Analgesic and Hemodynamic Effects of Buprenorphine in Acute Infarction of the Heart

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Summary
The analgesic, hemodynamic and respiratory effects of buprenorphine (0.3 mg i.v.) were monitored in 15 coronary care unit-admitted patients presenting with myocardial infarction who were in functional class I according to the Killip classification. At the time of the study, 8 of them had unequivocal precordial pain (group 1); the remaining 7 were painfree (group 2). The agent showed a prompt and potent analgesic action. It also induced a slight decrease in mean aortic pressure associated with a reduction in systemic vascular resistance and an increase in cardiac index, a rise in the pulmonary arterial pressure and arteriolar resistance and right atrial pressure, a reduction in arterial pO₂ and pH and an increase in pCO₂. Tension-time-indices of the left and right ventricles varied in parallel with variations in aortic and pulmonary artery pressure, respectively. These responses were probably unrelated to analgesia since they were similar in groups 1 and 2. Changes in systemic circulation were such as to possibly decrease the contractile effort and the oxygen need of the left ventricle and the size of infarction. On the contrary, the rise in pulmonary arterial pressure imposes a hemodynamic burden on the right ventricle that, depending on the patient's condition, may assume clinical importance. It is felt that the use of buprenorphine in myocardial infarction should be restricted to uncomplicated and selected cases.

Additional Indexing Words:
Analgesia Respiratory parameters Pulmonary hemodynamics
RELIEF of pain is an urgent therapeutic need in most subjects presenting with acute myocardial infarction. When analgesics are used in cardiac patients, mainly in the acute phase of infarction, lack of undesirable effects on circulation and respiration is crucially important. Although the opioid derivative, morphine, is most widely used in these circumstances, reports of variable and possibly detrimental\(^1\)-\(^3\) circulatory influences, as well as the potential development of physical dependence, suggest that morphine is not an ideal remedy and that more suitable drugs are still needed for these purposes.

Buprenorphine is a recently developed semisynthetic lipophilic agent derived from thebaine.\(^4\) Its analgesic action is 25 to 50 times greater than that of morphine.\(^5\) Similar to the opiate analgesics, buprenorphine causes respiratory depression, however, it seems to be less prompt and more prolonged.\(^6\) Influences on circulation are qualitatively similar to those of morphine\(^7\) and consist of mild reduction in systolic pressure and heart rate.\(^8\)

Information concerning the efficacy of buprenorphine on pain in the acute phase of myocardial infarction is scanty\(^9\) and the concomitant circulatory effects have not been fully investigated.

In this study we evaluated the systemic and pulmonary hemodynamic changes during analgesia induced by buprenorphine in patients with acute myocardial infarction.

**Methods**

Fifteen coronary care unit-admitted patients suffering from acute myocardial infarction (confirmed by serial enzyme and electrocardiographic evaluations) were investigated in the 24 hours following the onset of symptoms. At the time of the study all of the patients were class I according to Killip's functional classification,\(^10\) and 8 of them still presented with unequivocal precordial pain (group 1). They were asked to score the degree of pain at baseline and the level of pain relief at 15, 30, 60 and 120 min after buprenorphine injection (0.3 mg i.v.), utilizing a linear analogue scale.\(^11\) In order to assess the influence of analgesia itself on the circulatory response to the drug, the remaining 7 subjects, who were painfree when the study was performed (group 2), were also given buprenorphine (0.3 mg i.v.).

In each case hemodynamic measurements were performed immediately before administration of the drug and 15, 30, 60 and 120 min after. For pressure measurements in the right side of the heart and in the pulmonary circulation, as well as for cardiac output determination, a 7F thermodilution triple lumen balloon-tipped catheter was inserted percutaneously into an
antecubital vein, floated to the pulmonary artery, and advanced, when necessary, to the wedge position. Systemic arterial pressure was derived from a 5F Teflon catheter positioned into the ascending aorta via the brachial artery. Left (LVET) and right (RVET) ventricular ejection times were measured from the beginning upstroke to the trough of the incisura of the systemic and pulmonary arterial tracings, respectively\(^1\); both of which were recorded at a paper speed of 100 mm/sec (average of 5 consecutive beats). Pressures were determined with Hewlett-Packard 1280 C and 1280 B strain gauge transducers and recorded on an eight channel Hewlett-Packard recorder, model 7758 A. Cardiac output was obtained (Edwards cardiac output computer, model 9520 A) with rapid injection of 10 ml ice cold saline solution into the right atrium; the average of three determinations was taken as the representative value of each period. Systemic vascular (SVR) and pulmonary arteriolar (PAR) resistances were calculated (dynes×sec×cm\(^{-5}\)) from the following formulas:

\[
\text{SVR} = (\text{mAP} - \text{mrap}) \times 1332 \times 60 / \text{CO}
\]
\[
\text{PAR} = (\text{mPAP} - \text{mWPP}) \times 1332 \times 60 / \text{CO}
\]

where mAP and mPAP are mean aortic and mean pulmonary artery pressures, respectively, mrap is mean right atrial pressure, mWPP is mean wedge pulmonary pressure, and CO is cardiac output.

Tension-time index per min\(^{13}\) of the left (LTTI) and of the right (RTTI) ventricle were calculated as follows:

\[
\text{LTTI} = \text{mSAP} \times \text{LVET} \times \text{HR}
\]
\[
\text{RTTI} = \text{mSPAP} \times \text{RVET} \times \text{HR}
\]

where mSAP and mSPAP are mean systolic aortic and pulmonary artery pressures, respectively, LVET and RVET are left and right ventricular ejection times, HR is heart rate per min. \(pO_2\), \(pCO_2\) and \(pH\) were determined through a Corning blood gas analyzer, model 168, on aortic blood samples withdrawn 15 min and 1 min before and 60 min and 120 min after injection of buprenorphine.

Statistical significance of changes from control at the various periods and differences between groups 1 and 2 were evaluated through the analysis of variance.

**RESULTS**

The 2 groups were homogenous with regards to age and location of the infarction (Table I). The analgesic efficacy of buprenorphine was such as to
### Table I. Sex, Age and Location of Infarction in the Study Population

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (with pain)</th>
<th>Group 2 (without pain)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Males</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Females</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Age (mean±SEM)</td>
<td>59.2±2.7</td>
<td>62.5±2.6</td>
</tr>
<tr>
<td>Localization of infarction:</td>
<td>IW 4</td>
<td>AW 2</td>
</tr>
<tr>
<td></td>
<td>OthW 2</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: IW=inferior wall; AW=anterior wall; OthW=other walls.

### Table II. Time Course of Changes of Cardiac Pain and of the Circulatory Variables Following Buprenorphine

<table>
<thead>
<tr>
<th></th>
<th>Group</th>
<th>Control</th>
<th>15 min</th>
<th>30 min</th>
<th>60 min</th>
<th>120 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensity of pain</td>
<td>1</td>
<td>4.6±0.8</td>
<td>1.6±0.7</td>
<td>1±0.2</td>
<td>0.6±0.2*</td>
<td>0.1±0.1</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>76.3±6.0</td>
<td>77.5±5.4</td>
<td>77.1±5.6</td>
<td>77.5±4.5</td>
<td>76.7±4.6</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>1</td>
<td>77.4±5.3</td>
<td>82.2±6.4</td>
<td>82.1±6.7</td>
<td>79.4±5.1</td>
<td>80.0±5.6</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>1</td>
<td>100.2±3.6</td>
<td>98.5±2.2</td>
<td>94.2±3.6*</td>
<td>91.5±2.0*</td>
<td>94.1±3.5</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>98.2±5.1</td>
<td>94.4±4.1</td>
<td>91.5±2.8</td>
<td>89.2±2.5*</td>
<td>92.7±3.2</td>
</tr>
<tr>
<td>Cardiac index (l/min/m²)</td>
<td>1</td>
<td>3.28±0.17</td>
<td>3.45±0.15</td>
<td>3.37±0.14</td>
<td>3.49±0.18**</td>
<td>3.27±0.14</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>3.10±0.99</td>
<td>3.18±0.13</td>
<td>3.34±0.18</td>
<td>3.21±0.21</td>
<td>3.10±0.21</td>
</tr>
<tr>
<td>Systemic vascular resistance (dynes×sec×cm⁻²)</td>
<td>1</td>
<td>1332±130</td>
<td>1239±110</td>
<td>1198±114'</td>
<td>1113±84''</td>
<td>1227±97</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1300±102</td>
<td>1237±103</td>
<td>1178±90''</td>
<td>1182±76''</td>
<td>1280±110</td>
</tr>
<tr>
<td>Mean right atrial pressure (mmHg)</td>
<td>1</td>
<td>4.6±1.2</td>
<td>5.3±0.9</td>
<td>5.8±1.2*</td>
<td>5.7±1.2</td>
<td>5.5±1.2</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>4.7±1.2</td>
<td>5.8±1.4</td>
<td>6.1±1.4</td>
<td>6.8±1.3*</td>
<td>6.8±1.8</td>
</tr>
<tr>
<td>Mean pulmonary artery pressure (mmHg)</td>
<td>1</td>
<td>15.0±1.5</td>
<td>16.8±1.5''</td>
<td>16.8±1.2''</td>
<td>16.5±1.4</td>
<td>15.8±1.6</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>15.3±1.8</td>
<td>19.2±1.5'</td>
<td>19.5±1.2''</td>
<td>19.4±1.7''</td>
<td>19.1±1.6</td>
</tr>
<tr>
<td>Mean pulmonary artery wedge pressure (mmHg)</td>
<td>1</td>
<td>10.8±1.4</td>
<td>10.8±1.5</td>
<td>11.2±1.5</td>
<td>10.6±1.7</td>
<td>10.5±1.7</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>10.0±1.2</td>
<td>11.8±1.1</td>
<td>11.2±1.0</td>
<td>12.0±0.8</td>
<td>11.7±1.2</td>
</tr>
<tr>
<td>Pulmonary arteriolar resistance (dynes×sec×cm⁻³)</td>
<td>1</td>
<td>55±6.9</td>
<td>77±9.2'</td>
<td>73±11.9''</td>
<td>71±9.8</td>
<td>70±8.5</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>111±21.8</td>
<td>120±19.9''</td>
<td>125±12.3''</td>
<td>115±18.1</td>
<td>126±18.7</td>
</tr>
<tr>
<td>Left ventricular tension-time index (mmHg/sec/min)</td>
<td>1</td>
<td>2797±271</td>
<td>2653±249</td>
<td>2558±252''</td>
<td>2615±174</td>
<td>2587±326</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>3175±227</td>
<td>3088±351</td>
<td>2928±209''</td>
<td>2929±276</td>
<td>2942±199</td>
</tr>
<tr>
<td>Right ventricular tension-time index (mmHg/sec/min)</td>
<td>1</td>
<td>411±109</td>
<td>446±101''</td>
<td>482±60*</td>
<td>474±59''</td>
<td>489±98</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>450±77</td>
<td>665±134''</td>
<td>654±67''</td>
<td>582±53''</td>
<td>604±90</td>
</tr>
</tbody>
</table>

Differences between the 2 groups at the various periods were statistically not significant.

' p<0.01 vs control value,  " p<0.05 vs control value,  * p<0.05 vs 30 min value.
Fig. 1. Carbon dioxide and oxygen tension and pH of the arterial blood in the baseline and in the 2 hours following i.v. buprenorphine. Averages (+SEM).

Fig. 2. Correlation between changes from baseline of pulmonary arterio-
lar resistance (PAR) and arterial oxygen tension 60 min after buprenorphine.

attenuate pain by 65% of baseline at 15 min and to make pain free all but one of the patients in group 1, at 120 min. Type and prevalence of side effects in the whole study population were as follows: dizziness and lightheadedness (100%), drowsiness or sleep (40%), nausea or vomiting (26%).

Baseline values of the examined circulatory parameters were comparable in the 2 groups and varied in the same direction following the drug (Table II). In the systemic circulation there was a decrease in mean aortic pres-
sure, a reduction in vascular resistance and an increase in cardiac index. In the pulmonary circulation, on the contrary, both pulmonary artery pressure and arteriolar resistance were augmented; the pulmonary wedge pressure remained unchanged. Tension-time indices per min of the left and the right ventricles varied in the same direction as the aortic and the pulmonary artery pressure, respectively, ejection times of the two ventricles and heart rate having remained unchanged. Right atrial pressure showed a slight, but significant, increase following buprenorphine. All of these changes were already detectable at 15 min, reached a peak at from 30 to 60 min and then tended to recover.

After buprenorphine arterial pO₂ and pH decreased and pCO₂ rose in both groups (Fig. 1).

Change from baseline of the pulmonary arteriolar resistance correlated inversely and significantly with change in arterial oxygen tension (Fig. 2).

DISCUSSION

In this study, buprenorphine proved to exert a prompt and persistent analgesic action in the acute phase of myocardial infarction, and also to have some influence on the cardiovascular system. The effects on circulation were probably unrelated to analgesia since the hemodynamic variations were similar in the presence (group 1) and absence (group 2) of pain.

Changes from baseline in the hemodynamic functions, although not striking, were uniform and statistically significant; their pathophysiologic and clinical implications deserve some comment.

Mean aortic pressure decreased concomitantly with a rise in cardiac index, indicating that systemic vasodilatation had occurred; in fact, calculated peripheral vascular resistance declined by 16.4% of control in group 1 and to a similar extent in group 2. Whether the vasodilating effect was due to a peripheral (relaxation of vascular smooth muscle) or to a central action (depression of the neural adrenergic discharge), cannot be stated on the basis of the available data. Heart rate remained unchanged and cardiac index rose exclusively as a result of an increase in stroke output. An improved inotropic state or a reduced impedance to left ventricular ejection, as reflected by the decline in peripheral vascular resistance and wall tension (tension-time index), may have promoted an increase of the stroke output; enhancement in contractility seems unlikely, since a concomitant reduction in the filling pressure of the left ventricle (pulmonary wedge pressure) would be expected. This, however, was not observed in our patients.

These considerations, in addition to the lack of a response in heart rate
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...to systemic vasodilatation and blood pressure fall, support the interpretation that the neural influences on the heart were inhibited by buprenorphine, and that the augmented stroke output was primarily a consequence of the reduced impedance to left ventricular ejection. The response of the pulmonary circulation moved in an opposite direction. In fact, the driving pressure through the lungs (difference between mean pulmonary arterial and pulmonary wedge pressure) increased to a proportionally greater extent than did blood flow, so that pulmonary arteriolar resistance was raised. These changes are reasonably interpreted as reflecting a vasoconstrictor reaction. Resistance was already significantly augmented at 15 min after drug administration and remained so for the duration of monitoring. As a consequence of the increased pulmonary artery pressure, the tension developed by the right ventricle during systole was augmented and probably accounted for the elevation of the right ventricular filling pressure (mean right atrial pressure). This finding again is in favour of a withdrawal of inotropic support mediated through the adrenergic nervous system. It cannot be ruled out, however, that the increase in right atrial pressure resulted, entirely or partially, from blood displacement from the periphery to a central position.

The negative correlation existing between changes in pulmonary arteriolar resistance and oxygen partial pressure in the arterial blood, raises the possibility that pulmonary vasoconstriction depends upon lowered alveolar oxygen tension consequent to depressed alveolar ventilation (as supported by the rise in arterial carbon dioxide partial pressure) or on ventilation-perfusion mismatching, or on both mechanisms. A similar interpretation has already been proposed for the enhancement of pulmonary vasomotility observed with other potent analgesics.14,15

Some of the circulatory effects of buprenorphine in patients with acute myocardial infarction appear desirable and some do not. Obviously, benefits or detriments and their magnitude may largely depend upon the clinical situation, size and site and complications of the infarction. In this respect, it should be stressed that patients in this study belonged to class I according to Killip’s functional classification.10 Systemic vasodilatation, reduction of aortic pressure and tension-time index, and suppression of sympathetic activity all may contribute to decrease the contractile effort and the oxygen need of the left ventricle and, possibly, the size of the infarction.14 These effects should be balanced against depression of respiration and the hemodynamic burden imposed on the right ventricle by the pulmonary vasoconstriction. Both of these effects may be detrimental in cases such as those in which pulmonary blood pressure is already elevated or infarction involves the right ventricular wall. Right ventricular infarction, in fact, complicates inferior myocardial
infarction in 24–37% of cases.\textsuperscript{17,18}

Compared with morphine, buprenorphine has a stronger analgesic efficacy that makes repeated drug administration unnecessary in many cases; the influence of the two drugs on respiration and the pulmonary circulation (increase in blood pressure and arteriolar resistance associated with reduction of the arterial oxygen tension) seems quantitatively and qualitatively similar.\textsuperscript{14,15} As regards the systemic circulation, the reduction in vascular resistance and the increase in cardiac and stroke outputs by buprenorphine and not by morphine\textsuperscript{3,19} are potential advantages of the former drug since systemic and cardiac perfusion may be improved, left ventricular end-systolic volume and wall stress may be reduced and myocardial oxygen need may be lowered. Development of less pronounced physical dependence with buprenorphine\textsuperscript{20} is another important aspect of differentiation. Obviously, all these considerations apply to uncomplicated cases of myocardial infarction in which buprenorphine appears to represent a valuable alternative to morphine or even an advancement. Further studies are needed to evaluate whether buprenorphine may be advantageous and confidently used in a broader clinical spectrum of infarction of the heart.

REFERENCES

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