Cardiopulmonary Effects of Enprofylline*

A Xanthine with Weak Adenosine Receptor Antagonism in Patients with Severe Chronic Lung Disease

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The acute cardiovascular effects of a new xanthine, enprofylline, were studied in patients with chronic lung disease. The studies were done during cardiac catheterization (n = 12) and by radionuclide ventriculography (n = 6). Enprofylline was given intravenously, 2 mg/kg, and measurements were done after ten and 30 min. Enprofylline reduced the mean pulmonary artery pressure from 30 ± 10 to 26 ± 7 mm Hg (p<0.05) and the mean systemic arterial pressure from 92 ± 17 to 83 ± 15 mm Hg (p<0.01), increased the heart rate from 89 ± 15 to 100 ± 18 beats/min (p<0.01) and reduced the stroke volume from 55 ± 12 to 45 ± 12 ml (p<0.05) after 30 min. Radionuclide ventriculography revealed unchanged ejection fraction of left and right ventricles after enprofylline. None of the patients experienced serious side effects of the drug. Thus, enprofylline induced modest acute cardiovascular effects with a chronotropic response together with a small vasodilation in pulmonary and systemic circulation.

The development of cor pulmonale with pulmonary hypertension and right ventricular failure are well known complications of chronic lung diseases and are associated with a poor prognosis.1,2 Xanthines are widely used bronchodilators in these patients with cor pulmonale. However, drugs like theophylline which are metabolized in the liver, might have unpredictable half-lives in patients with heart failure.3,4 Furthermore, due to the adenosine-blocking effects of theophylline, the pharmacologic profile of the drug may be different in hypoxic situations with high adenosine production.5,6 Enprofylline is a new xanthine bronchodilator with a short half-life6 and which appears to be about five times as potent as theophylline in animals and asthmatic patients.11,12 Based on animal studies, enprofylline seems to have a more favorable pharmacologic profile with excretion of unmetabolized drug to the urine, and it seems to lack some of the extrapulmonary effects of theophylline like diuretic and central nervous system stimulant effects.8 The cardiovascular effects of enprofylline in man so far have been evaluated little, but studies are consistent with a positive inotropic and chronotropic effect of the drug.13,14

In this study, we examined the cardiovascular effects of a single intravenous dose of enprofylline in patients with severe chronic lung diseases. The studies included right heart catheterization and radionuclide ventriculography of right and left ventricles. Since a chronotropic effect of enprofylline has been reported,14 we also compared the hemodynamics after drug admin-

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METHODS

Patients

Eighteen patients with severe chronic lung disease were included in the study. They were ten men and eight women of an average age of 66 years (range, 36 to 81 years). None of the patients had clinical or electrocardiographic evidence of coronary or valvular heart disease, systemic hypertension or primary myocardial disease. The criteria for inclusion in the study were (1) chronic lung disease in stable condition; (2) no clinical evidence of left-sided heart failure; (3) mean pulmonary capillary wedge pressure <12 mm Hg at rest; and (4) mean pulmonary artery pressure >16 mm Hg at rest. The patients were allowed to take digitalis, diuretics and bronchodilator spray, but all other cardiovascular drugs were discontinued 12 to 24 hs before each study. The studies were performed after an overnight fast without premedication. Informed consent was obtained from all patients, and no complications resulted from the study. The study was approved by the Regional Ethical Committee at the University of Bergen and by the Norwegian Medicines Control Authorities.

Cardiac Catheterisation

Right heart catheterization was done with a balloon-tipped Swan-Ganz catheter introduced from a femoral veins. A short plastic catheter was inserted into a femoral artery for recording of pressure and blood sampling. Intravascular pressures were recorded through fluid-filled catheters with the transducer in the mid-axillary level. Cardiac output (CO [liters per minute] L/min) was measured in triplicate by the thermodilution method. Pulmonary vascular resistance (dynsecm-5) was calculated as

\[(PA - PCWP) \times 80/CO,\]

where PA is mean pulmonary artery pressure and PCWP is mean pulmonary capillary wedge pressure; systemic vascular resistance (dynsecm-5) as

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(AP – RA) × 80/CO,
where AP is mean systemic arterial pressure and RA is mean right arterial pressure; and right ventricular stroke work index (RVSWI) (g.m/m²) as
SVI × (PA – RA) × 0.0136,
where SVI is stroke volume index.

**Radionuclide Ventriculography**

Gated blood pool scintigraphy was done after in vivo labelling of erythrocytes with 15 mCi of 99mTc pertechnetate. The detector was located in left anterior projection. Left and right ventricular (LV and RV) end-diastolic and end-systolic contours were operator-outlined. Ejection fraction (EF) of the ventricles were calculated as end-diastolic counts minus end-systolic counts divided by end-diastolic counts after background subtraction. The coefficient of variation for duplicate measurements of LVEF and RVEF was 4 and 7 percent, respectively.

**Lung Function**

Forced vital capacity (FVC [in liters]) and one second forced expiratory volume (FEV₁ [in liters]) were measured on a Bernstein volume spirometer (Kifa, Lund, Sweden). Peak expiratory flow (PEF [liters per minute]) was measured with a standard Wright peak flow meter.

**Blood Gases**

Arterial and mixed venous blood was sampled into heparinized syringes and immediately analyzed for oxygen saturation (OSM2 Hemoximeter, Radiometer, Copenhagen, Denmark) and arterial blood oxygen and carbon dioxide tension (PaO₂ and PaCO₂) (ABL2 Acid-Base Laboratory, Radiometer, Copenhagen, Denmark). Systemic oxygen delivery (in milliliters per minute per square meter) was calculated as

\[ \text{CaO}_2 \times CI \]

where \( \text{CaO}_2 \) is oxygen content in arterial blood and CI is cardiac index. Arterial blood samples were taken before, and 10 and 30 min after drug administration for analysis of enprofylline concentrations by liquid chromatography.

**Study Protocol**

The study was done as an open study during cardiac catheterization in 12 patients receiving enprofylline (enprofylline group) and six patients receiving saline solution (control group). After the first six patients had received enprofylline, the following 12 patients were randomly assigned to receive either saline solution or enprofylline. The measurements were done with subjects in the supine position at rest, and 10 and 30 min following infusion of enprofylline or saline solution. Patients receiving enprofylline had an additional recording before drug infusion during atrial pacing at a heart rate about 10 beats per minute above resting heart rate. Radionuclide ventriculography was performed in six patients in the enprofylline group with measurements done before, and 10 and 30 min after drug administration.

**Enprofylline Infusion**

Enprofylline was given in a dose of 2 mg/kg intravenously as a slow infusion during 10 min. Femoral artery pressure was recorded continuously during drug infusion.

**Statistical Analysis**

Each patient served as his or her own control. Comparisons of differences in the results from before and after drug administration within each patient were done using the Wilcoxon test (two-tailed) for paired data and between enprofylline and control groups using Wilcoxon test for unpaired data (two-tailed). Linear regression analysis was used to determine the relationship between the blood pressure values before and the change after drug administration. To avoid the problem of arbitrary regression to the mean, significant results were also analyzed by relating the change in values to the average of values before and after drug administration. A probability value of <0.05 was regarded as statistically significant. All data are expressed as mean values ± 1 standard deviation.

**Results**

**Patient Characteristics**

All patients had chronic lung diseases with severely impaired lung function with FVC 1.6±0.9 L (mean ± SD) and FEV₁ 0.8±0.5 L (Table 1). Ten of 12 patients receiving enprofylline had severe chronic airflow limitations. On cardiac catheterization a majority of the patients had pulmonary hypertension with

**Table 1—Patient Characteristics and Lung Function**

<table>
<thead>
<tr>
<th>Case/Age/Sex</th>
<th>Diagnosis†</th>
<th>FVC, L</th>
<th>FEV₁, L</th>
<th>PaO₂ kPa</th>
<th>PaCO₂ kPa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enprofylline group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/68/F</td>
<td>COLD</td>
<td>1.3</td>
<td>0.7</td>
<td>6.5</td>
<td>6.2</td>
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<tr>
<td>2/38/F</td>
<td>COLD</td>
<td>2.0</td>
<td>1.0</td>
<td>6.8</td>
<td>5.8</td>
</tr>
<tr>
<td>3/73/M</td>
<td>COLD</td>
<td>1.0</td>
<td>0.7</td>
<td>5.0</td>
<td>8.7</td>
</tr>
<tr>
<td>4/62/M</td>
<td>FA</td>
<td>4.7</td>
<td>2.6</td>
<td>7.5</td>
<td>4.6</td>
</tr>
<tr>
<td>5/81/M</td>
<td>COLD</td>
<td>1.5</td>
<td>0.7</td>
<td>5.8</td>
<td>8.7</td>
</tr>
<tr>
<td>6/76/M</td>
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<td>0.5</td>
<td>5.4</td>
<td>8.0</td>
</tr>
<tr>
<td>7/75/M</td>
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<td>0.6</td>
<td>6.3</td>
<td>6.9</td>
</tr>
<tr>
<td>8/36/F</td>
<td>CF</td>
<td>1.0</td>
<td>0.6</td>
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<td>6.8</td>
</tr>
<tr>
<td>9/67/M</td>
<td>COLD</td>
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<td>0.6</td>
<td>7.9</td>
<td>7.1</td>
</tr>
<tr>
<td>10/63/M</td>
<td>COLD</td>
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<td>0.6</td>
<td>7.1</td>
<td>5.3</td>
</tr>
<tr>
<td>11/62/F</td>
<td>FA</td>
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<td>1.1</td>
<td>7.1</td>
<td>9.0</td>
</tr>
<tr>
<td>12/59/M</td>
<td>COLD</td>
<td>1.2</td>
<td>1.0</td>
<td>6.7</td>
<td>9.0</td>
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<tr>
<td>Control group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13/71/F</td>
<td>COLD</td>
<td>0.8</td>
<td>0.6</td>
<td>9.8</td>
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<tr>
<td>14/70/F</td>
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<td>5.1</td>
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<tr>
<td>15/67/F</td>
<td>COLD</td>
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<td>0.6</td>
<td>6.2</td>
<td>6.2</td>
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<tr>
<td>16/73/F</td>
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<td>8.3</td>
<td>6.2</td>
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<tr>
<td>17/69/M</td>
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<td>1.0</td>
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<tr>
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<td>COLD</td>
<td>1.0</td>
<td>0.4</td>
<td>7.5</td>
<td>5.6</td>
</tr>
</tbody>
</table>

*FVC = forced vital capacity; FEV₁ = forced expiratory volume in one second; PaO₂ = arterial oxygen tension; PaCO₂ = arterial carbon dioxide pressure.
†CF = cystic fibrosis; COLD = chronic obstructive lung disease; FA = fibrosing alveolitis.
Cardiac index, Heart rate, beats/min, volume, PA, Mean g.m/sqm, RVSWI, PVR, tPA = vs Mean dyn, SVR, Hg increased pulmonary elevation index was seven Hg PEF, L/min E 134±113 148±115± 147±124±
C 111±40 — —
PaO₂, kPa E 6.6±0.9 6.6±1.0 6.7±1.2
C 7.2±0.8 7.1±0.8 7.4±0.7
PaCO₂, kPa E 7.3±1.3 7.1±1.5 6.9±1.6
C 6.6±0.8 6.7±0.8 6.9±0.9
SaO₂, %§ E 80±6 81±5 81±7
C 84±6 84±6 85±5
SvO₂, %§ E 57±8 58±5 57±5
C 60±5 59±6 60±5
O₂ delivery, ml/min/sq m§ E 440±54 458±88 438±72
C 476±91 463±119 483±98

Table 2—Cardiovascular Effects of Intravenously Administered Enprofylline (2 mg/kg) or Saline in Patients with Chronic Lung Diseases*

<table>
<thead>
<tr>
<th>Factors†</th>
<th>Before Drug</th>
<th>10 min</th>
<th>30 min</th>
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<tbody>
<tr>
<td>Heart rate, beats/min</td>
<td>E 89±15</td>
<td>104±20†§</td>
<td>100±18§</td>
</tr>
<tr>
<td></td>
<td>C 87±16</td>
<td>86±17</td>
<td>85±15</td>
</tr>
<tr>
<td>Cardiac index, L/min/m²</td>
<td>E 2.9±0.5</td>
<td>2.9±0.6</td>
<td>2.8±0.6</td>
</tr>
<tr>
<td></td>
<td>C 2.9±0.6</td>
<td>2.8±0.8</td>
<td>2.9±0.6</td>
</tr>
<tr>
<td>Stroke volume, ml</td>
<td>E 55±12</td>
<td>49±14†</td>
<td>48±12§</td>
</tr>
<tr>
<td></td>
<td>C 54±11</td>
<td>55±16</td>
<td>56±13</td>
</tr>
<tr>
<td>Mean PA, mm Hg</td>
<td>E 30±10</td>
<td>27±8§</td>
<td>26±7¶</td>
</tr>
<tr>
<td></td>
<td>C 28±7</td>
<td>27±6</td>
<td>27±6</td>
</tr>
<tr>
<td>Mean AP, mm Hg</td>
<td>E 92±17</td>
<td>86±14†</td>
<td>83±15‡</td>
</tr>
<tr>
<td></td>
<td>C 99±18</td>
<td>94±17</td>
<td>96±19</td>
</tr>
<tr>
<td>PVR, dyn • s • cm⁻³</td>
<td>E 395±198</td>
<td>345±132‡</td>
<td>348±138</td>
</tr>
<tr>
<td></td>
<td>C 323±97</td>
<td>333±124</td>
<td>339±136</td>
</tr>
<tr>
<td>SVR, dyn • s • cm⁻³</td>
<td>E 1,497±332</td>
<td>1,377±276¶</td>
<td>1,407±409</td>
</tr>
<tr>
<td></td>
<td>C 1,709±496</td>
<td>1,657±124</td>
<td>1,617±450</td>
</tr>
<tr>
<td>RVSWI, g • m • sq m</td>
<td>E 11.7±4.9</td>
<td>9.8±4.8∥</td>
<td>8.5±3.4¶</td>
</tr>
<tr>
<td></td>
<td>C 10.1±3.6</td>
<td>10.0±3.5</td>
<td>10.2±3.4</td>
</tr>
</tbody>
</table>

*E = enprofylline group (n = 12 patients); C = control (saline) group (n = 6 patients). All values are means ± SD.
†PA = pulmonary artery pressure; AP = systemic arterial pressure; PVR = pulmonary vascular resistance; SVR = systemic vascular resistance; RVSWI = right ventricular stroke work index.
‡p<0.01 vs values before drug administration; ¶p<0.05 vs values before drug administration; §p<0.05 vs changes in control group.

Elevation of pulmonary artery pressure (mean PA >30 mm Hg in five, 26 to 30 mm Hg in four, 20 to 25 mm Hg in seven and <20 mm Hg in two patients), increased pulmonary vascular resistance while the cardiac index was within the normal range (Table 2).
7.9±3.4 mg/L after 10 min and fell to 4.6±1.1 mg/L 30 min after the start of drug infusion.

**Lung Function**

A small increase in PEF was observed both 10 and 30 min after infusion of enprofylline (p<0.01) (Table 3). No significant linear correlation was found between changes in PEF and changes in mean pulmonary artery pressure (r = 0.23, n = 12, NS) or mean systemic arterial pressure (r = 0.50, n = 12, NS) 30 min after the start of drug infusion.

**Cardiovascular Effects**

Enprofylline increased the heart rate in all patients by an average of 15 beats per minute after 10 min (p<0.01) and 11 beats per minute after 30 min (p<0.01) (Table 2, Fig 1). Cardiac index was not significantly changed by the drug while stroke volume fell by 11 percent (p<0.05) and 13 percent (p<0.01) after 10 and 30 min, respectively. A small reduction of the elevated mean pulmonary artery pressure was seen after enprofylline by an average of 10 percent (p<0.05) and 13 percent (p<0.01), but pulmonary vascular resistance was not significantly changed (Fig 2). The mean arterial pressure was reduced by 7 percent (p<0.05) and 10 percent (p<0.01) (Fig 2), and similar changes were found for systolic pressure, \( \Delta PA, \text{mm Hg} \) and \( \Delta AP, \text{mm Hg} \).

\[ \Delta PA, \text{mm Hg} \]

\[ \Delta AP, \text{mm Hg} \]

\[ \Delta PVR, \text{dyn. sec cm}^{-5} \]

\[ \Delta SVR, \text{dyn. sec cm}^{-5} \]

\[ \text{Time (minutes)} \]

**Figure 2.** Effects of enprofylline, 2 mg/kg intravenously. Changes from values before drug administration are given for mean pulmonary artery pressure (\( \Delta PA \)), pulmonary artery resistance (\( \Delta PVR \)), mean aortic pressure (\( \Delta AP \)) and systemic vascular resistance (\( \Delta SVR \)). Asterisk = p<0.05 and double asterisks = p<0.01 vs values before drug with basal heart rate; * = p<0.05 and ** = p<0.01 vs before drug during atrial pacing, and dagger = p<0.05 and double daggers = p<0.01 vs control group.

\[ \Delta PA, \text{mm Hg} \]

\[ r = 0.82 \]

\[ n = 12 \]

\[ p < 0.01 \]

**Figure 3.** Relationship between mean pulmonary artery pressure (PA) and changes in pressure (\( \Delta PA \)) 30 min after enprofylline infusion.

which was reduced from 129±28 mm Hg by 5 percent (p<0.05) and 8 percent (p<0.01), and in diastolic pressure from 69±12 mm Hg by 6 percent (p<0.05) and 7 percent (p<0.01) after 10 and 30 min, respectively.

A positive linear correlation was found between mean pulmonary artery pressure before and the change in mean pulmonary artery pressure 30 min after enprofylline infusion (r = 0.82, n = 12, p<0.01) (Fig 3). When the change in pressure was related to the average value before and after enprofylline, the correlation was still significant (r = 0.76, n = 12, p<0.01). No significant correlation was established between mean systemic arterial pressure before and the change in pressure after drug administration (r = 0.41, n = 12, NS).

When the cardiovascular changes during enprofylline administration were compared with values obtained during atrial pacing, no significant change in cardiac index or stroke volume was found (Fig 1). However, enprofylline induced a significant reduction in mean pulmonary artery pressure, mean arterial pressure and in right ventricular stroke work index when compared with values during atrial pacing before drug administration (Fig 1 and 2). In the control group no significant cardiovascular changes were found in the observation period (Table 2).
changes found in the control group and enprofylline-treated patients revealed significant changes after 30 min in heart rate, stroke volume, right ventricular stroke work index (Table 2, Fig 1), and mean pulmonary artery pressure (Fig 2).

Radionuclide Ejection Fraction

Right ventricular ejection fraction was 39±5 percent in the control state and was abnormal (<45 percent) in five of the six patients. Enprofylline infusion did not significantly change the ejection fraction after either 10 min (42±8 percent) or 30 min (42±8 percent). The LV ejection fraction was 62±8 percent before and did not change 10 min (65±9 percent) or 30 min (62±6 percent) after enprofylline infusion.

Effects on Blood Gases

No changes were observed in arterial or mixed venous blood gases or in systemic oxygen delivery.

Side Effects

Two patients experienced side effects. Both complained of nausea starting 10 and 20 min after start of drug infusion. The first patient also had mild epigastric discomfort and vomiting, which lasted two to three hrs, while the second patient had nausea lasting for about 10 min.

Discussion

The role of xanthines in the treatment of obstructive lung diseases is a matter of dispute, mainly due to the narrow therapeutic window observed by the use of theophylline. In the patients with chronic lung diseases and cor pulmonale, serious cardiac side effects of these drugs have been reported.5,16,20 These cardiotoxic effects might be due to unpredictable high plasma concentrations of the drug in patients with heart failure, but might also be related to the adenosine blocking properties of theophylline.5,6

This study demonstrates a bronchodilating effect of enprofylline in seriously ill patients with chronic lung diseases and hypoxemia. The bronchodilating effect of enprofylline has been reported previously in patients with bronchial asthma9,10 and recently also in patients with moderate chronic obstructive lung disease.21 There was, however, no correlation between the improvement in lung function and the hemodynamic changes, indicating that different mechanisms might be responsible for the ventilatory and circulatory effects.

The infusion of enprofylline in this study induced a modest tachycardia and reduction of blood pressure in both systemic and pulmonary circulation. The fall in pulmonary artery pressure during enprofylline therapy could be due to an active dilation or recruitment of pulmonary vessels, or could be secondary to an improvement in ventilation or gas distribution. A direct vasodilating effect of enprofylline on the pulmonary vessels seems to be more likely than recruitment of vessels since the cardiac output and the pulmonary flow were unchanged. The reduction of pulmonary pressure was most pronounced in those patients with highest pulmonary artery pressure before drug infusion, suggesting that an active vasodilation-striction is an important factor in the development of pulmonary hypertension in these patients. Also for other vasodilating agents in the pulmonary circulation like hydralazine, a close association between the degree of pulmonary blood pressure reduction and the pretreatment value has been reported.22,23

Enprofylline has been reported to increase left ventricular contractility as determined by increased force of contraction in isolated guinea-pig left atria in a dose-dependent manner.15 Using systolic time intervals in normal individuals, enprofylline was reported to have a positive inotropic effect at plasma concentrations exceeding 2 mg/L.14 The results obtained in this study, however, are not consistent with any positive inotropic effect of enprofylline. First, the radionuclide study showed unchanged ejection fractions of right and left ventricles after enprofylline. Second, the stroke volume at constant heart rate was not improved by enprofylline in spite of the lowering of blood pressure in both systemic and pulmonary circulation with consequent reduction of biventricular afterload.

The cardiovascular response to enprofylline infusion in this study appears to differ somewhat from that observed by theophylline. Although the hemodynamic profile with tachycardia and reduction of blood pressure are similar for the two drugs, the reduction in pulmonary vascular resistance seems, from reports in the literature, to be more prominent for theophylline.24,25 A comparison of the cardiovascular effects of theophylline and enprofylline should, however, be conducted in a randomly designed trial. This is consistent with the hypothesis that adenosine may be a potent pulmonary vasoconstrictor.7,26 Also the lack of increase in contractile function after enprofylline is in contrast to the findings by use of theophylline in therapeutic concentration.27,28 Although the exact intracellular mechanism for the bronchial and cardiovascular effects of xanthines are largely unknown, it has been attributed to their phosphodiesterase inhibitory activity,29 alteration of calcium flux30 and release of catecholamines.31 Additionally, at therapeutic concentrations theophylline has an inhibitory effect on adenosine receptors which is not shared by enprofylline.5,6 Adenosine increases coronary flow and has a cardio-depressive effect which reduces the myocardial metabolic demand.26 In situations with limited oxygen supply, adenosine protects the ischemic myocardium.
from development of necrosis.28 Adenosine may have a protective effect on the heart under stress conditions like myocardial ischemia or during beta-adrenergic stimulation,26 which are potent stimuli for increased endogenous production of adenosine. It has been suggested that the cardiotoxic effect of theophylline might be explained by its adenosine blocking action, and enprofylline might thus have therapeutic advantages. In this study we did not observe any serious side effect of enprofylline. The transient nausea experienced in two patients was at the time of maximal serum concentrations. Harmful systemic hypotension, a potentially deleterious effect of vasodilators when used in patients with cor pulmonale and right ventricular dysfunction, did not occur in our patients. Some vasodilators which affect pulmonary vasculature have been shown to change arterial blood oxygenation with lowering of PaO₂16,18 due to worsening of the ventilation/perfusion mismatching in these patients. Lowering of PaO₂ in hypoxemic patients has also been reported after use of xanthines. In this acute study, however, we could not demonstrate any fall in PaO₂ after enprofylline.

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