Myocardial Energetics in Patients With Dilated Cardiomyopathy

Influence of Nitroprusside and Enoximone

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With the technical assistance of Friederike Schopfer

Cardiotonic agents influence myocardial energy consumption by vasodilation, which may reduce energy demand, and by inotropism, which may increase it. To distinguish between the two effects, myocardial oxygen consumption must be analyzed in relation to its hemodynamic determinants. The coupling of myocardial oxygen consumption with its determinants was investigated in 22 patients with idiopathic dilated cardiomyopathy (NYHA Class II and III). Predicted myocardial oxygen consumption by the pressure-work index, the Bretschneider index, and the pressure-volume area correlated moderately with measured myocardial oxygen consumption \( r=0.57, p<0.001; r=0.52, p<0.005; \) and \( r=0.63, p<0.001 \). Multiple regression analysis, including left ventricular peak systolic wall stress, systolic stress-time integral, pressure-volume work, maximum rate of left ventricular pressure rise, and mean velocity of circumferential fiber shortening indicated that systolic stress-time integral is the major determinant of myocardial oxygen consumption \( r=0.75, p<0.001 \) in these patients. Enoximone, a phosphodiesterase inhibitor, has an inotropic and a vasodilating effect. To investigate the inotropic portion of the energy cost of this phosphodiesterase inhibitor, the influence of enoximone on myocardial oxygen consumption and systolic stress-time integral was compared with the effects of nitroprusside, which is a vasodilator only. Nitroprusside (10 patients) and enoximone (12 patients) reduced left ventricular systolic stress-time integral from 109±22 to 71±21 \( p<0.005 \) and from 104±23 to 42±10 \( p<0.001 \) \( 10^3 \) dynes \( \cdot \) sec/cm², respectively. Myocardial oxygen consumption decreased from 159±44 to 112±23 \( p<0.005 \) and from 134±28 to 109±21 \( p<0.001 \) \( \mu l/\text{beat}/100 \text{ g} \), respectively. In both groups, there was a significant correlation between the decrease in myocardial oxygen consumption and the decrease in systolic stress-time integral. The slopes of the respective linear regression lines were significantly different \( 1.27 \) for nitroprusside and \( 0.51 \text{ ml} \cdot \text{cm}^2/100 \text{ g} \cdot \text{dynes} \cdot \text{sec} \) for enoximone, \( p<0.05 \), indicating a smaller decrease of myocardial oxygen consumption for a given decrease of stress-time integral with enoximone. Applying the pressure-work index or the pressure-volume area instead of systolic stress-time integral yielded comparable results. Thus, vasodilation reduces myocardial oxygen consumption in proportion to the reduction of stress-time integral. With enoximone, the energy-saving effect of vasodilation is counteracted in part by the increased energy demand of inotropic stimulation. \( \text{Circulation} \ 1989;80:51–64 \)

In the search for therapeutic alternatives in treating congestive heart failure, several new cardiotonic drugs have been developed and are currently under investigation.\(^1,2\) Although most of these drugs have yielded short-term hemodynamic improvement, the long-term benefit is controversial.\(^3–5\) Moreover, detrimental effects of increased myocardial oxygen consumption due to inotropic stimulation of the myocardium have recently been discussed.\(^6,7\) The influence of most clinically available cardiotonic agents on myocardial energy consumption has been investigated in clinical\(^8–15\) and experimental studies.\(^16–24\) Whereas direct measurements of
the energetic consequences of inotropic stimulation can be made in experimental studies, myocardial oxygen consumption measurements are influenced by both the inotropic and the vasodilating effects of those agents in clinical studies. Inotropic stimulation of the myocardium may increase myocardial oxygen demand in proportion to or in excess of the increase in contractile force. Vasodilation resulting from direct effects on the peripheral vasculature or from effects secondary to increased cardiac performance may reduce myocardial oxygen demand according to its altered hemodynamic determinants. To distinguish between the two effects and to characterize the energy costs resulting from inotropism, myocardial oxygen consumption must be analyzed in relation to its hemodynamic determinants.

The determinants of myocardial oxygen consumption have been extensively investigated in animal experiments, and several indexes used to predict myocardial oxygen consumption from hemodynamic data have been previously developed. Close correlations to measured myocardial oxygen consumption have been obtained for most of these indexes in experimental studies. None of these indexes, however, has been validated in humans. In patients with left ventricular hypertrophy, peak systolic wall stress and systolic stress-time integral have been shown to be linearly related to myocardial oxygen consumption per minute. No previous analysis, however, has taken heart rate into account. Because heart rate is a major determinant of myocardial oxygen consumption, it must be considered when interindividual differences in heart rate exist or when heart rate changes as a consequence of interventions.

The purpose of the present study was to differentiate between the inotropic and the vasodilating effect of enoximone on myocardial oxygen consumption in patients with dilated cardiomyopathy. Therefore, the following questions were addressed: 1) which hemodynamic variables and indexes correlate with measured myocardial oxygen consumption? 2) how does enoximone influence these correlations? and 3) is the influence of enoximone on the relation between hemodynamic variables and myocardial oxygen consumption different from the effects of nitroprusside, which is a vasodilator only?

Exoximone was chosen because it represents a new class of inotropic agents that inhibit phosphodiesterase activity and subsequently increase cyclic adenosine monophosphate. The hemodynamic effects of enoximone have been investigated in great detail; beneficial effects of intravenous enoximone were shown in patients with advanced cardiac failure. The influence of enoximone on myocardial oxygen consumption, however, has not been clarified. Nitroprusside was chosen because it is a vasodilator only and does not directly affect the myocardium.

Patients

Twenty-two patients with idiopathic dilated cardiomyopathy were included in the study. All patients were in sinus rhythm. Patients with mitral regurgitation exceeding angiographic degree 1+ were excluded from the study. Seventeen were men and five were women. The mean age was 48±9 years, ranging from 24 to 60 years. Nine patients were in New York Heart Association functional Class II, and 13 were in Class III. Idiopathic dilated cardiomyopathy was defined by increased left ventricular end-diastolic volume (>220 ml) and reduced left ventricular ejection fraction (<55%) in the absence of coronary or valvular heart disease or a history of arterial hypertension.

Study Protocol

The study protocol was reviewed and approved by the Ethical Committee of the University Clinics of Freiburg. All patients had given written, informed consent before participating in the study. Cardiac catheterization was performed in the fasting state. All previous medications (digoxin in 11 patients, hydrochlorothiazide-triamterene in two patients, nifedipine in one patient, and propafenone in one patient) were withheld at least 48 hours before catheterization. Left and right heart catheterization was performed by the femoral approach. Catheterization of the coronary sinus was accomplished through a brachial vein. After coronary angiography had been performed, left ventriculography with simultaneous pressure measurement was performed with a Millar microtipped catheter pressure transducer (Houston, Texas). Thereafter myocardial blood flow was measured by the argon method. Blood samples were taken from the aorta and the coronary sinus for oxygen saturation measurements. Cardiac output was measured by the thermodilution technique. Upon completion of basal measurements, the following interventions were performed.

Enoximone was given in 12 patients. Eight were in New York Heart Association functional Class III, and four were in Class II. Enoximone was administered intravenously at a dose of 1 mg/kg at a rate of 12.5 mg/min while aortic pressure was measured continuously. Five minutes after completion of the enoximone infusion, the aortic pressure was read again. If mean aortic pressure was decreased by more than 15% or was below 75 mm Hg, no additional enoximone was infused. In five patients, an additional dosage of 1 mg/kg was given at the same rate to achieve similar changes in aortic pressure in all patients. Five patients received 2 mg/kg, and seven patients received 1 mg/kg. Fifteen minutes after the infusion of enoximone had been completed, myocardial blood flow and oxygen saturation were repeatedly measured, cardiac output was measured, and left ventriculography with
simultaneous pressure measurement was performed. This procedure was used because within 10 minutes after intravenous application of enoximone a stable hemodynamic effect is reached and maintained for 5–6 hours. Plasma samples for determining norepinephrine plasma levels were taken from the aorta and the coronary sinus during the control period and after enoximone administration.

Nitroprusside was given to 10 patients. Five patients were in New York Heart Association functional Class III, and five were in Class II. The infusion was begun at a rate of 25 μg/min. The infusion rate was increased by 12.5 or 25 μg/min until either mean aortic pressure had decreased by more than 15% or was below 75 mm Hg. The average dosage was 71±58 μg/min, ranging from 25 to 200 μg/min. After mean aortic pressure had been stable for 10 minutes, myocardial blood flow and oxygen saturation were measured again, cardiac output was measured, and left ventriculography with simultaneous pressure measurement was performed.

The comparison between enoximone and nitroprusside was performed in two groups of patients because the requirement of two ventriculographies for each study did not allow us to investigate both drugs in an individual patient. For the same reason, patients with severe congestive heart failure (NYHA Class IV) were not included in the study. Aortic pressure was used instead of cardiac output to adjust the dosages of enoximone and nitroprusside because changes in hemodynamic variables subsequent to altered left ventricular load and the corresponding changes in myocardial oxygen consumption were of primary interest for the present study.

Hemodynamic Variables

Aortic and left ventricular pressures were measured with pigtail Millar microtipped catheter pressure transducers (PC-485 A, 8F). Left ventriculography was performed at 50 frames/sec by power injection of 40 ml nonionic contrast solution. The projection was a 10° caudally angulated 45° right anterior oblique view. Left ventricular pressure was recorded simultaneously. Maximum rate of left ventricular pressure rise was determined from continuous differentiation of left ventricular pressure tracings. Heart rate was determined from the continuous recording of the electrocardiogram. During one cardiac cycle, left ventricular volumes were calculated from each cineframe at intervals of 20 msec with the Sandler and Dodge method. Left ventricular muscle mass was calculated by a modification of the method of Rackley et al. Instantaneous wall thickness was calculated at intervals of 20 msec with a special computer program (HERRATH II). This program calculates instantaneous wall thickness from wall mass, instantaneous volume, and major and minor hemiaxes. Instantaneous wall stress values were calculated with the ellipsoid model of Mirsky:

\[
S = P \cdot b/h \cdot (1-b^2/2a^2-h/2b+h^2/8a^2)
\]

where \(S\) is instantaneous left wall stress, \(P\) is instantaneous left ventricular pressure, \(b\) is instantaneous left ventricular wall thickness, \(a\) is major hemiaxis, \(b\) is minor hemiaxis; \(a\) and \(b\) were derived from the calculated volumes by the area-length method. The systolic stress-time integral (STI, \(10^3\) dynes \(\text{sec} / \text{cm}^2\)) was calculated by integrating instantaneous stress values from end diastole to end systole. End-diastolic wall stress was defined as the wall stress value at end-diastolic pressure, and end-systolic wall stress was defined as the stress value derived from the cineframe before left ventricular volume increased. Pressure-volume work (PV-work, mm Hg · l/100 g) was calculated as the area of the pressure-volume loop obtained by relating instantaneous pressure to volume every 20 msec and normalizing for 100 g wall mass. Cardiac output was measured by the thermodilution technique, and stroke volume was obtained by dividing cardiac output by heart rate. Mean velocity of circumferential fiber shortening (MVcf, circ/sec) was calculated from the formula:

\[
MV_{cf} = (LVEDD - LVESD)/(LVEDD \times LVET),
\]

where LVEDD is left ventricular minor diameter at end diastole, LVESD is left ventricular minor diameter at end systole (both derived by the area-length method), and LVET is left ventricular ejection time measured from central aortic tracings. Left ventricular ejection fraction (EF, %) was calculated from the formula:

\[
E_F = (LVEDV - LVESV/LVEDV),
\]

where LVEDV is left ventricular end-diastolic volume, and LVESV is left ventricular end-systolic volume. Bretschneider’s formula was calculated as follows:

\[
E_v = E_0 + E_1 + E_2 + E_3 + E_4
\]

where \(E_0 = 0.7, E_1 = 0.03 \cdot t_{sy} \cdot HR, E_2 = (0.0014 \cdot LVSP^{1.5} \cdot LVET \cdot HR)/(dP/dt)^{1/3}, E_3 = 1.2 \cdot 10^{-5} \cdot dP/dt \cdot HR, E_4 = 8.0 \cdot 10^{-7} \cdot (dP/dt)^{1.5} \cdot HR, t_{sy} = QT-duration, HR = heart rate, LVSP is left ventricular peak systolic pressure, LVET is left ventricular ejection time, and \(dP/dt_{max}\) is maximum rate of left ventricular pressure rise. The pressure-work index was calculated as follows:

\[
MV_{O_2} = (0.08 \cdot 10^{-4} \cdot (LVSP \cdot HR) + 3.25 \cdot 10^{-4} \cdot (0.8 \cdot LVSP + 0.2 \cdot DAP) \cdot HR \cdot SV/BW + 1.43
\]

where \(DAP\) is diastolic aortic pressure, \(SV\) is stroke volume (measured by thermodilution technique), \(BW\) is body weight (kg).

The pressure-volume area (PVA, mm Hg · ml/100 g) was calculated with a modification of the method of Suga:

\[
PVA = PV-work + LVESP \cdot LVESV_a \div 2
\]

where PV-work is pressure-volume work (see above), LVESP is left ventricular end-systolic pressure (determined as the pressure of the dicrotic

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Downloaded from http://circ.ahajournals.org/ on October 29, 2017.
Measurement notch in the aortic pressure tracings), and LVESV, is left ventricular end-systolic volume normalized for 100 g wall mass.

Myocardial Blood Flow and Oxygen Consumption

Myocardial blood flow was measured by the argon method. Argon blood concentrations were determined by gas chromatography. Calculation of myocardial blood flow (ml/min/100 g) was performed with the Kety and Schmidt formula. Myocardial oxygen consumption per minute (ml/min/100 g) was determined as the product of myocardial blood flow multiplied by the arterial-coronary-sinus oxygen content difference (ml/100 ml). The latter was derived from oxygen saturation measurements by oximetry (AO Unistat oximeter, Munich, FRG). Myocardial oxygen consumption per beat (μl/beat/100 g) was obtained from myocardial oxygen consumption per minute and heart rate. External myocardial efficiency was obtained as the ratio of pressure-volume work divided by myocardial oxygen consumption per beat. Both were normalized for 100 g wall mass and converted to the same units assuming 1 mm Hg · ml = 31.79 μcal and 1 μl O₂ = 5 μcal.

Measurement of Norepinephrine Plasma Levels

Norepinephrine plasma levels were determined with a radioenzymatic assay. Plasma samples for analysis were obtained from the aorta abdominalis and the coronary sinus. The plasma was immediately separated and stored at -20°C until analyzed.

Statistical Analysis

The statistical analyses were performed with the SPSS/PC+ computer program. The relation between myocardial oxygen consumption and hemodynamic variables was evaluated by multiple regression analyses. Values are expressed as mean ± SD.

For each drug, the variables were compared with control values by paired t test. Comparison of control values between groups was performed with unpaired t test. Probability values less than 0.05 were accepted as significant.

Results

Hemodynamic Variables and Myocardial Oxygen Consumption in Patients With Idiopathic Dilated Cardiomyopathy

In all patients, left ventricular end-diastolic volume was increased (317±74 ml), and ejection fraction was reduced (40±11%). The mass to volume ratio was slightly below the normal range (0.94±0.15 g/ml). Myocardial blood flow and myocardial oxygen consumption were 99±34 ml/min/100 g and 12.4±3.8 ml/min/100 g, respectively. External myocardial efficiency was reduced (17.5±6.1%). No significant differences were found in any hemodynamic or energetic variable between the patients receiving enoximone (12 patients) and those receiving nitroprusside (10 patients).

Hemodynamic Variables and Myocardial Oxygen Consumption After Nitroprusside Administration

Hemodynamic variables before and after administration of nitroprusside are given in Table 1. With nitroprusside, left ventricular pressure and volume decreased significantly. Consequently, there was a significant reduction of peak wall stress from 270±52 to 198±48 10³ dynes/cm², of systolic stress-time integral from 109±22 to 71±21 10³ dynes · sec/cm², and of pressure-volume work from 3.6±1.4 to 2.7±0.9 mm Hg · 1/100 g. Mean velocity of circumferential fiber shortening increased significantly from 0.67±0.26 to 1.01±0.35 circ/sec; maximum rate of left ventricular pressure rise did not change significantly (1.046±202 before and 947±245 mm Hg/sec

| Table 1. | Left Ventricular Hemodynamic Variables Before and After Administration of Nitroprusside

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<th>LVEDV (ml)</th>
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HR, heart rate; LVSP, left ventricular peak systolic pressure; LVEDP, left ventricular end-diastolic pressure; LVEDV, left ventricular end-diastolic volume; dP/dtmax, maximum rate of left ventricular pressure rise; STI, systolic stress-time integral; C, control; N, nitroprusside.
after administration of nitroprusside). Cardiac index was 3.4±0.4 during control and was 3.4±0.8 l/min/m² with nitroprusside. Myocardial oxygen consumptions per minute and per beat were significantly reduced with nitroprusside by 26% and 30%, respectively (Table 2). External myocardial efficiency was 14.8±6.2% during control and 16.1±6.6% with nitroprusside (p>0.05).

**Table 2. Myocardial Blood Flow and Oxygen Consumption Before and After Administration of Nitroprusside**

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<th>ACSDO₂ (ml/100 ml)</th>
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MBF, myocardial blood flow; ACSDO₂, arterial-coronary-sinus oxygen content difference; MVO₂/min, myocardial oxygen consumption per minute; MVO₂/beat, myocardial oxygen consumption per beat; C, control; N, nitroprusside.

**Table 3. Left Ventricular Hemodynamic Variables Before and After Administration of Enoximone**

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not change significantly, and myocardial oxygen consumption per beat decreased significantly by 19% (Table 4). External myocardial efficiency was 19.8±5.3 during control and 16.2±6.9 with enoximone (p>0.05).

**Relation Between Hemodynamic Variables and Myocardial Oxygen Consumption**

The measured myocardial oxygen consumption was compared with predicted myocardial oxygen consumption by Bretschneider’s index, the pressure-work index, and the pressure-volume area. These indexes correlated moderately with measured myocardial oxygen consumption (Figure 1, Table 5).

A multiple regression procedure was used to analyze the relation between left ventricular peak systolic wall stress, systolic stress-time integral, pressure-volume work, maximum rate of left ventricular pressure rise, and mean velocity of circumferential fiber shortening on the one hand and

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**Table 4. Myocardial Blood Flow and Oxygen Consumption Before and After Administration of Enoximone**

<table>
<thead>
<tr>
<th>Patient</th>
<th>MBF (ml/min/100 g)</th>
<th>ACSDO₂ (ml/100 ml)</th>
<th>MVO₂/min (ml/min/100 g)</th>
<th>MVO₂/beat (µl/beat/100 g)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C</td>
<td>E</td>
<td>C</td>
<td>E</td>
</tr>
<tr>
<td>1</td>
<td>70</td>
<td>85</td>
<td>14.1</td>
<td>13.5</td>
</tr>
<tr>
<td>2</td>
<td>72</td>
<td>83</td>
<td>13.1</td>
<td>11.3</td>
</tr>
<tr>
<td>3</td>
<td>82</td>
<td>66</td>
<td>12.9</td>
<td>11.2</td>
</tr>
<tr>
<td>4</td>
<td>81</td>
<td>111</td>
<td>13.8</td>
<td>12.5</td>
</tr>
<tr>
<td>5</td>
<td>130</td>
<td>99</td>
<td>11.0</td>
<td>11.7</td>
</tr>
<tr>
<td>6</td>
<td>168</td>
<td>143</td>
<td>10.4</td>
<td>10.2</td>
</tr>
<tr>
<td>7</td>
<td>109</td>
<td>156</td>
<td>11.9</td>
<td>9.3</td>
</tr>
<tr>
<td>8</td>
<td>88</td>
<td>97</td>
<td>12.1</td>
<td>11.4</td>
</tr>
<tr>
<td>9</td>
<td>117</td>
<td>129</td>
<td>10.8</td>
<td>10.6</td>
</tr>
<tr>
<td>10</td>
<td>63</td>
<td>41</td>
<td>14.0</td>
<td>13.0</td>
</tr>
<tr>
<td>11</td>
<td>78</td>
<td>53</td>
<td>13.3</td>
<td>12.2</td>
</tr>
<tr>
<td>12</td>
<td>78</td>
<td>66</td>
<td>14.0</td>
<td>14.2</td>
</tr>
<tr>
<td>Mean</td>
<td>95</td>
<td>94</td>
<td>12.6</td>
<td>11.8</td>
</tr>
<tr>
<td>±SD</td>
<td>±31</td>
<td>±36</td>
<td>±1.3</td>
<td>±1.4</td>
</tr>
<tr>
<td>p</td>
<td>NS</td>
<td>&lt;0.01</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

MBF, myocardial blood flow; ACSDO₂, arterial-coronary-sinus oxygen content difference; MVO₂/min, myocardial oxygen consumption per minute; MVO₂/beat, myocardial oxygen consumption per beat; C, control; E, enoximone.

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**Figure 1. Relation between measured and predicted myocardial oxygen consumption (MVO₂).** Regression lines were calculated from the control values of all patients and the values obtained with nitroprusside administration. Regression analyses are given in Table 5. Left panel: Measured myocardial oxygen consumption per minute compared with predicted myocardial oxygen consumption by Eₜ (Bretschneider’s index). Middle panel: Measured myocardial oxygen consumption per minute compared with the predicted myocardial oxygen consumption by the pressure-work index. Right panel: Measured myocardial oxygen consumption per beat compared with the pressure-volume area. ○, control values of the patients receiving nitroprusside; □, values obtained after administration of nitroprusside; ▲, control values of the patients receiving enoximone; △, values obtained after administration of enoximone.
TABLE 5. Relations Between Myocardial Oxygen Consumption and Hemodynamic Variables

<table>
<thead>
<tr>
<th>Linear regression analysis</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>MV02 (ml/min/100 g)=</td>
<td>r</td>
<td>p</td>
</tr>
<tr>
<td>A 1.46·E1+1.69</td>
<td>0.52</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>B 1.61·E1+0.65</td>
<td>0.58</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>A 1.43·PWI−0.34</td>
<td>0.57</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>B 1.40·PWI−0.11</td>
<td>0.60</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>A 1.11·10−3·STI·HR+2.55</td>
<td>0.77</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>B 0.79·10−3·STI·HR+5.82</td>
<td>0.65</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>A 3.90·10−4·Smax·HR+3.27</td>
<td>0.72</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>B 3.45·10−4·Smax·HR+4.57</td>
<td>0.66</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>A 9.60·10−3·PV-work·HR+8.71</td>
<td>0.30</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>B 9.42·10−3·PV-work·HR+8.65</td>
<td>0.29</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>A 4.42·10−3·dP/dtmax·HR+7.51</td>
<td>0.37</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>B 4.26·10−3·dP/dtmax·HR+7.21</td>
<td>0.39</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>A −7.94·10−3·MVo·HR+12.09</td>
<td>−0.07</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>B −1.25·10−4·MVo·HR+11.30</td>
<td>0.00</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

MV02 (ml/beat/100 g)=
A 1.02·STI+37.93       0.75 <0.001
B 0.74·STI+68.42       0.71 <0.001
A 0.36·Smax+45.94      0.61 <0.001
B 0.31·Smax+59.93      0.61 <0.001
A 8.77·PV-work+104.21  0.32 >0.05
B 9.47·PV-work+96.75   0.35 >0.05
A 9.90·10−3·dP/dtmax+124.73 | 0.06 >0.05 |
B 2.79·10−3·dP/dtmax+124.87 | 0.02 >0.05 |
A −28.27·MVo+157.23   −0.23 >0.05
B −25.81·MVo+150.69   −0.27 >0.05
A 0.012·PVA+59.40     0.63 <0.001
B 0.011·PVA+65.90     0.62 <0.001

A, regression analysis performed with control values of all patients (n=22) and values obtained under conditions of nitroprusside (n=10). B, regression analysis performed with values of A (n=32) and values obtained under conditions of enoximone (n=12).

MV02 (ml/min/100 g) or (ml/beat/100 g), myocardial oxygen consumption per minute or per beat; E1 (ml/min/100 g), Brechtsoeder’s index; PW1 (ml/min/100 g), pressure-work index; STI (105 dynes · sec/cm²), left ventricular systolic stress-time integral; HR (min⁻¹), heart rate; Smax (10⁶ dynes/cm²), left ventricular peak systolic wall stress; PV-work (mm Hg · l/100 g), pressure-volume work; dP/dtmax (mm Hg/sec), maximum rate of left ventricular pressure rise; MVo (circ/sec), mean velocity of circumferential fiber shortening; PVA (mm Hg · ml/100 g), pressure-volume area.

myocardial oxygen consumption on the other. Differences in heart rate were taken into account by calculating both myocardial oxygen consumption and hemodynamic variables per beat as well as per minute (Table 5). The best correlation was found between myocardial oxygen consumption and systolic stress-time integral (Figure 2). Peak systolic wall stress correlated moderately with myocardial oxygen consumption (Figure 3). There was no relevant correlation between myocardial oxygen consumption and pressure-volume work, maximum rate of left ventricular pressure rise, or mean velocity of circumferential fiber shortening (Figure 3). Consideration of pressure-volume work, maximum rate of left ventricular pressure rise, or mean velocity of circumferential fiber shortening did not significantly improve the relation between myocardial oxygen consumption and systolic stress-time integral. When the correlation between myocardial oxygen consumption and systolic stress-time integral obtained from all control and nitroprusside data points was extrapolated to zero stress-time integral, the energy utilization for the nonmechanical activity of the mycardium was 2.55 ml/min/100 g (Figure 2). By including stress-time integral and myocardial oxygen consumption data obtained under conditions of enoximone in the regression analysis, we found that the y-axis intercept was increased and the slope was decreased, whereas this inclusion reduced the correlation coefficient (Table 5).

Comparative Effects of Enoximone and Nitroprusside on the Relation Between Hemodynamic Variables and Myocardial Oxygen Consumption

A multiple regression procedure was applied to analyze the relation between the changes of myocardial oxygen consumption and the changes of left ventricular peak systolic wall stress, systolic stress-time integral, pressure-volume work, maximum rate of left ventricular pressure rise, and mean velocity of circumferential fiber shortening after nitroprusside administration. A close linear correlation existed between the decrease of myocardial oxygen consumption and the decrease of systolic stress-time integral (r = 0.82, p < 0.005) (Figure 4). This correlation did not significantly improve when the other variables were taken into account. A significant linear correlation between the decrease of myocardial oxygen consumption and the decrease of systolic stress-time integral was also observed after the administration of enoximone. However, the slope of the regression line was significantly lower under conditions of enoximone (0.51 vs. 1.27, p < 0.05), indicating a smaller decrease of myocardial oxygen consumption for a given reduction of stress-time integral with enoximone.

Applying the pressure-work index (Figure 5) and the pressure-volume area (Figure 6) instead of systolic stress-time integral yielded similar results. When Brechtsoeder’s index was used, the predicted and the measured changes of myocardial oxygen consumption were not correlated (r = 0.54, p > 0.05 with nitroprusside; and r = 0.56, p > 0.05 with enoximone).

Norepinephrine Plasma Levels

Norepinephrine plasma levels did not significantly change after administration of enoximone. Norepinephrine plasma levels measured from the aorta were 0.30 ± 0.14 ng/ml before and 0.35 ± 0.17 ng/ml after administration of enoximone. Norepinephrine plasma levels measured from the coronary sinus were 0.41 ± 0.27 and 0.47 ± 0.32 ng/ml.
**Discussion**

*Relation Between Hemodynamic Variables and Myocardial Oxygen Consumption*

In the first part of this investigation, the relation between myocardial oxygen consumption and hemodynamic variables in patients with dilated cardiomyopathy was evaluated. The calculations were performed for two different sets of data. The control values of all patients and the values obtained with nitroprusside were included in the first set. This analysis is based on the assumption that nitroprusside has no direct effects on the myocardium. The correlations obtained with these data are considered to represent basal conditions. Second, the data obtained with enoximone were added to the control and nitroprusside values to evaluate any deviation from basal conditions that may result from enoximone. When the predicted myocardial oxygen consumption by the pressure-work index, Bretschneider's index, and the pressure-volume area was correlated with measured myocardial oxygen consumption, only moderate correlations were obtained. This is in contrast to the findings in normal dog hearts and may be because left ventricular volume and wall thickness are inadequately considered in these indexes. Consideration of left ventricular geometry may be especially relevant in these patients with enlarged hearts. Of emphasis, the pressure-volume area was calculated by a modification of the method given by Suga assuming the volume-axis intercept, V₀, was zero.

To develop an index that considers left ventricular volume and wall thickness, the coupling of myocardial oxygen consumption with left ventricular hemodynamic variables, including peak systolic wall stress and systolic stress-time integral, was investigated. The rationale for the performed multiple regression analyses using heart rate, wall stress, and velocity of myocardial contraction was based on experimental data suggesting that they are major determinants of myocardial oxygen consumption; the additional influence of external myocardial work on energy consumption is unclear.

Consideration of heart rate is relevant for the present analysis because heart rate increased significantly with enoximone but remained unchanged with nitroprusside. The increase in heart rate with enoximone may have resulted from peripheral vasodilation or from direct effects of enoximone on the sinoatrial node. Heart rate was taken into account by calculating both myocardial oxygen consumption and hemodynamic variables for one cardiac wave form.
FIGURE 3. Relation between myocardial oxygen consumption (MV\(\text{O}_2\)) and peak systolic wall stress (upper left-hand panel); pressure-volume work (upper right-hand panel); maximum rate of left ventricular pressure rise (dP/dt\(_\text{max}\)) (lower left-hand panel); mean circumferential fiber shortening (MV\(_f\)) (lower right-hand panel). Only peak systolic wall stress correlated significantly with myocardial oxygen consumption per beat. Correlation coefficients were calculated from the control values of all patients and the values obtained with nitroprusside. Regression analyses are given in Table 5. ●, control values of the patients receiving nitroprusside; △, control values of the patients receiving enoximone; ○, values obtained after administration of nitroprusside; ◀, values obtained after administration of enoximone.

FIGURE 4. Relation between the decrease of left ventricular systolic stress-time integral and the measured decrease of myocardial oxygen consumption per beat (MV\(\text{O}_2\)) after the administration of nitroprusside (●) and enoximone (△). Under both conditions, the decrease of systolic stress-time integral correlated significantly with the decrease of myocardial oxygen consumption. Slopes of both regression lines were significantly different (p<0.05), indicating less decrease of myocardial oxygen consumption for a given reduction of stress-time integral with enoximone.
cycle or per minute. This presupposes that the relation between myocardial oxygen consumption per beat and hemodynamic variables is not substantially influenced by changes in heart rate. Unaltered myocardial oxygen consumption to pressure-volume area relation when heart rate was increased by 60% has been shown by Suga et al.50 Similarly, Rooke and Feigl17 showed that myocardial oxygen consumption per beat is not substantially influenced by heart rate when hemodynamic variables remain constant.

Left ventricular systolic stress-time integral was found to be the major determinant of myocardial oxygen consumption in these patients with dilated cardiomyopathy. Systolic wall stress as a function of pressure, volume, and wall thickness represents the force developed per unit cross-sectional area of myocardium necessary to produce the intraventricular...
ular pressure at the given geometry. In addition to peak wall stress, systolic stress-time integral includes the pattern of stress development and maintenance and therefore describes the entire period of mechanical activity. 29,48,51 This may explain the stronger correlation between myocardial oxygen consumption and stress-time integral compared with peak stress. In contrast to experiments in normal dog hearts, 52,53 in these patients, indexes of contraction velocity such as maximum rate of left ventricular pressure rise (isovolumic phase) and mean velocity of circumferential fiber shortening (ejecting phase) were not significantly related to myocardial oxygen consumption. The lack of correlation between pressure-volume work and myocardial oxygen consumption may be because pressure-volume work is reduced relative to stress-time integral in patients with dilated cardiomyopathy. 54 Extrapolation of the oxygen consumption–stress-time integral relation to zero stress-time integral yields an intercept of 2.55 ml/min/100 g, which represents the energy utilization for the nonmechanical activity of the myocardium. Oxygen consumption of the empty beating dog heart was recently reported by Gibbs et al 55 to be 3.8 ml/min/100 g at a heart rate of 158 beats/min. After arrest caused by potassium chloride, basal myocardial oxygen consumption was 1.74 ml/min/100 g in this study. Suga et al 19 reported a value of 5.24 ml/min/100 g at a rate of 138 beats/min and of 1.47 ml/min/100 g after arrest.

When values obtained during enoximone administration were included, the y-axis intercept of the regression line increased, and the slope decreased, whereas the correlation coefficient was reduced. In Figure 2, 11 of 12 enoximone values are above the regression line, indicating higher oxygen consumption per unit stress-time integral under conditions of enoximone.

**Comparative Effects of Enoximone and Nitroprusside on Myocardial Energetics**

To distinguish the energetic consequences of the inotropic and the vasodilating effects of enoximone, the influence of enoximone on myocardial oxygen consumption and hemodynamic variables was compared with the effects of nitroprusside. After the administration of both drugs, there was a significant correlation of the decrease in myocardial oxygen consumption with the decrease in systolic stress-time integral. However, for a given reduction of stress-time integral, the decrease of myocardial oxygen consumption was smaller with enoximone. The diminished savings in oxygen subsequent to reduced systolic stress-time integral reflects the extra energy demand of the inotropic effect of enoximone that masks the energy-saving effect of vasodilation.

Although the pressure-work index and the pressure-volume area were only moderately correlated to myocardial oxygen consumption when absolute values were analyzed, close correlations were obtained when the nitroprusside-induced changes of either index were plotted against the corresponding changes of myocardial oxygen consumption. The better correlations may reflect that absolute values of left ventricular geometry are less relevant when changes in indexes are used. By applying the pressure-work index and the pressure-volume area instead of systolic stress-time integral, we found similar energetic differences between nitroprusside and enoximone.

Because the reduction of preload and afterload was more pronounced with enoximone than with nitroprusside, the question arises whether the energetic changes observed might have been caused by an increase in plasma catecholamines rather than by the direct effects of enoximone on the myocardium. This possibility can be excluded, however, because norepinephrine plasma levels did not significantly change after the administration of enoximone.

Whether myocardial oxygen consumption decreases, increases, or remains unchanged in response to enoximone depends on the degree by which the energetic consequences of peripheral vasodilation offset the increased energy cost of the inotropic effect. In these patients with moderate congestive heart failure, enoximone exerted a pronounced vasodilating effect that compensated for the increased energy demand due to inotropic stimulation. However, because the quantitative response to vasodilation varies with the degrees of heart failure, the presence of peripheral edema and concomitant medication, global myocardial oxygen consumption may increase in another group of patients. 56,57 This may also explain the conflicting results of clinical studies on the effect of enoximone on myocardial oxygen consumption per minute in which oxygen consumption decreased by 18%, 13 remained unchanged (present study), or increased significantly by 7% 12 or 33%. 14

External myocardial efficiency that was reduced during basal conditions compared with normal values showed the tendency to increase with nitroprusside and to decrease with enoximone. Efficiency was significantly increased while myocardial oxygen consumption was decreased after enoximone in the study of Amin et al. 13 Efficiency was not calculated in the studies of Martin et al 12 and Viquerat et al 14 in which myocardial oxygen consumption increased significantly. Efficiency here is defined as the ratio of pressure-volume work to myocardial oxygen consumption, and it describes the efficiency of the left ventricle as a pump. Because pressure-volume work is not significantly correlated with myocardial oxygen consumption (Figure 3, Table 5) and because efficiency is load dependent, external myocardial efficiency is not ideal for evaluating the energetic consequences of cardiotonic agents on the myocardium.

The influence of enoximone on cardiac index, right heart pressures, and pulmonary and peripheral circulation has been extensively investigated 4,12–14,34 and was not of primary interest here. Of note,
however, the cardiac index did not increase after the administration of enoximone in these patients. This is in contrast to studies performed in patients with severe congestive heart failure in which a pronounced increase of cardiac index has been observed with doses of enoximone comparable to those used here.4,12-14,34 In view of the energetic effects of enoximone, the lack of increase in cardiac index suggests that the inotropic action of enoximone was counteracted by the pronounced decrease of left ventricular preload (Frank-Starling mechanism) or that the dose regimen was inappropriate to increase cardiac index in these patients.

Increased energy consumption of force development after enoximone was recently shown in animal experiments with a myothermical technique.20 Because similar energetic effects have also been shown for catecholamines,20,21 it is interesting to postulate that intracellular cyclic AMP concentration has a fundamental influence on the coupling between myocardial mechanics and energy demand. Cyclic AMP through protein phosphorylation increases the number of calcium ions delivered into the cytoplasm, accelerates the calcium reuptake by the sarcoplasmic reticulum, and reduces the sensitivity of the troponin-tropomyosin system for calcium ions.1,2,58 Therefore, more energy per beat is necessary for calcium transport.19,21-24 Furthermore, cyclic AMP is supposed to have direct effects on the contractile proteins, increasing the cross-bridge cycling rate59,60 and decreasing the cross-bridge economy.61 Sonnenblick et al53 concluded from their experiments in dog myocardium that the additional oxygen consumption associated with catecholamines can be explained by elevated velocity of contraction and thus by the additional energy demand of the contractile proteins. Increased energy consumption relative to developed stress (rabbit myocardium) or pressure-volume area (dog myocardium) with catecholamines has also been described by Gibbs et al22,23 and Suga et al,19 respectively. These groups, however, interpreted their findings in terms of increased energy turnover of activation (calcium transport) and constant energy turnover of mechanical processes. Increased energy turnover for calcium transport as well as decreased cross-bridge economy after the administration of enoximone have been observed in experimental studies20,61 and could explain the energetic differences between enoximone and nitroprusside.

Assuming that the inotropic mode of action determines the influence of cardiotoxic agents on myocardial energetics,61 qualitatively similar effects obtained with enoximone would be expected with other phosphodiesterase inhibitors or catecholamines. Cardiotoxic drugs that do not increase cyclic AMP, for example, cardiac glycosides or pure calcium sensitizers, may have different energetic profiles.

Conclusions and Clinical Implications

Left ventricular systolic stress-time integral is the major determinant of myocardial oxygen consump-

tion in patients with dilated cardiomyopathy and moderate congestive heart failure. Vasodilation with nitroprusside or enoximone reduces myocardial oxygen consumption in proportion to the reduction of systolic stress-time integral; however, the amount of oxygen reduction is significantly smaller with enoximone. This indicates that enoximone has both an energy-saving effect due to its vasodilating properties and an energy-consuming effect by inotropically stimulating the myocardium. Measured myocardial oxygen consumption reflects the energetic consequences of both pharmacologic properties of enoximone.

The clinical application of enoximone is harmless in terms of myocardial energy consumption provided the vasodilating and inotropic effects of enoximone are balanced. If, however, the inotropic effect of enoximone becomes dominant, myocardial energy demand increases. This must be considered particularly if an initial vasodilating effect is lost or attenuated during long-term therapy,3 especially in patients with congestive heart failure due to ischemic heart disease. Although the clinical relevance of energy metabolism for the pathogenesis and progression of idiopathic dilated cardiomyopathy is not understood yet, increased energy demand due to inotropic stimulation may have harmful effects7 if mitochondrial or microvascular dysfunctions are present in this disease.6,62

Acknowledgments

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KEY WORDS • energetics, myocardial • nitroprusside • enoximone • dilated cardiomyopathy

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