Beneficial effects of nifedipine on rest and exercise myocardial energetics in patients with congestive heart failure

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ABSTRACT Rest and exercise systemic hemodynamic parameters, coronary blood flow, and myocardial energetics were assessed before and 15 min after the sublingual administration of 20 mg of nifedipine in 10 patients with idiopathic congestive cardiomyopathy. When compared with control, nifedipine increased rest and exercise cardiac index by 37% and 28%, respectively (p < .001). Peripheral vasodilation was demonstrated with a drop in systemic arterial pressure, exercise pulmonary capillary wedge pressure, and systemic vascular resistance (p < .05). The calcium-channel blocker did not alter myocardial oxygen consumption; however, coronary blood flow increased by 32% at rest (p < .01) while coronary vascular resistance diminished both at rest and after exercise compared with control (p < .05). Nifedipine elicited a decrease in the rest and exercise aortocoronary sinus oxygen difference while the coronary sinus oxygen saturation increased (p < .01). In this group of patients with idiopathic congestive cardiomyopathy, nifedipine enhanced myocardial performance while increasing coronary blood flow and favorably altering the myocardial oxygen supply-demand balance.


IDIOPATHIC congestive cardiomyopathy is associated with diminished coronary blood flow per unit mass of myocardium.1-3 Coronary reserve may also be significantly attenuated.4 A number of studies have clearly demonstrated increased susceptibility of subendocardial tissue to ischemia and necrosis, most notably in patients with left ventricular hypertrophy.5-8 The relative reduction in coronary blood flow may actually potentiate ventricular dysfunction and initiate chest pain syndromes in patients with idiopathic dilated cardiomyopathy.9-11

Nifedipine, a calcium-channel blocker, demonstrates potent systemic and coronary vasodilator capacity.12-14 The net circulatory effect of nifedipine is modulated via a complex interaction of specific myocardial activity, direct coronary and systemic vascular effects, and reflex central and peripheral circulatory responses.14-16 In select groups of patients with both ischemic and nonischemic heart disease, nifedipine favorably alters various parameters of both systolic and diastolic function.17-20 This study was designed to assess the specific effects of nifedipine on rest and exercise central hemodynamics, coronary blood flow, and myocardial energetics in patients with idiopathic congestive cardiomyopathy.

Materials and methods

Patients. Ten patients with congestive heart failure (New York Heart Association functional class III) were studied. The group consisted of one woman and nine men, mean age 52 years (range 41 to 62). The diagnosis of idiopathic congestive cardiomyopathy was substantiated by cardiac catheterization performed within 2 months of the study. The mean ejection fraction was 27% (range 15% to 33%). All patients were receiving conventional cardiac medications: six were taking digitals, eight diuretics, and three antiarrhythmics. Both nitrates and diuretics were discontinued 24 hr before study onset. Exclusion criteria included other forms of cardiac disease, significant mitral or tricuspid regurgitation, anemia, and uremia. Written informed consent was obtained from each patient before the study began. The protocol was approved by the institutional review board.

Catheterization. Before the study began, a thermocatheter was placed via the right internal jugular vein in the pulmonary artery to measure central hemodynamic variables. An arterial catheter placed in the radial artery was used for sampling arterial blood and monitoring systemic blood pressure. A thermocatheter coronary sinus catheter (Wilton-Webster Laboratory) was introduced through the left subclavian vein into the coronary sinus, with the proximal thermistor positioned greater than 2 cm from the coronary sinus os. Catheter position
was confirmed angiographically and by temperature assessment\textsuperscript{22, 23} to ensure stable flow curves and to avoid right atrial admixture.\textsuperscript{22, 23}

Central hemodynamic variables included systemic arterial, pulmonary arterial, and pulmonary capillary wedge pressures determined by techniques previously described.\textsuperscript{24} Cardiac output (thermodilution technique)\textsuperscript{25} was measured in triplicate with less than 10% variation by means of a Gould SP 1435 computer and SP 2009 recorder. Coronary sinus flow measurements (thermodilution technique)\textsuperscript{21, 26} were performed in triplicate (7% variation for repeated measures) with a No. 7F model CCS-7U-90B coronary sinus catheter interfaced with a Wilson Webster CBA-210 two-channel Wheatstone bridge. A multichannel Electronics for Medicine recorder transcribed simultaneous thermistor signals. Oxygen content was measured by the electrochemical technique (Lex-O2-Con, Lexington Instruments). Serum lactate determinations were performed with an enzymatic method (ACA-3, Dysart).

Protocol. Patients were brought to the laboratory in the postabsorptive state. Supine resting hemodynamic measurements included systemic and pulmonary arterial pressures, pulmonary capillary wedge pressure, cardiac output, and coronary sinus flow. Aliquots of systemic arterial, mixed venous, and coronary sinus blood were obtained for oxygen and lactate determinations. After resting determinations, supine bicycle ergometry was initiated (200 kilopond-meters at 60 cycles/min). Supine exercise was performed in a specially designed exercise carriage, with fluoroscopic monitoring of catheter position performed at 2 min intervals. A radiopaque marker was used throughout the study to confirm stable catheter position. Repeat hemodynamic and metabolic determinations were made during steady-state exercise between 5 and 10 min after onset of pedaling. After a return to stable baseline hemodynamic values, nifedipine (20 mg aspirated from the capsule) was administered sublingually. Repeat rest and exercise measurements (performed at matched workload levels) were begun 15 min after single-dose nifedipine and completed by 30 min.

Calculations. The following central hemodynamic calculations\textsuperscript{27} were made: cardiac index, stroke volume index, systemic vascular resistance, and left ventricular stroke work index. Coronary hemodynamic and myocardial metabolic calculations included coronary sinus flow, coronary vascular resistance, myocardial oxygen consumption, and myocardial oxygen extraction ratio, determined by formulas previously reported.\textsuperscript{3}

Statistics. Mean values and standard deviation were calculated during control periods at rest and with exercise; measurements were repeated after nifedipine. Student’s t test for paired data was used to compare control with postnifedipine data. A probability value of <.05 was used to indicate significant change.

Results

Systemic hemodynamics. The central hemodynamic data are presented in tables 1A and 1B. Resting control values substantiate moderate ventricular dysfunction with depressed cardiac index (2.4 ± 0.6 liters/min/m\textsuperscript{2}), elevated pulmonary capillary wedge pressure (17 ± 7 mm Hg), and elevated systemic vascular resistance (1797 ± 467 dynes-sec-cm\textsuperscript{-5}). With supine exercise, cardiac index significantly increased with a concomitant elevation of heart rate, systemic arterial pressure (mean and peak systolic), and pulmonary capillary wedge pressure. Nifedipine lowered both rest and exercise mean arterial blood pressure by 10% and 15%, respectively. Pulmonary capillary wedge pressure was unchanged at rest but diminished with exercise after nifedipine. Heart rate increased modestly at rest (11%) but remained unchanged from control with exercise. Systemic vascular resistance diminished at rest and with exercise compared with control. Cardiac index increased at rest (37%) and with exercise (28%) compared with control values. Similar changes were noted in stroke volume index. Concomitant with these changes in cardiac output, left ventricular stroke work index and total body oxygen consumption (rest and exercise) remained unaltered with nifedipine.

Coronary blood flow and myocardial energetics. The effects of nifedipine on coronary blood flow and myocardial energetics are presented in tables 2A and 2B and figures 1 to 4. Analysis of control data demonstrates an anticipated marked increase in coronary flow and myocardial oxygen consumption during exercise with a concomitant drop in coronary vascular resistance. Coronary perfusion pressure, aortocoronary sinus oxygen difference, coronary sinus oxygen saturation, and lactate extraction remained essentially unaltered during exercise. After administration of nifedipine, coronary sinus blood flow was augmented at rest (32%) while both rest and exercise coronary vascular resistance diminished. The mean arterial pressure minus wedge pressure, an estimate of coronary perfusion pressure, was unaltered by nifedipine at rest but modestly decreased with exercise. Myocardial oxygen consumption (rest and exercise) remained unchanged from control. Nifedipine, at rest and with exercise, elicited a decrease in the aortocoronary sinus oxygen difference while coronary sinus oxygen saturation significantly increased. Lactate extraction, essentially normal at baseline, remained unchanged after nifedipine.

Discussion

In the setting of congestive heart failure, depressed cardiac output, diminished coronary perfusion pressures, increased ventricular filling pressures and wall tension, and myocardial hypertrophy are but a few of the factors that may interfere with adequate myocardial perfusion. Patients with both pressure- and volume-induced ventricular hypertrophy demonstrate diminished coronary vascular reserve.\textsuperscript{28-30} The actual link between myocardial perfusion and ventricular performance is uncertain; however, depressed coronary flow, diminished subendocardial perfusion, and altered coronary reserves may play an integral role in the pathogenesis of ventricular dysfunction in idiopathic congestive cardiomyopathy.\textsuperscript{28}
**TABLE 1A**

Effects of oral nifedipine on central hemodynamic measurements at rest

<table>
<thead>
<tr>
<th>Patient</th>
<th>C</th>
<th>N</th>
<th>C</th>
<th>N</th>
<th>C</th>
<th>N</th>
<th>C</th>
<th>N</th>
<th>C</th>
<th>N</th>
<th>C</th>
<th>N</th>
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<tbody>
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<td>86</td>
<td>108</td>
<td>101</td>
<td>85</td>
<td>85</td>
<td>112</td>
<td>115</td>
<td>11</td>
<td>10</td>
<td>3.6</td>
<td>3.9</td>
</tr>
<tr>
<td>AP (mm Hg)</td>
<td>54</td>
<td>60</td>
<td>111</td>
<td>113</td>
<td>21</td>
<td>19</td>
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<tr>
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<td>57</td>
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<td>128</td>
<td>12</td>
<td>10</td>
<td>2.9</td>
<td>4.5</td>
<td>40</td>
<td>51</td>
<td>1709</td>
<td>845</td>
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<tr>
<td>CI (l/min/m²)</td>
<td>52</td>
<td>59</td>
<td>86</td>
<td>85</td>
<td>32</td>
<td>30</td>
<td>2.0</td>
<td>3.1</td>
<td>16</td>
<td>26</td>
<td>1797</td>
<td>1123</td>
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<tr>
<td>SVI (ml/m³)</td>
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<td>88</td>
<td>80</td>
<td>10</td>
<td>12</td>
<td>2.2</td>
<td>3.2</td>
<td>26</td>
<td>33</td>
<td>1530</td>
<td>995</td>
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<td>SVR (dyn-sec-cm⁻¹)</td>
<td>67</td>
<td>72</td>
<td>68</td>
<td>62</td>
<td>21</td>
<td>18</td>
<td>2.3</td>
<td>2.9</td>
<td>26</td>
<td>28</td>
<td>1309</td>
<td>941</td>
</tr>
<tr>
<td>LVSWI (g/m²)</td>
<td>71</td>
<td>78</td>
<td>117</td>
<td>91</td>
<td>17</td>
<td>29</td>
<td>1.7</td>
<td>2.5</td>
<td>24</td>
<td>28</td>
<td>2521</td>
<td>1363</td>
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<tr>
<td>VO₂ (ml/min/m²)</td>
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<td>90</td>
<td>100</td>
<td>95</td>
<td>17</td>
<td>13</td>
<td>2.1</td>
<td>2.5</td>
<td>26</td>
<td>28</td>
<td>1730</td>
<td>1357</td>
</tr>
</tbody>
</table>

Mean | 84 | 93 | 104 | 94 | 17 | 16 | 2.4 | 3.3 | 29 | 35 | 1797 | 1174 | 41 | 46 | 131 | 127 |

SD | ±18 | ±16 | ±19 | ±16 | ±6.9 | ±8.3 | ±0.6 | ±0.7 | ±8.0 | ±9.6 | ±467 | ±237 | ±16 | ±19 | ±24 | ±18 |

p value | <.001 | <.05 | NS | <.001 | <.01 | <.001 | NS | NS |

AP = arterial pressure; C = control; CI = cardiac index; HR = heart rate; LVSWI = left ventricular stroke work index; PCW = pulmonary capillary wedge pressure; SVI = stroke volume index; SVR = systemic vascular resistance; VO₂ = total body oxygen consumption; N = nifedipine.

Nifedipine induces peripheral arteriolar dilatation and dilates large coronary arteries and coronary resistance vessels. These smooth muscle vascular effects are accompanied by diminished ventricular afterload plus enhanced coronary blood flow. The potent vasodilator properties of nifedipine are certainly subject to modification in the setting of heart failure. Direct negative inotropic properties may potentially diminish cardiac output, drop systemic pressure, reduce coronary perfusion pressure, and actually compromise myocardial perfusion with resultant exacerbation of ventricular dysfunction and cardiac failure. However, direct coronary dilatation, diminished ventricular afterload, and improved ventricular diastolic properties could result in augmented coronary blood flow, enhanced subendocardial perfusion, and improved ventricular function.

In patients with coronary artery disease and impaired baseline left ventricular function, nifedipine improved left ventricular ejection fraction and cardiac output while favorably influencing diastolic pressure-volume curves. Although nifedipine demonstrates negative inotropic properties in vitro, previous studies have shown improved ventricular performance in

**TABLE 1B**

Effects of oral nifedipine on central hemodynamic measurements during exercise

<table>
<thead>
<tr>
<th>Patient</th>
<th>C</th>
<th>N</th>
<th>C</th>
<th>N</th>
<th>C</th>
<th>N</th>
<th>C</th>
<th>N</th>
<th>C</th>
<th>N</th>
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<th>N</th>
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<td>122</td>
<td>160</td>
<td>130</td>
<td>25</td>
<td>19</td>
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<td>6.5</td>
<td>45</td>
<td>53</td>
<td>1125</td>
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<td>76</td>
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<td>128</td>
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<td>64</td>
<td>1449</td>
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<td>PCW (mm Hg)</td>
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<td>150</td>
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<td>6.6</td>
<td>39</td>
<td>62</td>
<td>1383</td>
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<td>30</td>
<td>1269</td>
<td>842</td>
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<td>SVI (ml/m³)</td>
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<td>LVSWI (g/m²)</td>
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<td>143</td>
<td>121</td>
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<td>51</td>
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<td>3.5</td>
<td>22</td>
<td>30</td>
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<td>1255</td>
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<tr>
<td>VO₂ (ml/min/m²)</td>
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<td>110</td>
<td>120</td>
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<td>32</td>
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<td>30</td>
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<td>1170</td>
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<td>Mean</td>
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<td>106</td>
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<td>4.6</td>
<td>34</td>
<td>42</td>
<td>1354</td>
<td>935</td>
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</table>

SD | ±22 | ±15 | ±27 | ±20 | ±12 | ±13 | ±0.9 | ±1.3 | ±12 | ±14 | ±296 | ±188 | ±28 | ±30 | ±108 | ±85 |

p value | NS | <.01 | <.001 | <.01 | <.01 | <.001 | NS | NS |

Abbreviations as in table 1A.
TABLE 2A

| Patients with congestive heart failure secondary to the pronounced vasodilative properties of the agent. Two recent reports, one a review of vasodilator therapy in patients with heart failure and the second an original study by Elkayam et al., emphasize caution regarding the use of calcium antagonists in patients with depressed ventricular function (ejection fraction less than 30%) and cite a few isolated reports of deterioration of myocardial performance after the use of these agents.

A recent study suggested that the combination of digoxin and nifedipine elicited short-term improvement in cardiac performance in patients with both coronary disease and congestive cardiomyopathy. Our subset of six patients on maintenance dosages of digoxin did not respond differently than the group as a whole. There was no evidence of more pronounced systemic or coronary vasoconstriction in the digitalized patients. Concomitant use of digoxin and nifedipine may result in increased plasma concentrations of digoxin.

In our patients with moderate ventricular dysfunction, nifedipine favorably altered rest and exercise systemic hemodynamic parameters. Nifedipine increased

| TABLE 2B

| Effects of oral nifedipine on coronary blood flow and myocardial energetics during exercise |

<table>
<thead>
<tr>
<th>Patient</th>
<th>CSF (ml/min)</th>
<th>CVR (mm Hg/ml/min)</th>
<th>AP-PCW (mm Hg)</th>
<th>(A - CSO₂) (ml/l)</th>
<th>CSO₂ (ml/l)</th>
<th>MVO₂ (ml/min)</th>
<th>O₂ (% extraction)</th>
<th>Lactate (% extraction)</th>
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<td>1</td>
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<td>0.4</td>
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<td>111</td>
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<td>181</td>
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<td>185</td>
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<td>4</td>
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<td>6</td>
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<td>9</td>
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<td>101</td>
<td>95</td>
<td>116</td>
<td>0.5</td>
</tr>
</tbody>
</table>

| Mean    | 216          | 251                 | 0.5            | 0.4               | 91           | 80             | 126              | 0.4                 |

| SD      | ±122         | ±118                | ±0.2           | ±0.2              | ±30          | ±24            | ±22              | ±18                 |

| p value | <.05         | <.01                | <.01           | <.01              | NS           | <.02           | NS               |

Abbreviations as in table 2A.
rest and exercise cardiac index and stroke volume index while systemic vascular resistance was significantly reduced (figure 1). Nifedipine demonstrated evidence of peripheral vasodilation with diminished systemic arterial and pulmonary capillary wedge pressure. In spite of the marked augmentation of cardiac output, the left ventricular stroke work index and total body oxygen consumption remained unchanged (tables 1A and 1B). No individual patient demonstrated evidence of systemic hemodynamic deterioration after nifedipine.

Coronary blood flow was estimated by an indwelling thermodilution catheter placed in the coronary sinus. The positioning of the catheter (a minimum of 2 cm distal to the coronary sinus ostium) minimizes right atrial admixture while precluding measurement of total coronary sinus flow. Meticulous attention to the position of the catheter was maintained throughout exercise by means of fluoroscopy and an internal radiopaque marker. Mobility of the catheter tip during exercise tachycardia was no greater than that observed at similar paced heart rates. Coronary flow measurements, obtained in triplicate both at rest and during exercise, demonstrated less than 7% variance in re-
peated measurements for individual subjects. The variability was not increased with exercise. Although this technique does not provide for measurement of total coronary blood flow and vascular resistance, it does permit reproducible assessment of coronary flow at baseline, during exercise and after pharmacologic intervention (nifedipine).

After administration of nifedipine, resting coronary sinus flow increased while rest and exercise coronary vascular resistance diminished (figure 2). When individual patients were studied, the relative decrease in systemic vs coronary vascular resistance after nifedipine remained fairly balanced (figure 3). The ratio of coronary blood flow to myocardial oxygen consumption was increased (at rest and with exercise) with nifedipine while the arteriovenous oxygen difference increased (figure 4). These changes suggest enhanced myocardial perfusion but do not firmly establish a direct causal relationship between improved perfusion and augmented myocardial performance. Lactate metabolism remained unchanged with no demonstrable increase in lactate extraction across the coronary vascular bed. Arterial lactate levels (rest and exercise) did not change between baseline and postnifedipine studies. Any alteration of transmural distribution of coronary perfusion remains speculative; however, previous investigators have suggested redistribution of flow toward the left ventricular subendocardium.41

These hemodynamic and metabolic observations represent short-term responses and may not persist with prolonged drug administration. Long-term hemodynamic assessment is certainly necessary to better define the actual clinical utility of this drug.

In conclusion, nifedipine demonstrated prominent systemic and coronary vascular effects, with favorable alteration of rest and exercise central hemodynamic parameters. Myocardial performance was enhanced, coronary blood flow increased, and the balance between myocardial oxygen supply and demand was favorably altered. Nifedipine demonstrates short-term salutary hemodynamic effects in patients with idio-pathic congestive cardiomyopathy.

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References


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