic blood flow and oxygen supply. On the other hand, in IDCM oxygen demand is greater because of increased wall stress. Consequently, during stress there may emerge repeated episodes of oxygen demand-supply mismatch, myocardial ischemia, chronic myocardial hypoperfusion, myocardial hibernation, or even necrosis and deterioration of LV dysfunction that may further aggravate coronary blood flow abnormalities in a vicious circle (microvascular ischemic hypothesis).

This pathophysiologic mechanism of reciprocal interaction between flow and function is strongly supported, not only by our finding of a significant correlation between regional CFR and the corresponding contractile reserve, but also by the significant correlation between CFR and LV end-diastolic pressure, at least for the LAD and LCx vascular territories.

The absence of such correlation in RCA territory could be explained first by the smaller number of myocardial segments assigned to this vascular territory (4 instead of 5 for LCx or 7 for LAD), second by the lower number of patients analyzed (because 2 patients had left dominant coronary circulation), third by the different coronary blood flow pattern in the RCA (that is not diastolic predominant and is consequently less affected from diastolic dysfunction [26]), and last by non-homogenous involvement from the disease process.

Previous studies. Until now coronary blood flow has been assessed noninvasively, using positron emission tomography (2,4,6,8,10,11), or invasively, by measurement of either coronary flow velocity (3,7,9) or great cardiac vein flow (5). Irrespective of the method used, there is general agreement that IDCM is associated with impairment of coronary flow at maximal hyperemia leading to reduced CFR, in accordance with our findings.

In contrast, there is some controversy on coronary flow at baseline. Two studies from the same center (2,11) have shown that baseline coronary flow is reduced in patients with idiopathic LV dysfunction compared with control subjects. Nevertheless, differences in the selection criteria for the control subjects (the control group was the same in both studies) as well as in sample size may explain the discrepancy, because our study and all others (3–10) found no significant differences in baseline coronary flow.

Although data on flow velocities do not exist for all three coronary arteries, at least for the LAD, the available data from a recent invasive study (26) are comparable with our findings. In agreement with our findings, LV end-diastolic pressure has been associated with CFR in both of the other studies that examined their relation (4,11).

In a previous study (27), vascular territories with reduced CFR in patients with heart failure showed an ischemic response in the corresponding areas during dobutamine echocardiography, which is concordant with our findings. However, this was observed in the non-stenotic coronary arteries of patients with ischemic cardiomyopathy.

Study limitations. In the present study, coronary flow was assessed using intracoronary Doppler measurement of flow velocity. Although flow velocity does not actually represent volumetric flow, extensive animal studies have proved the accuracy of this technique in the assessment of changes of coronary flow (28,29). Consequently, given that flow velocities at baseline were similar in patients with IDCM and in control subjects, whereas changes in coronary artery diameter were avoided by intracoronary nitroglycerin administration, it seems reasonable to assume that flow velocity at maximal hyperemia provided a valid means of comparing coronary flow in the two groups.

The relatively small number of patients in this study is another limitation. This was due to the strict screening criteria we employed for both patients and controls, in order to exclude most of the other factors that might influence coronary microvascular flow. Despite, or perhaps because of, this and the constant heart rate in patients and controls, we were able to obtain statistically significant results.

Possible implications. According to the microvascular ischemic hypothesis in IDCM, chronic myocardial hypoperfusion and/or repetitive ischemia as the result of impaired microvascular flow cause progressive left ventricular dilation and systolic dysfunction; this in turn may affect coronary blood flow in a vicious circle.

Consequently, any intervention (pharmacologic or other) that could stop this vicious circle may halt, retard, or even reverse the evolution of the disease. This may be one of the mechanisms that could explain the beneficial effects of beta-blocker therapy in patients with dilated cardiomyopathy, as beta-blockade has been proved to increase maximal coronary blood flow and CFR (30).

Although this scenario has to be confirmed, our clinical and research approach to the evolution of the disease should perhaps be redirected towards therapies related to coronary blood flow.

Conclusions. Patients with IDCM have alterations in regional coronary flow and reduced CFR. Furthermore, the significant relationship between regional CFR and the corresponding contractile reserve indicates that microvascular dysfunction may be the key point in the progress of the disease.

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REFERENCES


