Endothelium-Dependent Dilation of the Coronary Microvasculature Is Impaired in Dilated Cardiomyopathy

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Dilator reserve of the coronary microvasculature is diminished in patients with dilated cardiomyopathy. Although increased extravascular compressive forces, tachycardia, and increased myocardial mass can explain some impairment, recent evidence suggests the possibility of intrinsic microvascular disease. We tested the hypothesis that impairment of endothelium-dependent dilation of the microvasculature could be a contributing mechanism. We infused the endothelium-dependent dilator acetylcholine (Ach) (10^{-7} to 10^{-6} M) and the smooth muscle vasodilator adenosine (AD) (10^{-4} to 10^{-3} M) into the left anterior descending coronary artery in eight patients with dilated cardiomyopathy (mean ejection fraction, 28%) and seven controls (atypical chest pain). Small vessel resistance was assessed by measuring coronary blood flow (CBF) at constant arterial pressure with a Doppler velocity catheter (corrected for cross-sectional area by angiography). With Ach, control patients increased CBF 232±40% (mean±SEM), whereas CBF did not significantly change in cardiomyopathy patients (41±24%) (p<0.0001, control vs. cardiomyopathy). With AD, control patients increased CBF 422±56% and cardiomyopathy patients increased CBF 268±43% (p=0.13). An index of the proportion of coronary flow reserve attributable to endothelium-dependent vasodilation was obtained by standardizing each patient’s Ach dose response to his maximal AD flow response. In seven control patients receiving both Ach and AD, 56±9% of the maximal AD flow response was attained with the endothelium-dependent vasodilator Ach, whereas in seven cardiomyopathy patients receiving both Ach and AD, only 23±14% of the maximal AD response was attained (p<0.01). Thus, endothelium-dependent vasodilator function is impaired in the coronary microvasculature of patients with dilated cardiomyopathy. There might be pathogenetic links between dysfunction of the endothelium and myocardial failure. (Circulation 1990;81:772–779)

Coronary flow reserve is diminished in patients with dilated cardiomyopathy (DC). Elevated filling pressures, increased heart rate, decreased coronary perfusion pressure, and increasing left ventricular mass out of proportion to microvascular growth can partially account for the impairment of flow reserve. Intrinsic microvascular disease can also be present.

Although morphologic changes have been reported in the microvasculature of hypertrophic hearts,6,7 most investigators have found no evidence of microvascular structural abnormalities in DC.8,9 In patients with idiopathic DC and chest pain, however, Cannon et al8 found an increased sensitivity to ergonovine in the setting of increased microvascular resistance. In 12 patients with DC and a history of chest pain, ergonovine precipitated anginal symptoms in 11. Factor10–12 and others13 have found evidence of coronary microvascular spasm in the developmental stages of the hereditary cardiomyopathy in Syrian hamsters. Calcium channel antagonists

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effectively prevented microvascular spasm and averted the development of cardiomyopathy, suggesting an etiologic role of the microvasculature in this disease.

The vascular endothelium has been recognized as playing a pivotal role in maintaining vascular tone through the release of endothelium-derived relaxing factor(s) (EDRF). EDRF-mediated vasodilatation is seen in both large and small coronary vessels in response to a variety of agents including acetylcholine. Loss of normal endothelial function in atherosclerosis, Kawasaki’s, and other diseases might predispose the patient to vasospasm.

The goals of this study were to determine whether endothelium-dependent vasodilator function is abnormal in DC and whether this abnormality could contribute to the disturbed coronary flow regulation found in this disease.

**Methods**

**Patient Population**

Eight patients with DC (defined as markedly impaired left ventricular systolic function with no epicardial atherosclerotic coronary artery disease detectable by angiography) and seven normal controls (atypical chest pain) undergoing diagnostic catheterization were studied. All patients had angiographically normal coronary arteries. Patients with valvular heart disease, hypertrophic cardiomyopathy, hypertensive heart disease, congenital heart disease, evidence of restrictive or constrictive physiology, or uncontrolled heart failure (pulmonary capillary wedge pressure >25 mm Hg at the time of catheterization) were excluded.

**Protocol**

Written informed consent was obtained from all patients before the diagnostic catheterization, in accordance with guidelines established by the Committee for the Protection of Human Subjects at Brigham and Women’s Hospital. Nitrates, calcium channel antagonists, β-adrenergic receptor blocking drugs, and angiotensin converting enzyme inhibitors were discontinued 18–24 hours before catheterization.

Diagnostic right and left heart catheterization and coronary angiography were performed by a standard percutaneous femoral approach. After completion of the diagnostic catheterization, an additional 5,000 units of heparin were given intravenously and an 8F guiding catheter was positioned in the ostium of the left coronary artery. A 20 MHz pulsed Doppler crystal mounted on the tip of a 2.5F infusion catheter (Millar Instruments Inc., Houston, Texas) was advanced through the guiding catheter into the proximal segment of the left anterior descending artery (LAD). The use of this device to assess changes in intracoronary blood flow velocity has been described in detail. The Doppler catheter was connected to a photographic multichannel oscillographic recorder (Electronics for Medicine VR16, Pleasantville, New York) to display phasic and mean velocity waveforms. Before beginning the experimental protocol, the position of the Doppler flow velocity catheter and the range gate control were adjusted to optimize the audio flow velocity signal and the phasic flow velocity waveform. The Doppler catheter position and the range gate control were not changed thereafter.

Serial 2-minute intracoronary infusions of acetylcholine and adenosine were administered at 0.8 ml/min through the central lumen of the Doppler catheter in the following sequence: control (5% dextrose with heparin 1 unit/ml); graded concentrations of acetylcholine (to achieve estimated final blood concentrations of $10^{-8}$, $10^{-7}$, and $10^{-6}$ M based on assumed LAD blood flow of 80 ml/min in normal subjects and in patients with DC), repeat control (0.9% sodium chloride), and graded concentrations of adenosine (Sigma Chemical Co., St. Louis, Missouri) (to achieve estimated final blood concentrations of $10^{-6}$, $10^{-5}$, and $10^{-4}$ M assuming resting blood flow in the LAD of 80 ml/min). With the increase in blood flow observed at higher doses, the actual concentrations were proportionately lower. Just before the end of each infusion, coronary arteriography was performed in biplane orthogonal views with the use of a power injection of nonionic contrast medium (Omniopaque, Winthrop-Breon, New York). Throughout each infusion, the heart rate, arterial pressure, coronary flow velocity, and electrocardiogram (lead I) were monitored continuously, and all measurements were recorded in steady-state conditions.

**Quantitative coronary angiography.** Quantitative coronary angiography was performed by a previously validated technique. Nonionic contrast medium was injected into the left coronary artery at the rate of 5–10 ml/sec to a total of 7–12 ml with the use of a power injector (Medrad, Pittsburgh, Pennsylvania) to optimize the quality and reproducibility of the injections. A biplane system (Polydiagnost-C, Philips Medical Systems, Inc., Shelton, Connecticut) with two image intensifiers was used, and the LAD was positioned in the center of each field of view and at a single position in space (isocenter).

**Analysis of arterial dimensions.** Quantitative angiography of the epicardial coronary artery was performed for two reasons. The first purpose was to determine cross-sectional area near the Doppler tip to convert flow velocity to an estimate of coronary arterial flow. (As shown in Figure 1, an arterial segment 2–4 mm distal to the Doppler tip was selected for quantitative analysis in all patients.) The second purpose was to exclude limitations of coronary artery flow due to epicardial coronary artery constriction in response to acetylcholine (flow limitation defined as >50% diameter constriction in the most constricting segment). Quantitative angiographic analysis was similar to that described in previous studies. The four digitized cine frames for each infusion were summed and averaged along the segment profile to give a mean diameter and standard deviation at each point. A single mean and a
pooled standard deviation for the segment (at each infusion) were obtained by averaging each of these measurements along the segment profile. Suitable segments were required to have a mean standard deviation less than 5% of the mean diameter.

**Estimates of coronary blood flow changes.** Estimates of relative changes in coronary blood flow were made by correcting changes in mean coronary blood flow velocity, as measured directly by the Doppler catheter, for changes from control in estimated vessel cross-sectional area at the catheter tip as determined from the change in diameter measured in the optimal single plane view.

**Statistical Analysis**

Differences in dose-response curves to serial doses of acetylcholine and adenosine were evaluated among groups by analysis of covariance for repeated measures. Differences in individual doses from baseline were evaluated with one-sample t tests. Differences in hemodynamic and echocardiographic parameters were analyzed by Wilcoxon rank sum tests. Statistical significance was assumed if the null hypothesis (two-tailed) could be rejected at the 0.05 probability level. All data are expressed as the mean±SEM.

**Results**

**Baseline Clinical and Hemodynamic Characteristics**

Patients with DC were 46±7 years old (range, 19–68 years); all were male (Table 1). One DC patient had a significant history of alcohol ingestion (1.4 quarts of brandy per day for 20 years), and two DC patients had a history of alcohol use in quantities reported to be inadequate to cause myocardial dysfunction (six beers per night for 15 years and four beers per night for 10 years). Two DC patients had a family history of DC.

Six of eight DC patients underwent endomyocardial biopsy. Marked myocyte hypertrophy and fibrosis were present on all six specimens. No patient had active myocarditis on biopsy.

Control patients (C) were 40±2 years old (range, 31–48 years). One was female (Table 2). They consisted of patients with atypical chest pain, normal wall thickness and ventricular function on echocardiogram, and angiographically normal coronary arteries at the time of catheterization.

Echocardiographic evaluation revealed a left ventricular posterior wall thickness of 1.1±0.1 cm in DC patients and 0.99±0.01 cm in C patients (p=0.04), left ventricular end-diastolic dimension of 7.0±0.4 cm in DC patients and 5.0±0.1 cm in C patients (p<0.001), and left ventricular end-systolic dimension of 5.9±0.4 cm in DC patients and 3.1±0.2 cm in C patients (p<0.0001).

The mean baseline heart rate of DC patients was 75±4 beats/min versus 63±3 beats/min for C patients (p=0.05). The mean baseline systemic arterial pressure was 90±5 mm Hg for DC patients and 89±6 mm Hg for C patients (p=NS). Left ventricular end-diastolic pressure was 14±2 mm Hg in DC patients and 12±2 mm Hg in C patients (p=NS). Left ventricular ejection fraction was 0.28±0.03 for DC patients (by ventriculography) and 0.76±0.04 for...
C patients (by ventriculography in four and echocardiography in three) \((p<0.0001)\).

**Systemic Hemodynamic Responses**

Heart rate did not change significantly with acetylcholine or adenosine in either group (DC [beats/min]: baseline, 75±4; peak acetylcholine, 74±3; recontrol, 70±5; peak adenosine, 76±4; and C [beats/min]: baseline, 63±3; peak acetylcholine, 62±3; recontrol, 62±4; peak adenosine, 59±4; all, \(p=NS\)). Mean systemic arterial pressure did not change significantly with acetylcholine in either group (DC [mm Hg]: baseline, 89±6; peak acetylcholine, 91±6; and C [mm Hg]: baseline, 89±6; peak acetylcholine, 89±8; \(p=NS\)). Mean systemic arterial pressure did increase slightly with adenosine in both groups but this change did not reach statistical significance (DC [mm Hg]: recontrol, 93±4; peak adenosine, 98±7, \(p=0.50\); C [mm Hg]: recontrol, 89±7; peak adenosine, 96±8; \(p=0.52\)). One C patient experienced flushing and a mild headache that resolved promptly after discontinuation of the adenosine infusion.

**Quantitative Analysis of Epicardial Dimensions**

Quantitative analysis of the epicardial coronary artery was performed 2–4 mm distal to the Doppler tip to allow estimation of relative changes in coronary blood flow from measured changes in coronary blood flow velocity. At peak dose of acetylcholine, epicardial arteries constricted 6±3% in patients with DC and 2±6% in normal controls \((p=NS)\). Large vessels uniformly dilated 15±4% at peak dose in patients with DC who were treated with adenosine, and 23±2% in normal controls \((p=NS)\).

**Coronary Flow Responses**

Infusion of acetylcholine over the range of \(10^{-8}\) to \(10^{-6}\) M into the LAD coronary artery produced a dose-dependent increase in estimated coronary blood flow in C patients but not in DC patients (Figure 2). Estimated blood flow did not change in DC patients (24±17% with \(10^{-8}\), 26±18% with \(10^{-7}\) and 41±24% with \(10^{-6}\) M acetylcholine; all, \(p>0.05\) vs. baseline value). C patients experienced an

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**Table 1. Clinical Characteristics of Dilated Cardiomyopathy Patients**

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>History</th>
<th>Symptoms</th>
<th>Treatment</th>
<th>LVPWT</th>
<th>LVEDD</th>
<th>LVEDS</th>
<th>HR</th>
<th>MAP</th>
<th>LVEDP</th>
<th>LVEF</th>
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<td>M</td>
<td>FH of CM</td>
<td>SOB, Arrh</td>
<td>D,A</td>
<td>1.4</td>
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<td>Ethanol</td>
<td>SOB</td>
<td>D,Dig,AC</td>
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<td>6.0</td>
<td>4.8</td>
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<td>96</td>
<td>4</td>
<td>0.30</td>
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<tr>
<td>63</td>
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<td>IDIO(ETOH)</td>
<td>SOB, Arrh</td>
<td>D,A</td>
<td>1.0</td>
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<td>4.7</td>
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<td>103</td>
<td>7</td>
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</tr>
<tr>
<td>63</td>
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<td>7.1</td>
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<td>66</td>
<td>104</td>
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</table>

Mean±SEM

46±7 1.1±0.1 70±0.4 5.9±0.4 75±4 90±5 14±2 0.28±0.03

LVPWT, left ventricular posterior wall thickness (cm); LVEDD, left ventricular end-diastolic dimension (cm); LVEDS, left ventricular end-systolic dimension (cm); HR, heart rate (beats/min); MAP, mean arterial pressure (mm Hg); LVEDP, left ventricular end-diastolic pressure (mm Hg); LVEF, left ventricular ejection fraction (%). FH of CM, family history of dilated cardiomyopathy; SOB, shortness of breath (with exertion or while reclining); Arrh, arrhythmias; D, diuretic; A, antiarrhythmic; Ethanol, alcoholic cardiomyopathy; Dig, digoxin; AC, anticoagulant; IDIO(ETOH), idiopathic dilated cardiomyopathy with history of alcohol intake in amounts reported to be inadequate to cause myocardial damage; C, angiotensin converting enzyme inhibitor.

**Table 2. Clinical Characteristics of Normal Controls**

<table>
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<tr>
<th>Age</th>
<th>Sex</th>
<th>Symptoms</th>
<th>Medications</th>
<th>LVPWT</th>
<th>LVEDD</th>
<th>LVEDS</th>
<th>HR</th>
<th>MAP</th>
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<th>LVEF</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>M</td>
<td>Atyp CP</td>
<td>B,CB</td>
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<td>5.2</td>
<td>3.2</td>
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<td>75</td>
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<tr>
<td>38</td>
<td>M</td>
<td>Atyp CP</td>
<td>N</td>
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<td>5.4</td>
<td>3.5</td>
<td>60</td>
<td>108</td>
<td>16</td>
<td>0.63</td>
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<tr>
<td>35</td>
<td>M</td>
<td>Atyp CP</td>
<td>B,N</td>
<td>0.9</td>
<td>5.1</td>
<td>3.0</td>
<td>60</td>
<td>111</td>
<td>11*</td>
<td>0.72†</td>
</tr>
<tr>
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<td>F</td>
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<td>CB,A</td>
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<td>66</td>
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<td>6</td>
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</tr>
<tr>
<td>48</td>
<td>M</td>
<td>Atyp CP</td>
<td>CB</td>
<td>1.0</td>
<td>5.2</td>
<td>3.5</td>
<td>54</td>
<td>81</td>
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<td>47</td>
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<td>2.4</td>
<td>72</td>
<td>92</td>
<td>13</td>
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</table>

Mean±SEM

40±2 0.99±0.01 5.0±0.1 3.1±0.2 63±3 89±6 12±2 0.76±0.04

LVPWT, left ventricular posterior wall thickness (cm); LVEDD, left ventricular end-diastolic dimension (cm); LVEDS, left ventricular end-systolic dimension (cm); HR, heart rate (beats/min); MAP, mean arterial pressure (mm Hg); LVEDP, left ventricular end-diastolic pressure (mm Hg); LVEF, left ventricular ejection fraction (%); Atyp CP, atypical chest pain; B, \(\beta\)-adrenergic receptor antagonist; CB, calcium channel blocker; N, nitrate; A, antiarrhythmic.

*Pulmonary capillary wedge pressure (mm Hg); †LVEF estimated from echocardiogram.
increase of 32±15% with $10^{-8}$, 128±40% with $10^{-7}$, and 232±40% with $10^{-6}$ M acetylcholine (p=0.07, 0.02, and 0.0004 vs. baseline value, respectively). A significant difference was demonstrated between the dose-response curves to acetylcholine (% change CBF/−log[acetylcholine]) in C (slope, 105) and DC (slope, 8) patients by analysis of covariance for repeated measures (p<0.0001). One DC patient with the most extensive history of alcohol use had a relatively preserved flow response to acetylcholine (117% increase in estimated blood flow to $10^{-6}$ M acetylcholine). Two DC patients with family histories of DC had markedly impaired flow responses to acetylcholine (0% and −15%).

Infusion of adenosine over the range of $10^{-6}$ to $10^{-4}$ M into the LAD coronary artery produced a dose-dependent increase in estimated coronary blood flow in DC and C patients (Figure 3). Estimated blood flow increased 113±19% with $10^{-6}$, 180±24% with $10^{-5}$, and 268±43% with $10^{-4}$ M adenosine in DC patients (all, p<0.05 vs. baseline value) and 163±45% with $10^{-6}$, 292±47% with $10^{-5}$, and 424±56% with $10^{-4}$ M adenosine in C patients (all, p<0.05 vs. baseline value). No significant difference between the dose-response curves to adenosine in C (slope, 134) and DC (slope, 70) patients was demonstrated by analysis of covariance for repeated measures (p=0.13).

To examine the endothelium-dependent component of vasodilation, the increase in flow to acetylcholine in each patient was standardized to his/her own maximal flow response to adenosine. These data (Figure 4) show that the acetylcholine response (endothelium-dependent), standardized to the maximal response to adenosine (endothelium-independent), was deficient in the DC patients. The standardized dose-response curve to acetylcholine in the seven DC patients who received both acetylcholine and adenosine (slope, 0.07) was significantly lower than the standardized dose-response curve to acetylcholine in the seven C patients who received both acetylcholine and adenosine (slope, 0.23) (p<0.01, by analysis of covariance for repeated measures).

Discussion

This study demonstrates impaired relaxation of the microvasculature in patients with DC in response to the endothelium-dependent vasodilator acetylcholine. This impairment is out of proportion to the mildly impaired response to adenosine, a dilator of vascular smooth muscle. The loss of relaxation to acetylcholine with a relatively intact relaxation response to adenosine suggests that extravascular factors do not explain the pronounced differences in acetylcholine responses between normal and cardiomyopathic patients and suggests a role for endothelial dysfunction in the microvasculature of hearts with DC.

Coronary flow reserve has been shown to be diminished in patients with DC. Horwitz et al1 first reported impaired coronary blood flow responses to the intravenous administration of isoproterenol in heart failure. Subsequently, studies using the thermodilution method of measuring coronary sinus blood flow3,5 and the argon washout method4 demonstrated impaired dilator capacity during rapid
atrial pacing and after dipyridamole. Intracoronary administration of adenosine in our patients also demonstrated a trend toward impairment of coronary flow reserve in patients with DC. The present study, however, is the first to be able to differentiate the role of intrinsic microvascular disease from other extravascular factors that can alter coronary flow reserve.

Although studies of microvascular pathology in hypertrophic cardiomyopathy have demonstrated intimal hyperplasia and medial hypertrophy, most studies of the microvasculature in DC have failed to demonstrate any morphological abnormalities. Evidence from experimental models of DC as well as recent clinical studies, however, have convincingly documented disturbances in microvascular function. Factor10-12 and others13 have described microvascular spasm as a preventable cause of hereditary DC in the Syrian hamster. Silicone rubber-perfusion studies demonstrated microvascular spasm associated with adjacent areas of myocytolytic necrosis early in this disease. Administration of the calcium channel blocker verapamil, an agent effective in the treatment of vasospasm, halted the progression of myocardial necrosis and prevented the development of cardiomyopathy.1 Cannon et al18 studied 12 patients with DC, normal epicardial coronary arteries, and a history of chest pain, and found that 11 developed anginal symptoms with ergonovine administration. The apparent increased sensitivity to the vasoconstrictor stimulus ergonovine suggests an intrinsic functional abnormality of the coronary microvasculature.

The endothelium is fundamentally important in the local regulation of vascular tone. The release of EDRF is the mode of action for a variety of vasodilators including acetylcholine, adenosine diphosphate (ADP), adenosine triphosphate (ATP), histamine, bradykinin, substance P, thrombin, and calcitonin gene-related peptide. Even substances that are normally considered to be vasoconstrictors, such as α-adrenergic receptor agonists, vasopressin, and serotonin, can release EDRF. Diseases, such as atherosclerosis, which are associated with impaired endothelium-dependent relaxation, can lead to an imbalance between vasoconstrictor and vasodilator influences and result in vasospasm in the epicardial coronary arteries.

Although the majority of early studies of endothelial modulation of vascular tone have involved the large (conduit) arteries, there is convincing evidence that endothelium-mediated vasomotion also plays an important role in the control of the small (resistance) vessels. For example, in the perfused mesenteric arterial vasculature of the rabbit, vasodilation by acetylcholine was almost completely blocked after the removal of endothelial cells with collagenase. In the rat microvasculature, vasodilation by acetylcholine was markedly inhibited by hemoglobin, an agent that inactivates EDRF. The present study has shown that normal humans exhibit cholinergically mediated dose-dependent dilation of the coronary microvasculature, a function that is likely to be endothelium dependent.

A dysfunctional endothelium could contribute to the development or progression of cardiomyopathy by one of two mechanisms. In analogy to reports regarding hereditary cardiomyopathy in the Syrian hamster, microvascular spasm, triggered by impaired endothelium-dependent vasodilation, could impair the nutritive support of myocardium, interfere with its contractile function, and possibly induce focal areas of myocardial necrosis. Alternatively, impaired relaxation to acetylcholine could represent only one of a number of endothelial functions that are abnormal in this disease. Normal endothelium can provide trophic support to the surrounding tissues by producing a variety of growth factors such as platelet-derived growth factor, fibroblast growth factor, and insulin-like growth factor. Deranged regulation of the production or release of these growth factors or other trophic substances could be a pathogenic feature of cardiomyopathies.

The cause or causes of endothelial dysfunction in the coronary microvessels of DC hearts demonstrated in this study remain to be defined. It is possible that the endothelium is secondarily damaged in heart failure. Abnormal endothelium-mediated vascular regulation could lead to further damage in later stages of the disease. This concept is supported by the observations of Kaiser and colleagues who found impaired endothelium-dependent vasodilation to acetylcholine in the hindlimb of dogs with experimental heart failure. Alternatively, endothelial dysfunction could represent an early primary defect. The two most impaired responses to acetylcholine in this study were observed in patients with a family history of DC. Possibly, a genetic defect could affect the endothelium primarily. There are also external stimuli that have been associated with the development of cardiomyopathies and that damage endothelial cells directly. For example, various viruses invade and destroy endothelial cells, and ethanol exposure produces injury to microvascular endothelial cells. Epicardial (conduit) arteries of cardiomyopathy and control patients did not differ significantly in their responses to acetylcholine or adenosine, suggesting that the impairment in endothelium-dependent relaxation affecting the heart might primarily involve the microvasculature.

One must also consider mechanisms other than dysfunction of endothelium that might explain the data presented in this study. A coupling defect between EDRF and smooth muscle cells could also explain our results.

Potential Limitations of the Study

Digitalislike drugs inhibit endothelium-dependent relaxation in some experimental preparations. When comparing our DC patients who had been receiving digoxin (n=3; peak acetylcholine flow response: mean, +78% increase; range, –22 to
+140%) with those who had not (n=5; peak acetylcholine flow response: mean, +41%; range, −19 to +140%), we found no difference, suggesting that digoxin was not responsible for the impaired endothelium-dependent relaxation in these patients. This study has shown that endothelium-dependent dilation of the coronary microvasculature is impaired in patients with DC. Further characterization of the mechanisms of endothelial dysfunction in DC could lead to a better understanding of the pathogenesis of heart failure and myocardial hypertrophy in this disease.

Acknowledgments

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**KEY WORDS** • resistance vessels • acetylcholine • adenosine
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