Filling Pressures of the Heart and Pulmonary Circulation of the Patient with Coronary-Artery Disease after Large Intravenous Doses of Morphine

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Filling pressures of the heart and hemodynamic responses were studied before, during, and after administration of morphine, 2 mg/kg, intravenously (5 mg per minute) in eight patients with coronary-artery disease and normal ventricular contractility requiring myocardial revascularization. Left-heart filling pressure (LHFP) was estimated by measuring balloon-occluded pulmonary arterial pressure via a Swan-Ganz catheter, and right-heart filling pressure (RHFP) by right atrial pressure measurements. LHFP and RHFP were unchanged until 1.5 mg/kg morphine had been administered; after 2 mg/kg, LHFP had risen from a control level of 6.9 ± 0.5 to 10.6 ± 1.1 mm Hg (P < .01) and RHFP from 2.9 ± 0.4 to 4.9 ± 0.8 mm Hg (P < .05). Heart rate (P < .01) and rate-pressure product (P < .05), an indirect index of myocardial oxygen consumption, decreased throughout the study period. Systemic arterial pressure, cardiac index, and left ventricular stroke work decreased significantly only at the 0.5 mg/kg dose level, while systemic vascular resistance and stroke index remained unchanged. Mean pulmonary arterial pressure increased (P < .05) after 1.5 mg/kg morphine, but pulmonary vascular resistance was unchanged. Pao, pH, base excess, and hematocrit were constant throughout the study period. These data indicate that doses of morphine to 2 mg/kg, iv, are well tolerated by, and, presumably, decrease the myocardial oxygen consumption of, patients with coronary-artery disease. The hemodynamic response resembles that seen in man without heart or lung disease. (Key words: Analgesics, narcotic morphine; Heart, function, morphine; Lung, intravascular pressures.)

LARGE INTRAVENOUS DOSES OF MORPHINE (1–3 mg/kg) are widely utilized to provide profound analgesia during cardiac surgery because of lack of circulatory depression. Although the systemic hemodynamic responses to large intravenous doses of morphine in human volunteers and in patients with valvular or coronary-artery disease have been described, no study has included evaluation of the effects of morphine on left- and right-heart filling pressures. The Swan-Ganz flow-directed balloon-tipped pulmonary-artery catheter makes it possible to define more closely the effects of clinical doses of morphine on cardiac performance. The present study reports the hemodynamic consequences of intravenous administration of morphine to patients with severe coronary-artery disease and normal ventricular contractility.

Methods

Eight patients with chronic stable angina pectoris and angiographically proven coronary-artery disease with normal ventricular contractility were selected for the study. None had a history of previous congestive
heart failure, valvular heart disease, or evidence of abnormal left-ventricular wall motion. All medications except nitroglycerin were discontinued at least 48 hours prior to study. Premedication for operation included intramuscular administration of morphine (4 to 6 mg), diazepam (5 mg), and scopolamine (0.3–0.4 mg). Additional diazepam (5–10 mg) was given intravenously in 2.5-mg increments if the patient appeared apprehensive during insertion of monitoring cannulas and preparation for anesthesia.

Two size-16 standard wire gauge (SWG) cannulas were threaded from antecubital veins into the thoracic veins for measurement of right atrial pressure (RAP) and infusion of drugs; one size-14 SWG polyethylene cannula was inserted into a dorsal hand vein for fluid infusion; a size-18 SWG cannula was inserted into a radial artery for measurement of systemic arterial blood pressure (AP) and blood sampling. A 5-Fr Swan-Ganz catheter was inserted percutaneously into the pulmonary artery via an internal jugular vein for measurement of pulmonary arterial pressure (PAP) and balloon-occluded pulmonary arterial pressure (PAPo). Fitzpatrick and associates have suggested that when balloon catheters are used, the term “balloon-occluded arterial pressure” is preferable to “pulmonary arterial wedge pressure,” since the inflated balloon occludes a larger pulmonary artery branch, transmitting a pressure pulse that more closely resembles left atrial phasic pressure. The catheter’s position was checked subsequently by chest x-ray.

Duplicate control measurements of heart rate (HR), systemic arterial blood pressure, right atrial pressure, pulmonary arterial pressure, balloon-occluded pulmonary arterial pressure, and cardiac output (CO) were obtained while the patient was breathing room air. An arterial blood sample was obtained for blood–gas analysis and hematocrit. Oxygen was then administered via a standard face mask and anesthesia machine. Morphine was injected in 5-mg increments at 1-minute intervals to a dose of 0.5 mg/kg body weight, at which point the measurements were repeated. Each series of measurements took approximately 5 minutes to perform. The arterial blood sample was taken precisely 2.0 minutes following injection of the last bolus of morphine. The cycle of injection and measurement was repeated after total doses of 1.0, 1.5, and 2.0 mg/kg body weight. The mean total time between beginning and completion of morphine administration was 40 minutes. Succinylcholine (0.2 per cent) was infused when decreased responsiveness, abdominal-muscle rigidity, decreased respiratory rate, or a rise in end-tidal CO2 was observed. Ventilation was controlled in every case when the morphine dose exceeded 1.0 mg/kg. All measurements following paralysis were performed at end-expiration without end-expiratory pressure. The trachea was intubated following completion of the studies only. A mean of 231 ml of 5 per cent dextrose in water was administered during the study.

Pressures were transduced by Sanborn 267 BC transducers and recorded continuously on a Hewlett-Packard recorder. Heart rate was calculated from the EKG. Cardiac output was measured in duplicate by indocyanine green dye dilution using a Gilford 103-IR densitometer, and curve areas were measured according to the method of Hamilton. End-tidal CO2 was monitored by a calibrated Beckman LB-1 infrared analyzer.

The concentration of morphine in arterial blood was estimated by a modification of the radioimmunoassay method of Spector. This assay measures free morphine and its metabolites. Arterial blood gases, pH, and hematocrit were determined by routine methods. Systemic (SVR) and pulmonary (PVR) vascular resistances were calculated in resistance units as follows:

\[ \text{SVR} = \frac{\overline{\text{AP}} - \overline{\text{RAP}}}{\text{CO}} \]

and

\[ \text{PVR} = \frac{\overline{\text{PAP}} - \overline{\text{PAO}}}{\text{CO}} \]

Cardiac index (CI) was calculated by dividing cardiac output by body surface area, and stroke index (SI) by dividing CI by HR. Because of the absence of pulmonary vascular disease, mitral-valve disease, or ventricular aneurysm, PAO was utilized to estimate left ventricular filling pressure (LVFP). Left ventricular
### Table 1. Measured Values, Eight Patients (Mean ± SE)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>0.5</th>
<th>1.0</th>
<th>1.5</th>
<th>2.0</th>
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</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>71 ± 2.4</td>
<td>64 ± 3.4</td>
<td>60 ± 3.5</td>
<td>62 ± 4.5</td>
<td>60 ± 4.0</td>
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<tr>
<td>Systolic arterial pressure (mm Hg)</td>
<td>119.4 ± 6.1</td>
<td>112.9 ± 5.9*</td>
<td>121.9 ± 7.5</td>
<td>120.6 ± 8.3</td>
<td>115.9 ± 7.4</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>85.0 ± 4.1</td>
<td>76.9 ± 4.4*</td>
<td>86.3 ± 5.3</td>
<td>87.5 ± 6.8</td>
<td>82.8 ± 6.7</td>
</tr>
<tr>
<td>Diastolic arterial pressure (mm Hg)</td>
<td>68.1 ± 4.2</td>
<td>61.9 ± 4.6*</td>
<td>66.5 ± 3.6</td>
<td>66.3 ± 5.1</td>
<td>64.4 ± 4.9</td>
</tr>
<tr>
<td>Mean right atrial pressure (mm Hg)</td>
<td>2.9 ± 0.4</td>
<td>3.8 ± 0.6</td>
<td>4.6 ± 1.1</td>
<td>4.6 ± 0.8*</td>
<td>4.9 ± 0.8*</td>
</tr>
<tr>
<td>Mean pulmonary arterial pressure (mm Hg)</td>
<td>12.8 ± 1.2</td>
<td>12.5 ± 1.3</td>
<td>13.6 ± 1.3</td>
<td>15.1 ± 1.3*</td>
<td>15.0 ± 1.2*</td>
</tr>
<tr>
<td>Mean balloon-occluded pulmonary arterial pressure (mm Hg)</td>
<td>6.9 ± 0.8</td>
<td>7.1 ± 1.0</td>
<td>8.4 ± 1.6</td>
<td>10.5 ± 1.0</td>
<td>10.6 ± 1.1</td>
</tr>
<tr>
<td>Paco₂ (mm Hg)</td>
<td>43.0 ± 1.0</td>
<td>41.5 ± 1.8</td>
<td>44.0 ± 1.5</td>
<td>45.0 ± 2.8</td>
<td>45.0 ± 2.2</td>
</tr>
<tr>
<td>Dextrose in water, 5 per cent. infused (ml)</td>
<td>79 ± 17</td>
<td>121 ± 15</td>
<td>166 ± 19</td>
<td>231 ± 15</td>
<td></td>
</tr>
<tr>
<td>Morphine concentrations (ng/ml)</td>
<td>897 ± 208</td>
<td>1475 ± 408</td>
<td>1682 ± 300</td>
<td>2060 ± 404</td>
<td></td>
</tr>
</tbody>
</table>

* P < .05.
† P < .01.
‡ P < .001.

### Table 2. Derived Indices, Values from Eight Patients (Mean ± SE)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>0.5</th>
<th>1.0</th>
<th>1.5</th>
<th>2.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate–pressure product (beats/min x mm Hg)</td>
<td>8489 ± 577</td>
<td>7290 ± 499*</td>
<td>7291 ± 589*</td>
<td>7377 ± 596*</td>
<td>6899 ± 533*</td>
</tr>
<tr>
<td>LV minute work index (kg-m/min/m²)</td>
<td>2.5 ± 0.2</td>
<td>1.9 ± 0.51</td>
<td>2.3 ± 0.3</td>
<td>2.3 ± 0.2</td>
<td>2.0 ± 0.2</td>
</tr>
<tr>
<td>LV stroke work index (g-m/beat/m²)</td>
<td>35.6 ± 2.7</td>
<td>29.2 ± 2.8*</td>
<td>37.2 ± 3.9</td>
<td>36.8 ± 3.6</td>
<td>32.8 ± 3.2</td>
</tr>
<tr>
<td>Cardiac index (l/min/m²)</td>
<td>2.36 ± 0.14</td>
<td>1.95 ± 0.11†</td>
<td>2.09 ± 0.18</td>
<td>2.17 ± 0.19</td>
<td>2.00 ± 0.22</td>
</tr>
<tr>
<td>Stroke index (ml/beat/m²)</td>
<td>33.5 ± 2.0</td>
<td>30.8 ± 2.2</td>
<td>35.1 ± 2.8</td>
<td>35.1 ± 2.2</td>
<td>33.4 ± 2.5</td>
</tr>
<tr>
<td>SVR (units)</td>
<td>19.7 ± 1.6</td>
<td>20.9 ± 1.6</td>
<td>22.8 ± 2.9</td>
<td>22.5 ± 3.4</td>
<td>23.2 ± 3.0</td>
</tr>
<tr>
<td>PVR (units)</td>
<td>1.4 ± 0.2</td>
<td>1.6 ± 0.2</td>
<td>1.6 ± 0.3</td>
<td>1.3 ± 0.2</td>
<td>1.3 ± 0.2</td>
</tr>
</tbody>
</table>

* P < .05.
† P < .01.
‡ P < .001.

The rate–pressure product (RPP) was calculated by multiplication of the heart rate by the systolic arterial blood pressure.

stroke work index (LVSWI) and minute work index (LVMWI) in gram-meters/m² and kilogram-meters/min/m², respectively, were calculated using the formulas:

\[
\text{LVSWI} = \frac{1.36 (\bar{P} - P_{a0}) \times \text{CI}}{100 \times \text{heart rate}}
\]

\[
\text{LVMWI} = \frac{1.36 (\bar{P} - P_{a0}) \times \text{CI}}{100}
\]
Fig. 1. Rate-pressure product before and after intravenous administration of morphine, 2 mg/kg body weight, at a rate of 5 mg/min to eight patients with coronary-artery disease and normal ventricular contractility.

Mean and standard error of the mean were calculated for all values obtained and data were computed using the correlated t test. P < 0.05 was considered significant.

Results

The results are presented in tables 1 and 2. $P_{\text{A}}O_2$ and $P_{\text{A}}P$ were increased significantly after 1.5 and 2.0 mg/kg morphine. These increases were unaccompanied by a change in cardiac index, arterial blood pressure, stroke index, or systemic vascular resistance, although CI and arterial blood pressure were significantly decreased at 0.5 mg/kg morphine. The average value of $P_{\text{A}}O_2$ rose by 3.7 mm Hg following morphine, 2 mg/kg, and this was associated with a rise in PAP of 2.2 mm Hg. Both changes were significant, $P_{\text{A}}O_2, P < .01$; PAP, $P < .05$. No precipitous hypotension was observed during this study in spite of the negligible amounts of volume expanders administered. Heart rate was decreased significantly ($P < 0.01$) throughout the study.

Mean pulmonary arterial pressure was increased significantly ($P < .05$) after 1.5 and 2.0 mg/kg morphine, whereas PVR was unchanged throughout the study.

The rate–pressure product was decreased ($P < .05$) during the entire study period (fig. 1). Left ventricular minute work index was also decreased throughout the study, but the decrease reached significance ($P < .001$) only at the 0.5 mg/kg dose. Left ventricular stroke work index was decreased significantly ($P < .05$) after 0.5 mg/kg morphine only. LVSWI was plotted as a function of $P_{\text{A}}O_2$ (fig. 2) and superimposed upon normal left ventricular function curves, as described by Ross and Braunwald. Although all values from this study are within the normal range, there was a progressive shift to the right. Its physiologic importance is not evident at this time. These studies were performed under clinical conditions in patients who had received diazepam prior to, and succinylcholine during, the administration of morphine. We cannot rule out the contributions of these medications to the hemodynamic responses observed.

The morphine concentration of arterial blood increased progressively at each higher dose of morphine, peaking at a level of 2 $\mu$g/ml at 2.0 mg/kg body weight. $P_{\text{A}}O_2$, $\mu$H, calculated base excess, and hematocrit were not significantly changed during the study. All $P_{\text{A}}O_2$ values during breathing of oxygen exceeded 400 mm Hg.

Discussion

The present study demonstrates that morphine in doses of 0.5 to 2.0 mg/kg body weight diminishes the rate–pressure product, an indirect index of $MV_{\text{O}}$, in patients with coronary-artery disease and normal left ventricular contractility. A primary concern in the anesthetic management of the patient with coronary-artery disease is to avoid an increase in myocardial oxygen demand. The major determinants of myocardial oxygen demand include intramyocardial tension, contractile state, and heart rate. The rate–pressure product has been shown to correlate
Fig. 2. Left ventricular stroke work index plotted against balloon-occluded pulmonary arterial pressure (PA) before and after administration of morphine, 0.5, 1.0, 1.5, and 2.0 mg/kg body weight, to eight patients with coronary-artery disease and normal ventricular contractility. Values from this study are superimposed upon the normal left ventricular function curve.

well with myocardial oxygen consumption during rest and exercise both in intact man and during beta-adrenergic blockade, whereas left ventricular minute work correlates less well. Increases in rate-pressure product have been demonstrated to be a major cause of intraoperative myocardial ischemia in patients undergoing coronary-artery surgery. The data also indicate that intravenous administration of morphine in dosages of 1.5 and 2.0 mg/kg body weight to patients with coronary-artery disease under these circumstances is associated with a progressive slight increase in measured filling pressures of the left and right ventricles.

The small measured increase in VFP may be the result of changing from spontaneous to controlled ventilation, reflecting changes in pleural rather than transmural vascular pressures. If so, our data indicate a lack of change of ventricular performance by 2.0 mg/kg morphine. Increases in transmural ventricular filling pressure (VFP) in the absence of increased or redistributed blood volume or sympatholysis indicate decreases of ventricular compliance or impairment of ventricular performance, which may be due to direct myocardial depression. The results of other studies have been in conflict concerning the effect of morphine on myocardial contractility. In general, the saline-perfused myocardium appears to be depressed in a dose-related fashion, whereas the blood-perfused myocardium is unaffected. In neurally intact dogs, Vasco and associates found enhanced ventricular contractile force. This was not evident, nor was depression demonstrated, following morphine, 1 mg/kg, in dogs with surgical or pharmacologic sympathetic ablation. The sole previous suggestion that morphine causes myocardial depression in man was made by Wong et al., who reported prolongation of the pre-ejection period. This was present only 60 minutes after intravenous administration of 2 mg/kg morphine to normal volunteers. The concentration of morphine in the arterial blood achieved even after 2.0 mg/kg in the present study is far below that required to depress human atrial muscle in vitro.
Previous studies from our laboratory have demonstrated centrally mediated sympatholysis following morphine administration in dogs with enhanced sympathetic activity due to hemorrhage.\textsuperscript{17} Ward and associates have documented interference with alpha-adrenergic reactivity of peripheral veins after 0.5 mg/kg morphine in dogs.\textsuperscript{18} If sympatholysis contributes to the increased VFP noted in the present studies, withdrawal of beta-adrenergic stimulation must be hypothesized.

The increase in VFP may also be due to blood volume increases consequent to the administration of an average of 230 ml of 5 per cent dextrose in water during the approximately 30-minute study period. Parker and associates have demonstrated decreases in anginal threshold after an average volume of 127 ml of blood are infused into patients with coronary-artery disease.\textsuperscript{19} Against this is the well-known rapid redistribution of 5 per cent glucose in water throughout the body water, which implies a very small increase in blood volume. The lack of change in blood volume is also implied by the constancy of the hematocrit during this study. A final possibility is that succinylcholine, or unknown factors, caused a redistribution of blood volume from the peripheral to the central circulation.

No episode of the previously described precipitous transient hypotension was observed during morphine administration in this study.\textsuperscript{5} This is in contrast to our experience and that of others when morphine is administered at a rate of 10 mg/min or more.\textsuperscript{3} We attribute the lack of hypotension in the present investigation to limiting the rate of administration to 5 mg/min. Extensive clinical experience now indicates that precipitous hypotension is virtually nonexistent when the rate is limited to this level.

The effect of large doses of morphine upon the pulmonary circulation of man has not previously been described. In our patients who had normal control PVR’s, no effect upon the pulmonary vasculature was demonstrated. The increase in PAP appears to represent an obligatory response to the increase in LVFP. Whether morphine can affect the pulmonary vasculature in patients with elevated PVR’s in a fashion similar to its action on elevated systemic vascular resistance is not known.

The AP, SVR, CI, and SI sustained only minor and transient changes during this study. Heart rate was decreased in all periods following morphine. The hemodynamic response of patients with coronary-artery disease and normal ventricular contractility thus closely resembles that of normal adult volunteers\textsuperscript{15} and patients without cardiac or pulmonary disease.\textsuperscript{5} Whether this is also true in patients with impaired ventricular contractility remains to be determined. It is noteworthy that our control values were obtained while the patients were breathing room air, in order to avoid any stimulation of the patient by application of the anesthesia face mask. Thus, the initial decrease in cardiac index and the lack of change of SVR may be partially due to the peripheral vasoconstriction caused by breathing oxygen.\textsuperscript{20}

References


