Evaluation of Myocardial Blood Flow Reserve in Patients With Chronic Congestive Heart Failure Due to Idiopathic Dilated Cardiomyopathy

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This study demonstrates a significant impairment in coronary blood flow reserve in most patients with idiopathic dilated cardiomyopathy despite normal epicardial coronary arteries. This change may prevent appropriate increases in coronary blood flow and thus lead to myocardial ischemia and progression of disease. An association between decreased response to adenosine and acetylcholine supports previous observations indicating that adenosine-induced vasodilation of coronary microcirculation is dependent on endothelial nitric oxide production. ©2003 by Excerpta Medica, Inc.

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Impairment of myocardial blood flow reserve has been described in patients with idiopathic dilated cardiomyopathy (IDC) despite normal epicardial coronary arteries, and may lead to myocardial ischemia, progression of congestive heart failure (CHF) and increased mortality. Data on coronary flow reserve in IDC have been limited to either a few subjects, patients with new-onset CHF symptoms, or those with only mild to moderate symptoms (some without angiographic evidence for normal coronary arteries). The present study evaluates the incidence of myocardial blood flow impairment in IDC and angiographically normal coronary arteries.

TABLE 1 Characteristics of Patients With Idiopathic Dilated Cardiomyopathy (IDC) and Their Matched Controls

<table>
<thead>
<tr>
<th>Variable</th>
<th>IDC (n = 25)</th>
<th>Controls (n = 25)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>20 [80%]</td>
<td>20 [80%]</td>
<td>1.0</td>
</tr>
<tr>
<td>Age [yrs]</td>
<td>46 ± 13</td>
<td>47 ± 12</td>
<td>0.85</td>
</tr>
<tr>
<td>Body surface area [m²]</td>
<td>1.9 ± 0.2</td>
<td>2.0 ± 0.4</td>
<td>0.36</td>
</tr>
<tr>
<td>Total cholesterol [mg/dl]</td>
<td>154 ± 36</td>
<td>203 ± 41</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ejection fraction [%]</td>
<td>24 ± 9</td>
<td>65 ± 9</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

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Twenty-five clinically stable patients with a history of severe (New York Heart Association functional class III and IV), chronic (>3 months) CHF and angiographically normal coronary anatomy were included in the study. The study consisted of 20 men and 5 women (aged between 21 and 77 years [mean 46 ± 13]) with left ventricular systolic dysfunction documented by either contrast angiography or echocardiography. Mean angiographic left ventricular ejection fraction (21 patients) was 24 ± 9%. Mean hemodynamic values during cardiac catheterization were heart rate 91 ± 3 beats/min, mean blood pressure 92 ± 13 mm Hg, mean right atrial pressure 10 ± 9 mm Hg, mean pulmonary arterial pressure 30 ± 12 mm Hg, mean pulmonary capillary wedge pressure 20 ± 10 mm Hg, cardiac index 2.0 ± 0.6 L/min/m², systemic vascular resistance 1,738 ± 522 dynes·s·cm⁻⁵, and pulmonary vascular resistance 252 ± 186 dynes·cm⁻⁵.

Twenty-five age- and sex-matched patients who underwent cardiac catheterization for chest pain with normal left ventricular function and no evidence of obstructive coronary disease were used as a control group. All cardiovascular medications had been discontinued for ≥16 hours before cardiac catheterization, with nitroglycerin not being used during the procedure. A Doppler guidewire (FloWire; Endosonics Corp., Rancho Cordova, California), 0.014/0.018 inch in diameter was positioned in the midportion of the left anterior descending coronary artery, and baseline mean peak velocity was recorded. Intracoronary bolus injections (18 to 36 μg) of adenosine, a coronary vasodilator with a predominant effect on resistance vessels, were injected into the guiding catheter positioned in the ostium of the left main coronary artery to achieve maximal hyperemia, and the maximal mean peak velocity was recorded. After a 5-minute equilibration period, baseline mean peak velocity was recorded, followed by coronary angiography with use of nonionic contrast medium (Omnipaque, Amersham Health, Little Chalfont, Buckinghamshire, United Kingdom). Acetylcholine at concentrations of 10⁻⁶ M, 10⁻⁵ M, and 10⁻⁴ M to achieve estimated final blood concentrations in the coronary bed of 10⁻⁵ M, 10⁻⁴ M, and 10⁻³ M were infused for 3 minutes each when Doppler measurements and coronary angiography were repeated. To assure reproducibility of angiographic technique, the angles, skew rotation, and table height were kept constant during angiography, and the distances between the image intensifier and the x-ray tube to the patient were also kept the same. Coronary artery diameter was measured from cine films—5-mm distal to the tip of the Doppler wire—by an independent technician, with use of a computer-based image analysis system, as previously described.6 Inter- and intraobserver variabilities were randomly examined in 40 patients; their values were 7.0%, and 4.3%, respectively. Coronary blood flow (CBF) at baseline and during acetylcholine infusion was calculated from the Doppler mean peak velocity and vessel diameter using this formula: CBF = πr²v (mean peak velocity/2) (coronary artery diameter/2).2 Normal coronary flow reserve was defined as an increase of ≥2.5 in flow velocity after intracoronary administration of adenosine.7 The incidence of abnormal response to adenosine in patients with IDC and their control subjects was compared with Fisher’s exact test. Mean differences in response to both adenosine and acetylcholine between patients with IDC and the control group were analyzed using the paired t test. Differences between responders and nonresponders to adenosine were analyzed using the unpaired t test. All numeric data were reported as mean ± 1 SD. A p value <0.05 was considered statistically significant.
A comparison of demographic data between the studied patients and their control subjects is shown in Table 1. There were no statistically significant differences in age, gender, and body surface area between groups. In contrast, both mean total serum cholesterol and left ventricular ejection fraction were significantly higher in the control group. Patient values of adenosine-induced increase in flow in the IDC group varied between 0.9 and 5.2 times baseline. The group change in flow was significantly decreased in the IDC group when compared with that in the control group (2.2 ± 0.9 vs 3.3 ± 0.8, p = 0.00004 (Figure 1). An abnormal response to adenosine was seen in 18 patients with IDC (72%) and in 4 controls (16%) (p = 0.0002). A comparison between patients with normal responses (responders, n = 7) and those with abnormal responses (nonresponders, n = 18) to adenosine revealed no significant difference in age (39 ± 14 vs 49 ± 12 years, p = 0.08), left ventricular ejection fraction (22 ± 7% vs 25 ± 10%, p = 0.54), or any of the measured or calculated hemodynamic parameters. However, there was a significant difference in the acetylcholine-induced increase in coronary artery diameter and CBF (Figure 2) between the 2 groups (10 ± 12% and 163 ± 78%, respectively in responders vs -4 ± 13% and 58 ± 85%, respectively, in nonresponders; p = 0.01 for both). A comparison of the 2 subgroups with their control patients showed no significant difference in the adenosine-induced increase in flow in responders (3.3 ± 0.94 vs 3.4 ± 0.8 p = 0.79), but a significant difference between nonresponders and their controls (1.8 ± 0.4 vs 3.3 ± 0.8, p <0.00001; Figure 3).

The present report provides strong evidence for a limited vasodilatory capacity of the coronary microcirculation in most patients with chronic, severe CHF due to IDC despite angiographically normal epicardial coronary arteries. Potential causes for this finding include retention of sodium and water in the vascular wall as well as vasoconstriction due to enhanced levels of catecholamines, angiotensin, and endothelin or decreased prostaglandin production.9 Attenuated response to adenosine may also be due to vascular wall structural abnormalities, including alteration of extracellular matrix and vascular remodeling mediated by angiotensin II10,11 as well as by proinflammatory cytokines, tumor necrosis factor, and interleukin-1, all of which are increased in CHF.12 In contrast to our findings, Mathier et al5 described a normal microcirculatory response to adenosine in 10 patients with acute-onset IDC. The difference was probably related to a disparity in duration of CHF, as suggested by previous reports demonstrating depression of endothelium-independent peripheral vasodilation in patients with advanced but not with mild CHF,13,14 and by late development of reduced coronary response to adenosine in a canine CHF model.15 An abnormal CBF response to adenosine in patients with chronic CHF was also shown by Treasure et al,4 who reported a 422% adenosine-mediated increase in CBF in normal controls compared with 268% in patients with IDC. The results of the present study also support previous reports of impaired endothelium-dependent vascular relaxation in patients with CHF4,5,9,16 likely to be due to a loss of bioactive endothelial nitric oxide.16,17 Recent experimental studies have suggested that adenosine-induced coronary vasodilation may also be dependent on endothelial nitric oxide production.18 Attenuated CBF reserve in response to adenosine may therefore be related to nitric oxide deficiency, which has been shown to increase wall-to-lumen ratio and perivascular fibrosis in the coronary microcirculation19 and to cause alteration in the vascular matrix by an increased release of soluble collagen from vascular smooth muscle cells.20

Electrocardiographic Findings in Patients >100 Years of Age Without Clinical Evidence of Cardiac Disease

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Centenarians have a higher incidence of atrial fibrillation, left-axis deviation, premature beats, first-degree atrioventricular block, and nonspecific ST-T changes. Fewer men live long enough to reach 100 years of age, and they tend to have more significant conduction defects and old myocardial infarcts than women. ©2003 by Excerpta Medica, Inc. (Am J Cardiol 2003;92:1249–1251)

Since Balfour’s “The Senile Heart” (1896), a number of studies have been published that have attempted to define the geriatric electrocardiogram. Earlier published reports suggest that changes in conduction, voltage, and electrical axis could be expected in the aged as a result of the normal aging process. Work by previous investigators has suggested that the higher incidence of nonspecific ST-T changes, prolonged PR intervals, and left-axis deviation occur more frequently in older people. It is difficult to assess whether such changes in the geriatric population are due to the normal aging process or a reflection of underlying subclinical heart conditions, namely coronary artery disease, congestive heart failure, and age-related cardiac amyloidosis.

The study population was identified from electrocardiograms referred to our electrocardiography service from 1985 to 1995 in Nebraska. We included electrocardiograms of 132 people who were aged >100 years and were not confined to home or a nursing home but were seen either on visits to the office or on recent admission to outlying hospitals. No cardiovascular-related diagnosis was quoted in the indication for the test. Electrocardiograms were interpreted independently by 2 cardiologists according to the guidelines from the modified Minnesota code (1982). In cases of disagreement, the coding was settled by joint interpretation of the electrocardiogram.

Only unequivocal and clearly defined axis deviation and arrhythmias were included in the group with abnormal electrocardiograms. The electrocardiogram was considered abnormal if ST-T changes were seen in leads other than III and V_6. Normal QRS axis was between −30° and +120°. Sinus arrhythmia, sinus bradycardia and sinus tachycardia, and <6 premature beats/12-lead electrocardiogram were included in the group with abnormal electrocardiograms. The prevalence of electrocardiographic abnormalities between men and women was compared by chi-square or Fisher’s exact tests when expected frequencies were <5. Continuous parameters derived from the electrocardiogram were compared using Student’s t test.

Women outlived men in the centenarian group. Women were at least 3 times men in number (73% vs 27%). Mean age of the study population was 104 ± 2.5 years. The average age of centenarian women was 106 years and that of men, 102 years. Only 7% of the participants (all women) had normal electrocardiograms. There were 68% who had a normal sinus rhythm.

The most frequent electrocardiographic abnormalities found were atrial fibrillation (30%), first-degree atrioventricular block (17%), left-axis deviation (17%), left bundle branch block (17%), premature beats (23%; both premature atrial complexes and ventricular premature contractions), and left anterior hemiblock (13%). Men had a statistically significant higher incidence of left-axis deviation (p <0.001), third-degree atrioventricular block (p <0.001), aggregate intraventricular conduction defects (p = 0.004), aggregate atrioventricular conduction defects (p = 0.03), and old anterior infarcts (p = 0.025) than women. Men also had a higher incidence of myocardial infarction in the anterior (8% vs 1%) and inferior (17% vs 4%) regions. Women had a higher incidence of normal QRS axes (p = 0.001), atrial fibrillation, ST-segment depression, and normal electrocardiograms (Tables 1 and 2).

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