Non-invasive assessment of coronary flow reserve in idiopathic dilated cardiomyopathy: hemodynamic correlations

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Received 18 February 2004; received in revised form 10 May 2004; accepted 11 June 2004
Available online 28 July 2004

Abstract

Background

Impaired vasodilator myocardial blood flow response has been observed in dilated cardiomyopathy (DCMP). However, the mechanisms responsible for this blunted response are not clear. In the present study, we investigated whether the blunted vasodilator flow response is related to indices of left ventricular performance in patients with idiopathic dilated cardiomyopathy.

Methods and results

Eighteen DCMP patients and 12 healthy subjects (C) underwent transoesophageal echocardiography within 48 h from cardiac catheterization. Coronary flow velocity reserve (CFR) was measured in the proximal LAD as the ratio of the peak diastolic coronary flow velocity (Vd-M) after intravenous administration of adenosine to peak baseline diastolic flow velocity (Vd-R). Left ventricular (LV) mass index was positively correlated with baseline coronary diastolic velocity ($r = 0.415; p = 0.043$) and inversely correlated with coronary flow reserve ($r = -0.570; p = 0.003$). The baseline coronary diastolic velocity was higher in DCMP vs C (56 ± 13 cm/s vs 35 ± 12 cm/s; $p = 0.04$). In DCMP pts Vd-R positively correlated with end-diastolic wall stress ($r = 0.654; p = 0.01$). Vd increased in both C (96 ± 32 cm/s; $p < 0.05$ vs baseline) and DCMP patients (108 ± 20 cm/s; $p < 0.01$ vs baseline). The CFR was lower in DCMP patients vs C (1.93 ± 0.78 vs 2.99 ± 1.01; $p = 0.009$). In DCMP pts CFR was negatively correlated with right atrial pressure ($r = -0.595; p = 0.015$), LVEDP ($r = -0.576; p = 0.015$), pulmonary capillary wedge pressure (PCWP: $r = -0.772; p < 0.001$) and positively with ejection fraction (EF: $r = 0.683; p = 0.003$).

Keywords

Idiopathic dilated cardiomyopathy; Heart failure; Coronary flow reserve

Abbreviations:

LAD, left anterior descending artery; Vd-R, peak diastolic coronary velocity at rest; Vd-M, peak diastolic coronary velocity after administration of adenosine; CFR, coronary flow reserve; PCWP, pulmonary capillary wedge pressure; LVEDP, left ventricular end-diastolic pressure; RA, right atrium; EF, ejection fraction; DCMP, dilated cardiomyopathy.

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doi:10.1016/j.euje.2004.06.006
Conclusion

Pts with DCMP have lower CFR compared to controls. This blunted CFR is due to higher baseline coronary flow and reflects higher wall stress. The close relation between CFR and EF, PCWP and LVEDP suggests that not only a higher baseline Vd but also compressive forces due to left ventricular dysfunction might be responsible for the observed blunted adenosine-mediated coronary vasodilatation.

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Introduction

Structural alterations of the coronary microvasculature,\(^1,2\) humoral alterations\(^3\) and changes in coronary vasomotion\(^4\) cause myocardial ischemia and may account for the progressive left ventricular (LV) dysfunction observed in patients with idiopathic dilated cardiomyopathy (DCMP).\(^5\) In turn, extravascular compressive forces due to elevated filling pressures compromise subendocardial perfusion, and contribute to myocardial ischemia.\(^4,6\) In patients with idiopathic dilated cardiomyopathy the complex and critical interplay between myocardial metabolism and coronary perfusion is assessed by the coronary flow reserve. It is given as the ratio of hyperemic to baseline coronary diastolic velocity\(^7\) and can be evaluated non-invasively by Doppler transoesophageal echocardiography.\(^8\) In ischemic cardiomyopathy a reduced coronary flow reserve correlates with defects on nuclear perfusion scintigraphy\(^9\) and wall motion abnormalities on transthoracic echocardiography.\(^10\) In addition, recent data reported that myocardial blood flow is impaired in patients with DCMP supporting a role for ischemia in the transition from compensated to decompensated heart failure.\(^11\)

Accordingly, we compared coronary flow reserve (CFR) in DCMP patients and healthy control subjects using the transoesophageal approach.\(^8\) Because of the potential role of extravascular compressive forces in the pathogenesis of blunted coronary vasodilatation, the relations between coronary flow parameters and hemodynamic indices of LV performance were analyzed.

Methods

Patient selection

Eighteen patients with DCMP (NYHA class II–III heart failure) and 12 control subjects with atypical chest pain, angiographically normal epicardial coronary arteries, normal LV function by contrast ventriculography and no other detectable heart disease were studied at the time of diagnostic left and right heart catheterization.

Idiopathic dilated cardiomyopathy was diagnosed on the basis of a normal coronary angiogram with smooth epicardial coronary arteries and demonstration of abnormal LV function by means of contrast ventriculography. Patients presenting with atrial fibrillation or with other systemic and cardiologic disorders such as hypertrophic cardiomyopathy, valvular or hypertensive heart disease and acute pericarditis were excluded. All patients provided informed consent and the protocol was approved by the local ethical committee.

Protocol of left/right heart catheterization and coronary angiography

Coronary angiography and catheterization of the left and right sides of the heart were performed from the right femoral artery and vein. Right atrial (RA) pressure, pulmonary artery pressure and pulmonary capillary wedge pressure (PCWP) were measured by using Swan–Ganz catheter whereas LV pressure was recorded with a high tip fidelity micromanometer catheter, positioned in the LV cavity. LV angiograms were obtained in RAO and LAO position. Fast-paper speed recordings covering several respiratory cycles of LV pressure and of pulmonary artery or pulmonary capillary wedge pressure were obtained on a Gould ES 1000 multichannel recorder. LV ejection fraction (EF) was derived from the left ventricular angiogram using the area—length method.

Protocol of transoesophageal echocardiography

Transoesophageal echocardiography (HP SONOS 5000) was performed within 48 h following diagnostic left/right heart catheterization and coronary angiography. If necessary, induction of awake sedation was used. The left anterior descending artery (LAD) was visualized and Doppler signals were recorded as previously described.\(^8\) Attempts
were made to minimize the angle between the long axis of the vessel and the ultrasound beam. Maximal hyperemia was induced by intravenous adenosine at a dose of 140 μg/kg/min and measurements were repeated at steady state maximal hyperemia. Coronary flow velocity reserve (CFR) was calculated as the ratio of hyperemic (Vd-M) to basal peak coronary diastolic flow velocity (Vd-R).

Protocol of transthoracic echocardiography

Left ventricular dimensions were measured using M-mode echocardiography and the left ventricular diastolic meridional wall stress (EDW) was calculated from M-mode data in combination with pressure data, using the following formula,

\[ EDWS = 0.334 \times P \times LVID / (PWT \times (1 + PWT / LVID)) \]

where \( P \) is the left ventricular end-diastolic pressure, \( LVID \) is the left ventricular end-diastolic internal diameter and \( PWT \) is the posterior wall thickness at end-diastole.

Left ventricular mass was calculated by using the modified formula of Devereux et al. Echocardiographic assessment of LV mass and DWS was not possible in four DCMP and two control subjects due to technical limitations.

Statistical analysis

Mean and SD are expressed for the parametric data. The differences between baseline and hyperemic data within groups were tested using a paired two-tailed \( t \)-test. Differences between groups were compared using an unpaired two-tailed \( t \)-test. Hemodynamic and echocardiographic data were correlated with simple linear regression (least-squares method). Statistical significance was set at a two-tailed probability level of less than 0.05.

Results

Baseline characteristics of the study population—hemodynamic and angiographic data

Table 1 shows clinical and hemodynamic characteristics of the study population. The DCMP group consisted of seven women and 11 men (mean age, 53 ± 17 years) with an indexed LV end-diastolic volume of 139 ± 35 ml/m² and a LV ejection fraction of 31 ± 13%. For ethical reasons heart failure therapy was maintained at the time of the study and consisted of ACE-inhibitors \((n = 18)\) and diuretics \((n = 12)\). All patients were in NYHA class II—III heart failure and well compensated at the time of diagnostic left/right heart catheterization as evidenced by the PCWP. The control population consisted of 12 age-matched healthy subjects (five women, seven men; mean age 55 ± 14 years) with angiographically smooth coronary arteries. None of them were taking any cardiac medication at the time of the study. Smoking habitus and diabetes mellitus were not different between both groups.

Hemodynamic and transoesophageal Doppler data

Tables 1 and 2 summarize the hemodynamic and Doppler data of both groups at baseline and following adenosine infusion. Resting heart rate and cardiac output (CO) were similar in both groups. DCMP patients had a lower mean aortic pressure \((p = 0.04)\), a higher indexed LV end-diastolic volume \((p = 0.01)\), indexed LV end-systolic volume \((p < 0.001)\) and a lower LV ejection fraction \((p < 0.001)\) than the control group.

The baseline coronary diastolic velocity was higher in DCMP patients than in the control population \((p = 0.041)\). Adenosine infusion resulted in a rise in coronary diastolic velocity in DCMP pts \((p = 0.001)\) as well as in control subjects \((p = 0.04; \text{Fig. 1})\) whereas no significant change in heart rate, systolic and aortic blood pressure was noted in both groups. Following hyperemia the LAD diameter remained unchanged both in DCMP pts \((p = 0.532)\) and normals \((p = 0.622)\). During

### Table 1: Hemodynamic characteristics in control group and DCMP patients

<table>
<thead>
<tr>
<th></th>
<th>DCMP ((n = 18))</th>
<th>Control ((n = 12))</th>
<th>( p )-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>53 ± 17</td>
<td>55 ± 14</td>
<td>0.668</td>
</tr>
<tr>
<td>Aomean (mmHg)</td>
<td>93 ± 15</td>
<td>103 ± 21</td>
<td>0.045</td>
</tr>
<tr>
<td>CO (l/min)</td>
<td>4.56 ± 1.26</td>
<td>5.32 ± 0.58</td>
<td>0.380</td>
</tr>
<tr>
<td>EDVI (ml/m²)</td>
<td>139 ± 35</td>
<td>83 ± 26</td>
<td>0.010</td>
</tr>
<tr>
<td>ESVI (ml/m²)</td>
<td>83 ± 22</td>
<td>20 ± 9</td>
<td>0.001</td>
</tr>
<tr>
<td>EF (%)</td>
<td>31 ± 13</td>
<td>76 ± 9 &lt;0.001</td>
<td></td>
</tr>
<tr>
<td>LVEDP (mmHg)</td>
<td>18 ± 10</td>
<td>14 ± 4</td>
<td>0.315</td>
</tr>
<tr>
<td>PCWP (mmHg)</td>
<td>15 ± 11</td>
<td>15 ± 7</td>
<td>0.932</td>
</tr>
<tr>
<td>RA (mmHg)</td>
<td>5 ± 4</td>
<td>7 ± 6</td>
<td>0.499</td>
</tr>
</tbody>
</table>

Data presented are mean value ± SD. Aomean, mean aortic pressure; LVEF, left ventricular ejection fraction; PCWP, pulmonary capillary wedge pressure; LVEDP, left ventricular end-diastolic pressure; LVEDV, left ventricular end-diastolic volume; HR, heart rate; \( *p < 0.001 \) compared to rest; \( **p = 0.04 \) compared to rest.
maximal vasodilation, diastolic coronary flow velocity was similar in both groups ($p = 0.628$). Subsequently, coronary flow velocity reserve was significantly lower in DCMP patients compared to the control group ($p = 0.009$).

Correlations between coronary flow velocity reserve and hemodynamic data

LV mass index correlated with Vd-R ($r = 0.415$; $p = 0.043$) and inversely correlated with CFR ($r = -0.570$; $p = 0.003$; Fig. 2). In DCMP patients a significant correlation was observed between Vd-R and end-diastolic wall stress (Vd rest vs EDWS: $r = 0.654$, $p = 0.011$; Fig. 3; $n = 14$). In this group CFR inversely correlated with RA pressure (CFR vs RA pressure: $r = -0.595$, $p = 0.015$), PCWP (CFR vs PCWP: $r = -0.772$, $p < 0.001$), LV end-diastolic pressure (CFR vs LVEDP: $r = -0.576$, $p = 0.015$; Fig. 4) and positively with ejection fraction.

### Table 2  Hemodynamic and echocardiographic data during adenosine infusion

<table>
<thead>
<tr>
<th></th>
<th>DCMP</th>
<th>Control</th>
<th>$p$-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$(n = 18)$</td>
<td>$(n = 12)$</td>
<td></td>
</tr>
<tr>
<td>BP syst pre (mmHg)</td>
<td>118 ± 16</td>
<td>149 ± 33</td>
<td>0.003</td>
</tr>
<tr>
<td>BP syst post (mmHg)</td>
<td>113 ± 12</td>
<td>140 ± 18</td>
<td>0.011</td>
</tr>
<tr>
<td>BP diast pre (mmHg)</td>
<td>72 ± 9</td>
<td>85 ± 14</td>
<td>0.007</td>
</tr>
<tr>
<td>BP diast post (mmHg)</td>
<td>73 ± 12</td>
<td>82 ± 13</td>
<td>0.056</td>
</tr>
<tr>
<td>HR pre (bpm)</td>
<td>92 ± 18</td>
<td>80 ± 19</td>
<td>0.103</td>
</tr>
<tr>
<td>HR post (bpm)</td>
<td>96 ± 18</td>
<td>83 ± 19</td>
<td>0.076</td>
</tr>
<tr>
<td>Vd-R (cm/s)</td>
<td>56 ± 13</td>
<td>35 ± 12</td>
<td>0.041</td>
</tr>
<tr>
<td>Vd-M (cm/s)</td>
<td>108 ± 20**</td>
<td>96 ± 23**</td>
<td>0.628</td>
</tr>
<tr>
<td>CFR</td>
<td>1.93 ± 0.78</td>
<td>2.99 ± 1.01</td>
<td>0.009</td>
</tr>
<tr>
<td>LV mass (gm/m²)</td>
<td>3.7 ± 0.5</td>
<td>3.9 ± 0.4</td>
<td>0.234</td>
</tr>
<tr>
<td>LAD baseline (mm)</td>
<td>3.9 ± 0.6</td>
<td>4.1 ± 0.5</td>
<td>0.132</td>
</tr>
<tr>
<td>LAD hyperemia (mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data presented are mean value ± SD. BP, blood pressure; HR, heart rate; Vd-R, coronary diastolic velocity at rest; Vd-M, peak coronary diastolic velocity at the end of the adenosine infusion; LAD, left anterior descending artery. *$p < 0.001$ compared to rest; **$p = 0.04$ compared to rest.

![Figure 1](image1.png)  
**Figure 1**  Coronary diastolic velocity (Vd) at baseline (grey bar) and during adenosine induced hyperemia (black bar). Infusion of adenosine resulted in a significant rise in Vd in both groups.

![Figure 2](image2.png)  
**Figure 2**  Correlation between LV mass index and Vd at baseline (upper panel) and between LV mass index and CFR in the whole study population.

![Figure 3](image3.png)  
**Figure 3**  Correlation between end-diastolic wall stress (EDWS) and CFR in DCMP pts ($n = 14$).
fraction ($r = 0.683; p = 0.003$; Fig. 4). Similar correlations were absent in the control group.

**Discussion**

The present study demonstrates that in patients with dilated cardiomyopathy, reduced coronary flow velocity reserve is due to higher baseline flow rather than a decreased hyperemic flow. In addition, baseline flow correlates inversely with LV filling pressures. Furthermore, higher baseline flow is related to higher LV end-diastolic wall stress and parallels an increase in LV mass.

**CFR and LV hemodynamics**

The present study corroborates previous studies demonstrating a blunted myocardial blood flow response in patients with congestive heart failure. However, unlike in patients with ischemic cardiomyopathy, this low CFR does not result from epicardial narrowing or microvascular resistive dysfunction. In contrast, in patients with DCMP, previous studies suggested that elevated neurohormones, a blunted response of the microcirculation for adenosine, and an impaired endothelium dependent and independent vasodilatory capacity of the epicardial conduit arteries and the microcirculation are responsible for the observed blunted vasodilator response. Our study identifies two additional mechanisms that may contribute to the reduced CFR. First, baseline coronary flow was higher in patients with dilated cardiomyopathy than in normals. This is consistent with the persistent resting microvascular vasorelaxation and could by itself account for the lower CFR. Of note, baseline coronary flow was linearly related to LV mass index. Since, an increase in LV mass in patients with dilated cardiomyopathy is chiefly achieved by LV dilation without increase in wall thickness, it raises the hypothesis that hemodynamic stress may be responsible for the higher baseline flow. Consistent with this hypothesis, baseline coronary flow was strongly related to LV diastolic wall stress. Similar observation was reported by van den Heuvel et al., who also observed that blunted myocardial blood flow was related to the degree of LV wall stress. Since wall stress is strongly related to myocardial oxygen requirements, the observed parallel increase in baseline flow with higher LV mass and wall stress suggests higher metabolic needs in these patients. Thus, these data support the hypothesis that a lower CFR observed in dilated cardiomyopathy patients is partly related to higher baseline myocardial blood flow due to elevated metabolic needs. Second, coronary flow velocity reserve correlated

**Figure 4** Correlation between LV contractile parameters and CFR. Correlation between right atrial pressure (RA), pulmonary capillary wedge pressure (PCWP), LV end-diastolic pressure (LVEDP), ejection fraction (EF) and CFR in DCMP pts.
significantly with several indices of contractile performance. Patients with blunted coronary flow reserve were characterized by a lower ejection fraction, and higher LV filling pressures. This observation strongly suggests that increased diastolic compressive forces may affect the interaction between coronary flow and metabolism and contribute to the blunted microvascular vasodilator response. Our findings are consistent with recent animal and human data that demonstrated similar relations between myocardial blood flow reserve and LV hemodynamic profile.

Ischemia, myocardial stunning and idiopathic dilated cardiomyopathy

These data also support the hypothesis that relative ischemia may contribute to the progression of LV dysfunction in idiopathic dilated cardiomyopathy. In experimental setting of chronic low-flow ischemia, increased baseline coronary diastolic velocity and blunted coronary flow reserve were postulated as mechanisms of myocardial stunning and chronic myocardial dysfunction after episodes of demand ischemia. Whether ischemia plays a pivotal role in the LV dysfunction observed in idiopathic dilated cardiomyopathy and therefore whether a form of myocardial stunning in the absence of any coronary constriction or occlusion could be present in these patients remains unclear. We hypothesized that since DCMP patients with low coronary flow reserve are characterized by a higher baseline coronary diastolic velocity and wall stress, any increase in metabolic needs could not be met by an appropriate rise in coronary blood supply and could lead to a demand ischemia. Consistent with this hypothesis, in a dog model of heart failure due to cardiac hypertrophy, LV contractile dysfunction appeared to be related to blunted blood flow reserve and relative ischemia. Moreover, recent human PET data also related impaired myocardial blood flow to regional ischemia in patients with dilated cardiomyopathy. In addition, endomyocardial fibrosis was noted mostly in patients with high LV end-diastolic pressure and severely depressed myocardial perfusion which also fits with the hypothesis that ischemia contributes to LV dysfunction in patients with DCMP.

Limitations

There are several limitations of our study. First, several pitfalls of Doppler TEE of the left anterior descending should be considered. By this technique, the true coronary velocity could be over- or underestimated according to the alignment of a Doppler sampling. Nevertheless, this limitation is canceled out by calculating the CFR as a ratio of peak to baseline flow velocities. Second, we only measured coronary flow velocities and not absolute coronary or myocardial blood flow. Nevertheless, previous studies failed to demonstrate significant changes in proximal coronary diameter during adenosine infusion. This appears to justify the extrapolation of the flow velocity data to estimations of the absolute flow. Third, although TEE guided assessment of CFR has a relative good sensitivity, its specificity varies. In addition the technique is limited to the proximal LAD and therefore it remains difficult to extrapolate the results to the other coronary territories. However, as we are dealing with patients with normal coronary arteries one could speculate CFR to be similar in the other coronary arteries. Finally, we measured a CFR index using a simple ratio of two peak velocities. This, as previously pointed out by others, is, however a reliable indicator of CFR.

Conclusions and clinical implications

The reduced absolute coronary flow reserve after adenosine administration in patients with idiopathic dilated cardiomyopathy and its relation to LV contractile function supports the hypothesis that extravascular compressive forces modulate the coronary flow response. Higher metabolic needs due to elevated wall stress as well as the increase in LV mass result in higher baseline coronary diastolic velocities. We hypothesize that during periods of stress, ischemia and subsequently heart failure develop since increased metabolic needs are not fully halted by an appropriate rise in coronary blood flow. Beta-blockers alleviate the imbalance between oxygen supply and demand, reduce ischemia, improve wall motion abnormalities and favourably affect coronary flow reserve. The recently reported beneficial effects of this class of medications in DCMP could reflect, at least in part, restoration of this blunted coronary flow reserve. Further studies are needed to address these issues.

References


