Hemodynamic and Metabolic Effects of Morphine in the Critically Ill

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SUMMARY To assess the effects of i.v. injection of morphine, 0.5 mg/kg, hemodynamic studies were performed on 24 critically ill patients under controlled ventilation. An esophageal balloon was used to estimate intrapleural pressure and transmural cardiac filling pressures were calculated. After injection of morphine, there were significant decreases in heart rate (13%), cardiac index (18%), stroke index (17%) and arterial pressure (15%) and there was a nonsignificant increase in esophageal pressure (15%). Transmural cardiac filling pressures decreased significantly (21% for the pulmonary wedge pressure); intravascular filling pressures were unchanged. Oxygen consumption decreased significantly, by 21%, in 10 patients with initially elevated oxygen consumption and by 9% in 14 patients with initially normal oxygen consumption. The oxygen extraction ratio was unchanged, suggesting that the decrease in oxygen consumption was caused by decreased oxygen demand rather than by inadequate oxygen delivery. These results indicate that the hemodynamic effects of morphine (0.5 mg/kg) administered to critically ill patients were associated with a significant decrease in oxygen consumption, which probably reflected sedation and analgesia.

MORPHINE can soothe severe pain, depress respiration and induce sedation without loss of consciousness. In critically ill patients treated in surgical intensive care units, large doses of morphine (0.5–2 mg/kg) can be used to provide sedation and analgesia. Of the 294 patients treated in the Surgical Intensive Care Unit of Pitie-Salpetriere Hospital in 1978, 197 received 45,522 mg of i.v. morphine. Each patient received an average daily dose of 82 mg (range 20–240 mg). The use of such quantities of morphine requires knowledge of whether morphine-induced sedation is associated with deleterious hemodynamic effects. Several studies performed on cardiac patients and on healthy volunteers demonstrated an apparent lack of detrimental hemodynamic changes after i.v. morphine in doses of 0.5–2 mg/kg. Nevertheless, increased cardiac filling pressures occurred during these studies even though morphine was not known to have any deleterious effect on myocardial contractility. Lappas et al. hypothesized that this increase in measured cardiac filling pressures could reflect some changes in pleural rather than transmural vascular pressures.

The aim of this study was to evaluate the changes in hemodynamics and oxygen consumption after high doses of i.v. morphine in critically ill patients. As all patients were mechanically ventilated, the changes in intravascular and transmural cardiac filling pressures were compared.

Methods

Patients

Twenty-four acutely ill patients being treated in the intensive care unit were selected according to the following criteria: absence of known cardiac disease, presence of sinus rhythm and stable hemodynamic condition without evident hypovolemia; absence of cardiotonic or antiarrhythmic drugs; absence of morphine or sedative drugs in the 24 hours before the study; insertion of arterial and Swan-Ganz catheters within the preceding 3 days as an integral part of patient's care; adaptation to the respirator; and absence of acute sepsis.

All patients were studied when the most acute phase of the disease had passed (2–5 days) and they were hemodynamically and metabolically stable. After the study, all received continuous i.v. infusion of morphine for 2-23 days. Most of the patients were ventilated with usual tidal volumes (8–9 ml/kg). Nine patients (nos. 3, 4, 9–11, 16, 18, 19 and 22) received larger tidal volumes (10–15 ml/kg) to enhance adaptation to the respirator. Eighteen patients were ventilated with intermittent positive pressure and a 5-cm
H₂O positive end-expiratory pressure was added in six. In all cases the FiO₂ was adjusted to obtain a PaO₂ greater than 120 mm Hg. The clinical and biological conditions of the patients at the beginning of the investigation are summarized in table 1.

### Hemodynamic Studies

Twenty-four hemodynamic studies were performed using an arterial and a #7F Swan-Ganz catheter after informed consent had been obtained from the patient or a relative. Systolic, diastolic and mean arterial pressures, central venous pressure, mean pulmonary arterial pressure and pulmonary wedge pressure were measured with a calibrated Bentley T transducer and recorded together with heart rate on a Thompson multichannel recorder. Great care was taken to establish the zero-pressure baseline at the midatrial level. Intravascular cardiac filling pressures were considered to be the average of the pulmonary wedge pressure, the mean pulmonary arterial pressure and the central venous pressure. The cardiac output was measured in triplicate by the thermodilution technique (Edwards model 9500) after injection of 10 ml of 2.5% glucose at 0°C into the right atrium. Cardiocirculatory variables were calculated as follows: cardiac index = cardiac output/body surface area; stroke index = cardiac index/heart rate; total vascular resistance = (mean arterial pressure - central venous pressure)/cardiac index.

### Measurements of Esophageal Pressure

In each patient, an esophageal balloon (length 10 cm, diameter 1.4 cm, wall thickness 0.06 mm) sealed over a polyethylene catheter (length 50 cm) was inserted through the nose and placed in the esophagus, with the balloon tip 30–45 cm from the nare. Before each measurement, 20 ml of air were rapidly introduced in the catheter and withdrawn by syringe to distort the walls of the balloon evenly. Then, the balloon was filled with 1 ml of air and connected to a low-pressure calibrated Bentley T transducer. Esophageal pressure was then simultaneously recorded with the ECG and intravascular cardiac filling pressures on a Thompson four-channel recorder. Transmural cardiac filling pressure was derived by subtracting esophageal pressure from intravascular cardiac filling pressures (fig. 1). Because of the discrepancy between absolute pressures measured in the esophagus and pleural cavity in supine patients, the calculated transmural pressures were not considered exact reflections

### Table 1. Initial Status of Patients

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Outcome</th>
<th>Temperature (°C)</th>
<th>Oxygen consumption* (ml/min/m²)</th>
<th>pH</th>
<th>P&lt;sub&gt;CO₂&lt;/sub&gt; (mm Hg)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>45</td>
<td>M</td>
<td>Multiple trauma</td>
<td>S</td>
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<td>208</td>
<td>7.48</td>
<td>35</td>
</tr>
<tr>
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<td>183</td>
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<td>33</td>
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<td>Multiple trauma, coma</td>
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<td>7.39</td>
<td>34</td>
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<td>7.46</td>
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<td>M</td>
<td>Aortic aneurysm</td>
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<td>39</td>
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<td>8</td>
<td>56</td>
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<td>Gastrointestinal cancer</td>
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<td>9</td>
<td>24</td>
<td>M</td>
<td>Multiple trauma, coma</td>
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<td>148</td>
<td>7.55</td>
<td>29</td>
</tr>
<tr>
<td>10</td>
<td>56</td>
<td>M</td>
<td>Multiple trauma</td>
<td>D</td>
<td>38.3</td>
<td>143</td>
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<td>61</td>
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<td>F</td>
<td>Multiple trauma</td>
<td>D</td>
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<td>127</td>
<td>7.54</td>
<td>31</td>
</tr>
<tr>
<td>17</td>
<td>52</td>
<td>F</td>
<td>Acute pneumonitis</td>
<td>S</td>
<td>38.0</td>
<td>124</td>
<td>7.49</td>
<td>39</td>
</tr>
<tr>
<td>18</td>
<td>56</td>
<td>M</td>
<td>Cerebral aneurysm, coma</td>
<td>D</td>
<td>38.0</td>
<td>124</td>
<td>7.48</td>
<td>27</td>
</tr>
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<td>42</td>
<td>F</td>
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<td>122</td>
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<td>32</td>
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<tr>
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<td>M</td>
<td>Aortic aneurysm</td>
<td>D</td>
<td>38.0</td>
<td>121</td>
<td>7.49</td>
<td>32</td>
</tr>
<tr>
<td>22</td>
<td>46</td>
<td>M</td>
<td>Multiple trauma</td>
<td>S</td>
<td>37.8</td>
<td>118</td>
<td>7.61</td>
<td>25</td>
</tr>
<tr>
<td>23</td>
<td>64</td>
<td>F</td>
<td>Aortic aneurysm</td>
<td>D</td>
<td>36.5</td>
<td>96</td>
<td>7.48</td>
<td>37</td>
</tr>
<tr>
<td>24</td>
<td>61</td>
<td>F</td>
<td>Tetraplegia C₄</td>
<td>D</td>
<td>36.7</td>
<td>90</td>
<td>7.40</td>
<td>39</td>
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</table>

*Normal values, 110-130 ml/min/m².

Abbreviations: D = dead; S = survived.
of absolute transmural cardiac filling pressures. Nevertheless, changes in esophageal pressure closely approximate changes in pleural pressure if the esophageal balloon is placed in the middle third of the esophagus and if measurements are made when the lung volume is greater than 20% of the vital capacity. As these conditions were achieved in the study, changes in calculated transmural pressures were regarded as a reliable measure of changes in absolute transmural cardiac filling pressures.

**Figure 1.** Transmural pressures were calculated by subtracting esophageal pressure (●) measured at midrespiration from intravascular pressures measured simultaneously (arrows). In this patient, esophageal pressure was 3.3 mm Hg, intravascular mean pulmonary arterial pressure (●) was 23 mm Hg, transmural mean pulmonary arterial pressure was 19.7 mm Hg, intravascular central venous pressure (● ● ●) was 5.5 mm Hg and transmural central venous pressure was 2.2 mm Hg.

**Metabolic Measurements**

Systemic and pulmonary arterial blood samples were simultaneously withdrawn within 1 minute after measurement of cardiac output (in triplicate), P02, Pco2 and pH. Hemoglobin concentration and oxygen saturation (SaO2 and SVO2) were measured with a Co-oxymeter 182. Arterial and mixed venous oxygen contents (CaO2 and CVO2), arteriovenous oxygen difference (A-VO2), oxygen consumption (VO2) and oxygen extraction ratio (OER) were calculated using standard formulas:

\[
\text{CaO}_2 \ (\text{vol/100 ml}) = 1.34 \times \text{Hb} \times \text{SaO}_2 + 0.003 \text{Pao}_2 \\
\text{CVO}_2 \ (\text{vol/100 ml}) = 1.34 \times \text{Hb} \times \text{SVO}_2 + 0.003 \text{PVO}_2 \\
\text{A-VO}_2 \ (\text{vol/100 ml}) = \text{CaO}_2 - \text{CVO}_2 \\
\text{VO}_2 \ (\text{ml/min/m}^2) = \text{CI} \times \text{A-VO}_2 \\
\text{OER} \ (%) = \frac{\text{CaO}_2 - \text{CVO}_2}{\text{CaO}_2}
\]

**Procedures**

Each series of measurements, including esophageal pressure, hemodynamic pressures, heart rate, cardiac output, rectal temperature, arterial and mixed venous blood samples, took approximately 3 minutes to perform. Data were recorded before administration of morphine (control) and 15, 30, 60, 90, 120 and 180 minutes thereafter. Morphine hydrochloride, 0.5 mg/kg, was injected through the Swan-Ganz catheter into the right atrium at a rate of 5 mg/min. An average volume of 165 ml of 5% glucose was administered during the study. The mean, standard deviation and standard error of the mean were calculated for all values obtained, and data were computed using the correlated t test, with each patient serving as his own control; p < 0.05 was considered significant.

**Results**

**Sedative and Metabolic Effects of Morphine**

In the 21 conscious patients, sedation was observed in the minutes after administration of morphine. There was a marked variability in the degree and duration of sedation. Most of the patients dozed throughout the study, but all of them could be awakened easily and could understand simple questions. Metabolic data before and after morphine administration are summarized in table 2. Factors known to modify hemodynamics, such as pH, Pco2, hemoglobin blood level and temperature, remained unchanged throughout the study. There was a slight and insignificant widening of the arteriovenous oxygen difference. Oxygen consumption was significantly diminished after morphine administration. The magnitude of the decrease varied according to the initial status of oxygen consumption (fig. 2); the decrease was large and prolonged in 10 patients with an initially elevated oxygen consumption (patients 1–10, table 1) and moderate and transitory in 14 patients with an initially normal oxygen consumption (patients 11–24, table 1). The oxygen extraction ratio remained unchanged in all patients.

**Systemic Hemodynamic Effects of Morphine (table 3)**

Heart rate, cardiac index and stroke index were significantly diminished after morphine injection (fig. 3). The decreases in cardiac index and stroke index were immediate and moderate. The decrease in heart rate was more progressive and also moderate. Three
TABLE 2. Metabolic Data Before and After Intravenous Morphine (0.5 mg/kg) in 24 Acutely Ill Patients

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>15 min</th>
<th>30 min</th>
<th>60 min</th>
<th>90 min</th>
<th>90 min</th>
<th>120 min</th>
<th>180 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.51 ± 0.07</td>
<td>7.52 ± 0.07</td>
<td>7.53 ± 0.07</td>
<td>7.53 ± 0.07</td>
<td>7.52 ± 0.07</td>
<td>7.52 ± 0.07</td>
<td>7.52 ± 0.07</td>
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</tr>
<tr>
<td>PO2 (mm Hg)</td>
<td>32 ± 4.4</td>
<td>32 ± 4.5</td>
<td>30 ± 5.6</td>
<td>30 ± 6.2</td>
<td>31 ± 5.3</td>
<td>30 ± 7.1</td>
<td>32 ± 4.7</td>
<td></td>
</tr>
<tr>
<td>Hb (g/100 ml)</td>
<td>10.1 ± 2.1</td>
<td>9.9 ± 2.1</td>
<td>9.8 ± 2.1</td>
<td>9.8 ± 2.2</td>
<td>9.8 ± 2.1</td>
<td>9.9 ± 2.1</td>
<td>9.9 ± 2.3</td>
<td></td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>37.6 ± 0.7</td>
<td>37.6 ± 0.7</td>
<td>37.6 ± 0.7</td>
<td>37.5 ± 0.8</td>
<td>37.5 ± 0.6</td>
<td>37.5 ± 0.5</td>
<td>37.4 ± 0.6</td>
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</tr>
<tr>
<td>A-VO2 (vol/100 ml)</td>
<td>3.8 ± 1</td>
<td>3.9 ± 0.9</td>
<td>3.9 ± 1</td>
<td>4.0 ± 1.1</td>
<td>4.0 ± 1</td>
<td>4.1 ± 1.1</td>
<td>4.1 ± 1</td>
<td></td>
</tr>
<tr>
<td>VO2 (ml/min/m2)</td>
<td>141 ± 29</td>
<td>121 ± 29†</td>
<td>120 ± 29†</td>
<td>123 ± 35*</td>
<td>129 ± 30</td>
<td>127 ± 31</td>
<td>130 ± 29</td>
<td></td>
</tr>
<tr>
<td>OER (%)</td>
<td>0.28 ± 0.05</td>
<td>0.28 ± 0.06</td>
<td>0.29 ± 0.06</td>
<td>0.29 ± 0.06</td>
<td>0.29 ± 0.06</td>
<td>0.30 ± 0.07</td>
<td>0.30 ± 0.08</td>
<td></td>
</tr>
</tbody>
</table>

Patients with elevated VO2 at control (n = 10)
| VO2 (ml/min/m2) | 168 ± 21 | 135 ± 27† | 133 ± 30† | 136 ± 43† | 149 ± 26* | 146 ± 28* | 148 ± 38 |
| OER (%)         | 0.29 ± 0.04 | 0.28 ± 0.06 | 0.27 ± 0.06 | 0.29 ± 0.07 | 0.30 ± 0.06 | 0.30 ± 0.08 | 0.30 ± 0.08 |

Patients with normal VO2 at control (n = 14)
| VO2 (ml/min/m2) | 121 ± 13 | 111 ± 27 | 110 ± 25* | 114 ± 23 | 115 ± 25 | 113 ± 30 | 117 ± 30 |
| OER (%)         | 0.27 ± 0.06 | 0.27 ± 0.06 | 0.30 ± 0.06 | 0.30 ± 0.06 | 0.30 ± 0.06 | 0.30 ± 0.06 | 0.30 ± 0.08 |

Values are mean ± SD.
*p < 0.05 vs control.
†p < 0.01 vs control.
‡p < 0.001 vs control.
Abbreviations: PO2 = carbon dioxide tension; Hb = hemoglobin concentration; A-VO2 = arteriovenous oxygen difference; VO2 = oxygen consumption; OER = oxygen extraction ratio.

Figure 2. The effects of morphine (M) on oxygen consumption (VO2) in 10 patients with elevated oxygen consumption at control (O----O), in 14 patients with normal oxygen consumption at control (O—O), and in all patients (O—O). Absolute values are given in table 2. MN = minutes. Asterisk indicates p < 0.05 vs control.

Effects of Morphine on Esophageal Pressure

In 15 patients, esophageal pressure increased at the fifteenth minute, from 3.9 ± 2.4 mm Hg to 5.4 ± 2.1 mm Hg, and remained significantly elevated until the ninetieth minute. In nine patients, esophageal pressure decreased slightly at the fifteenth minute, from 5.9 ± 3.3 mm Hg to 5.1 ± 2.8 mm Hg, and remained unchanged thereafter. Morphine did not induce a

TABLE 3. Systemic Hemodynamic Effects of Intravenous Morphine in 24 Acutely Ill Patients

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>15 min</th>
<th>30 min</th>
<th>60 min</th>
<th>90 min</th>
<th>90 min</th>
<th>120 min</th>
<th>180 min</th>
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</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>95 ± 17</td>
<td>88 ± 17†</td>
<td>87 ± 17†</td>
<td>84 ± 15†</td>
<td>83 ± 15†</td>
<td>85 ± 16†</td>
<td>82 ± 13†</td>
<td></td>
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<tr>
<td>CI (1/min/m2)</td>
<td>3.7 ± 0.9</td>
<td>3.1 ± 0.8†</td>
<td>3.0 ± 0.7‡</td>
<td>3.1 ± 0.7†</td>
<td>3.2 ± 0.7†</td>
<td>3.2 ± 0.7†</td>
<td>3.2 ± 0.6*</td>
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<tr>
<td>SI (ml/m2)</td>
<td>40 ± 11</td>
<td>35 ± 14*</td>
<td>33 ± 16*</td>
<td>38 ± 11</td>
<td>38 ± 10</td>
<td>39 ± 10</td>
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<td>SAP (mm Hg)</td>
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<td>119 ± 24†</td>
<td>124 ± 25†</td>
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<td>128 ± 27†</td>
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<td>DAP (mm Hg)</td>
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<td>66 ± 12‡</td>
<td>68 ± 13†</td>
<td>70 ± 14*</td>
<td>69 ± 12*</td>
<td>69 ± 14*</td>
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<tr>
<td>MAP (mm Hg)</td>
<td>96 ± 17</td>
<td>82 ± 15†</td>
<td>84 ± 15‡</td>
<td>86 ± 17†</td>
<td>89 ± 15†</td>
<td>90 ± 15†</td>
<td>87 ± 16*</td>
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<tr>
<td>TVR (units/m2)</td>
<td>24 ± 8.2</td>
<td>24 ± 7.7</td>
<td>24 ± 7.8</td>
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<td>24 ± 6.8</td>
<td>26 ± 7.1</td>
<td>25 ± 7.0</td>
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</tbody>
</table>

Values are mean ± SD.
*p < 0.05 vs control.
†p < 0.01 vs control.
‡p < 0.001 vs control.
Abbreviations: HR = heart rate; CI = cardiac index; SI = stroke index; SAP = systolic arterial pressure; DAP = diastolic arterial pressure; MAP = mean arterial pressure; TVR = total vascular resistance.
significant change in esophageal pressure in any patient (fig. 4).

Effects of Morphine on Intravascular and Transmural Cardiac Filling Pressures

Transmural cardiac filling pressures significantly decreased during the first hour, whereas intravascular cardiac filling pressures remained unchanged (fig. 5, table 4).

Discussion

In contrast to other hemodynamic studies of the cardiovascular response to 0.5, 1 and 2 mg/kg of i.v. morphine,\textsuperscript{1,4} our patients were critically ill without evident heart disease and were under controlled ventilation before the study, so that intubation was not performed as part of the protocol. Further, Pco\textsubscript{2} remained constant throughout the study, the effects of morphine were analyzed for a period of 3 hours and esophageal pressure was recorded, permitting the estimation of transmural cardiac filling pressures.

Far from increasing, as previously reported,\textsuperscript{1,2,4} cardiac index decreased significantly in the minutes after morphine injection (fig. 3). The simultaneous decrease in stroke index and transmural cardiac filling pressures during the first hour strongly suggested a decrease in venous return, which corroborates reports of a morphine-induced increase in venous capacitance.\textsuperscript{8-10} For the next 2 hours, cardiac index remained significantly decreased because morphine had induced a prolonged slowing of heart rate (fig. 3), which can be attributed both to the sedation and analgesia produced and to a centrally mediated generalized increase in vagal tone.\textsuperscript{11} A slight and prolonged decrease in arterial pressure also occurred after morphine administration. Severe hypotensive episodes have been described,\textsuperscript{3,5} but were not observed, confirming that precipitous hypotension does not occur when the rate of administration is limited to 5 mg/min.\textsuperscript{3} Because the calculated total vascular resistance remained unchanged despite the decrease in cardiac index, it would be reasonable to assume that morphine induced arteriolar vasodilatation. Such an effect has been reported.\textsuperscript{8-10,12}

The differences in published data on the systemic hemodynamic consequences of high doses of morphine are probably related for the most part to conditions of vascular tone before injection of the drug. Lowenstein et al.\textsuperscript{13} showed in the independently perfused muscle that morphine could only induce a decrease in arteriolar tone if control vascular

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**Figure 3.** The effects of morphine (M) on stroke index ( ), heart rate (Δ—Δ) and cardiac index (•—•) in 24 acutely ill patients. Absolute values are given in table 3. MN = minutes. Asterisk indicates p < 0.05 vs control.

**Figure 4.** Changes in esophageal pressure (EP) 15 minutes (mn) after injection of morphine (M), 0.5 mg/kg. Esophageal pressure increased in 15 patients and decreased slightly in nine.

**Figure 5.** The effects of morphine (M), 0.5 mg/kg, on intravascular (•—•) and transmural (○—○) cardiac filling pressures in 24 acutely ill patients. Absolute values are given in table 4. CVP = central venous pressure; MPAP = mean pulmonary artery pressure; PWP = pulmonary wedge pressure; MN = minutes. Asterisk indicates p < 0.05 vs control.
TABLE 4. Effects of Morphine on Esophageal Pressure and Cardiac Filling Pressures in 24 Acutely Ill Patients

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>15 min</th>
<th>30 min</th>
<th>60 min</th>
<th>90 min</th>
<th>120 min</th>
<th>180 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravascular CVP (mm Hg)</td>
<td>8.3 ± 3.8</td>
<td>8.1 ± 3.5</td>
<td>8.1 ± 3.3</td>
<td>8.4 ± 3.7</td>
<td>8.7 ± 3.8</td>
<td>8.5 ± 3.7</td>
<td>8.6 ± 3.8</td>
</tr>
<tr>
<td>Transmural CVP (mm Hg)</td>
<td>3.8 ± 3</td>
<td>2.9 ± 2.9*</td>
<td>3.3 ± 2.9*</td>
<td>3.2 ± 2.9*</td>
<td>3.6 ± 3.2</td>
<td>3.9 ± 3.2</td>
<td>4.3 ± 2.6</td>
</tr>
<tr>
<td>Intravascular MPAP (mm Hg)</td>
<td>21.1 ± 6.6</td>
<td>19.7 ± 6.1</td>
<td>19.6 ± 5.7</td>
<td>19.6 ± 5.9</td>
<td>21.0 ± 6.2</td>
<td>21.1 ± 6.5</td>
<td>19.8 ± 5.5</td>
</tr>
<tr>
<td>Transmural MPAP (mm Hg)</td>
<td>16.5 ± 5.1</td>
<td>14.4 ± 5.1†</td>
<td>14.8 ± 4.4†</td>
<td>14.4 ± 5.4†</td>
<td>15.9 ± 5.2</td>
<td>16.5 ± 5.7</td>
<td>15.7 ± 4.4</td>
</tr>
<tr>
<td>Intravascular PWP (mm Hg)</td>
<td>11.4 ± 4.5</td>
<td>10.9 ± 4.1</td>
<td>10.6 ± 4.2</td>
<td>11.3 ± 4.9</td>
<td>11.8 ± 4.6</td>
<td>11.4 ± 4.8</td>
<td>10.8 ± 4.2</td>
</tr>
<tr>
<td>Transmural PWP (mm Hg)</td>
<td>6.8 ± 3.5</td>
<td>5.4 ± 3.8†</td>
<td>5.7 ± 3.3*</td>
<td>6.1 ± 4.4</td>
<td>6.7 ± 3.4</td>
<td>6.8 ± 3.8</td>
<td>6.6 ± 3.4</td>
</tr>
<tr>
<td>Esophageal pressure (mm Hg)</td>
<td>4.6 ± 3.1</td>
<td>5.3 ± 2.5</td>
<td>4.8 ± 2.9</td>
<td>5.2 ± 2.4</td>
<td>5.1 ± 2.6</td>
<td>4.6 ± 2.7</td>
<td>4.2 ± 2.8</td>
</tr>
</tbody>
</table>

Values are mean ± sd.
*p < 0.05 vs control.
†p < 0.01 vs control.
‡p < 0.001 vs control.
Abbreviations: CVP = central venous pressure; MPAP = mean pulmonary artery pressure; PWP = pulmonary wedge pressure.

Resistance were elevated. Ward et al.14 found that morphine had no direct vasodilator action in the experimental animal, but could selectively attenuate the venoconstrictor response to adrenergic stimulation. Because most critically ill patients have an elevated level of sympathetic activity,15 the administration of morphine probably results in at least partial abolition of their increased sympathetic tone. The effects on cardiac index will then depend on whether morphine decreases predominantly the arterial or the venous tone: If morphine induces marked decreases in venous tone and heart rate, the expected increase in cardiac index after the centrally mediated arteriolar vasodilation* may not occur. The initial decrease in stroke index observed in the 24 patients studied may reflect a predominant vascular effect of morphine on the venous side.

The decrease in cardiac filling pressures normally resulting from such variations may not be observed if transmural pressures are not considered (fig. 5). In fact, morphine induced an increase in esophageal pressure in 15 patients (fig. 4). A variation of this type may reflect either an increase in esophageal smooth muscle tone or an increase in intrapleural pressure. There is evidence that the second assumption is more likely. Morphine can produce muscle rigidity16 and tracheal constriction,17 which decrease thoracopulmonary compliance and increase intrapleural pressure. Such a morphine-induced modification of respiratory mechanics may explain the increase in intravascular cardiac filling pressures in patients being mechanically ventilated after administration of high doses of morphine.6,8 However, this has not been proved, as we did not measure thoracopulmonary compliance in this study.

Most patients with multiple injuries have a high catabolic rate induced by pain, anxiety, restlessness and hormonal stress response. Increased oxygen consumption generally reflects such a catabolic state.18 Increased cardiac index is one of the adaptive mechanisms to this situation. In this study, we showed that large doses of morphine can decrease oxygen consumption in critically ill patients, especially if their oxygen consumption is initially elevated (fig. 2). It is critical to know whether this decrease is related to a decrease in oxygen demand or to a decrease in oxygen delivery. The oxygen extraction ratio is an index of the efficiency of the circulation, with normal values around 0.25%. When it increases, inadequate oxygen delivery is involved: demand is out of proportion to supply. When the oxygen extraction ratio decreases, maldistribution and anatomic or physiologic shunting are possible.20 In our patients, the oxygen extraction ratio remained remarkably unchanged after morphine administration (table 2). This suggests that the decrease in oxygen consumption was mainly caused by decreased oxygen demand rather than by inadequate oxygen delivery. This decrease in oxygen demand probably reflected morphine-induced sedation and analgesia and contributed to the decrease in cardiac index. The hemodynamic and sedative effects of morphine are probably closely related in acutely ill patients. Morphine can partially antagonize adrenergically mediated cardiovascular response to stress, which in turn induces a more basal resting hemodynamic condition. That is, morphine may induce in acutely ill patients a genuine "hemodynamic sedation" that may be beneficial. Moreover, in contrast to other sedative drugs, morphine does not induce a comatose state, and therefore the clinical neurologic status can be accurately assessed. In addition, the subject accepts the ventilator more readily. For these
reasons the administration of morphine to normo-
volumeic critical ill patients may result in a more satis-
factory state.

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