Effects of Methylprednisolone on $P_{50}$, 2,3 Diphosphoglycerate and Arteriovenous Oxygen Difference in Acute Myocardial Infarction

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SUMMARY In a double-blind randomized study, 30 mg/kg of methylprednisolone sodium succinate (MPN) or 15 mg/kg of mannitol placebo (PL) were infused in 28 patients after acute myocardial infarction. Measurements were obtained immediately before and for 24 hours after the initial infusion. The partial pressure of oxygen at 50% saturation of hemoglobin ($P_{50}$) did not change significantly in vitro or in vivo after MPN, whereas 2,3 diphosphoglycerate (2,3 DPG) increased from 13.2 to 14.2 µmol/g Hb ($p < 0.05$) in the group receiving PL. The arteriovenous oxygen difference ($Ca-vO_2$) remained constant after MPN or PL. The cardiac index (CI) increased after MPN ($p < 0.02$) associated with an increase in the oxygen consumption index ($CI \times A-V \; O_2$) from 146 to 170 ml/min/m² ($p < 0.05$). These data show that MPN increases CI after acute myocardial infarction, but has no specific effects on $P_{50}$, 2,3 DPG or $Ca-vO_2$.

ACUTE MYOCARDIAL INFARCTION is characterized by a reduction in the left ventricular myocardial mass and is often associated with a reduction in blood flow.¹ Reduction in tissue perfusion may result in inadequate tissue oxygenation unless compensatory changes occur in the other determinants of oxygen supply: pulmonary gas exchange, the oxygen-carrying capacity of the blood and the shape and position of the oxyhemoglobin dissociation curve (ODC).⁷⁻¹⁰ A decrease in the affinity of hemoglobin (Hb) for oxygen enhances oxygenation of the tissues without increasing myocardial work and has been observed during angina pectoris, acute myocardial infarction, low-output cardiac failure and cardiogenic shock.⁷⁻⁹,¹¹⁻¹⁹ Pharmacologic manipulation of the ODC, favoring unloading of oxygen by Hb at the cellular level, is a logical approach to therapy in patients with compromised cardiac performance.⁹,¹¹⁻¹³,¹⁹,²¹ The partial pressure of oxygen at 50% saturation of Hb ($P_{50}$) represents the position of the ODC and may be influenced by temperature, pH, $PCO_2$, carboxyhemoglobin (HbCO) and 2,3 diphosphoglycerate (2,3 DPG).¹³,²⁰,²²⁻²⁶ In vitro studies have shown that increases in $P_{50}$, related to increases in 2,3 DPG, may be achieved by incubating red blood cells with MPN,¹⁸,²⁷⁻²⁹ McCaughtry et al.¹¹,³⁰ reported an increase in $P_{50}$ after MPN in patients with bacterial shock or after massive transfusions of stored blood. The increase in $P_{50}$ was not, however, consistently associated with an increase in 2,3 DPG.

In the present double-blind randomized study, MPN or mannitol placebo (PL) was administered to patients within 12 hours after the onset of acute myocardial infarction to evaluate the influence of MPN on $P_{50}$, 2,3 DPG and the arteriovenous oxygen content difference ($Ca-vO_2$).

Materials and Methods

Thirty patients admitted to our coronary care unit within 12 hours after the onset of acute myocardial infarction were studied during a 12-month period. Acute
myocardial infarction was diagnosed by the presence of persistent substernal chest pain and mild pulmonary vascular congestion, with unequivocal electrocardiographic changes and elevations of creatine phosphokinase (Killip class II). Exclusion criteria included cardiogenic shock, severe pulmonary edema, previous myocardial infarction within 10 weeks, recent major surgery, hemoglobin ≤ 10 g%, thyroid disorders, terminal illness, or chronic steroid use. Informed written consent was obtained from all patients and an immediate relative.

Two of the 30 patients who entered the study had equivocal enzyme criteria for acute myocardial infarction. Therefore, the data on 28 patients, 20 males and eight females (median age 56 years, range 39–74 years), were analyzed. Fourteen acute anterior wall and 14 acute inferior wall myocardial infarctions were identified.

A Swan-Ganz pulmonary arterial catheter was inserted in each patient. The catheter position was documented by characteristic pulmonary arterial pressure curves and on the chest roentgenogram. Cardiac output (CO) was measured in triplicate by the thermodilution method (Edwards Cardiac Output Computer model 9250), and the three values were averaged. Mixed venous blood and peripheral arterial blood were collected simultaneously before the CO determinations. The blood samples were placed in ice slush and were analyzed within 15 minutes for pH and partial pressures of oxygen (PO2) and carbon dioxide (PCO2) at 37°C with a blood analyzer (Instrumentation Laboratories, model 813). Oxyhemoglobin saturation (SO2), HbCO saturation and Hb concentration were measured with a spectrophotometer (Instrumentation Laboratories 282 Co-Oximeter). Arterial oxygen content (CaO2) and venous oxygen content (CVO2) were calculated using the formula Hb × SO2 × 1.39 + PO2 × 0.0031. The oxygen transport index (O2TI) was computed as the product of CaO2 and cardiac index (CI). The oxygen consumption index (VO2ind) was calculated as CI × a-vO2 × 10. The oxygen extraction ratio — the percentage of oxygen extracted from the CaO2 — was calculated as a-vO2/CaO2.

In vitro Pso at pH 7.40 and 37°C was calculated by the formula Pso = 26.6 × PO2C/PO2S, where PO2C is the measured PO2 of the mixed venous sample corrected to standard conditions and PO2S is the PO2 corresponding to the measured oxygen saturation on the standard ODC obtained with the aid of a computer program. No specific corrections were made for HbCO. The theoretical basis for the Pso equation is that the shape of the ODC at saturations of 20–90% remains constant even though the position of the curve may change. In a separate investigation of 24 patients, there was no significant difference between the calculated Pso and the Pso determined directly using two methods. With oxygen saturations of 20–90%, the reproducibility of the calculated Pso is ± 1 mm Hg. In vivo Pso was obtained by correcting the in vitro Pso to the patient's temperature and pH, as proposed by Severinghaus. In our laboratory, the normal value for Pso is 27 ± 1.3 mm Hg (SD). 2.3 DPG was measured in nine patients receiving MPN and eight patients receiving PL in mixed venous blood by the method of Rose and Liebowitz (Sigma analytic kit 665). Our normal value for 2.3 DPG is 13.2 ± 1.9 μmol/g Hb.

MPN (30 mg/kg) or PL (15 mg/kg) was dissolved in a vehicle that contained anhydrous sodium biphosphate, sodium phosphate and benzyl alcohol. Each solution was diluted with sterile water to a total volume of 50 ml and administered intravenously over 30 minutes in a double-blind randomized fashion. A second infusion was given 2.5 hours after the termination of the initial infusion. Measurements of CO and mixed venous blood were obtained from each patient immediately before and 1.5 hours after each infusion and 12 and 24 hours after the initiation of the study. Arterial samples were taken during the initial baseline study and 4.5 and 24 hours thereafter.

Statistical analyses were performed using t tests for unpaired data in the MPN and the PL groups and for paired data within groups.

Results

In vitro and in vivo Pso (table 1) were both normal at the initiation of the study. No significant changes in Pso occurred in the MPN group or the PL group during the 24-hour observation period. The concentration of 2.3 DPG increased slightly but significantly (p < 0.05) only in the PL group at 24 hours (13.2 to 14.2 μmol/g Hb). The changes in 2.3 DPG were not associated with comparable changes in the Pso. Although the arterial temperatures remained normal, they were slightly greater in the PL groups at 1.5 and 24 hours. In contrast to Pso, 2.3 DPG and rectal temperature, the pH increased to a similar extent in both groups. The changes in rectal temperature and pH did not significantly affect in vitro or in vivo Pso.

Despite randomization of patients, the initial Hb concentration was greater in the MPN group (16.4 g%) than in the PL group (15.1 g%) (p < 0.05). This may be related to the relatively small number of patients in each group or to the larger number of male patients in the MPN group than in the PL group (11 vs nine). Subsequently, Hb declined in both groups due to blood sampling and the mobilization of extravascular water into the intravascular space during bedrest. The arterial oxygen saturation and the percentage of HbCO did not change significantly in either group (table 2). However, the mixed venous oxygen saturation decreased from 72.5% to 68.0% (p < 0.05) in the PL group.

The changes in CaO2 and CVO2 reflected primarily the alterations in Hb concentrations. However, Ca-vO2 remained statistically unchanged for both groups. The oxygen extraction ratio (Ca-vO2/CaO2) increased from 0.25 to 0.29 (p < 0.05) in the PL group, reflecting the changes in CaO2.

The CI increased from 2.76 to 3.06 l/min/m² (p < 0.02) 4.5 hours after MPN (table 3), while the changes in O2TI paralleled the changes in CI and
Table 1. \( p_{50} \) and Related Metabolic Measurements

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Baseline</th>
<th>1.5 hr</th>
<th>3 hr</th>
<th>4.5 hr</th>
<th>12 hr</th>
<th>24 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>( P_{50} ) (27 ± 1.3 mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In vivo</td>
<td>MPN</td>
<td>26.6 ± 1.1</td>
<td>26.7 ± 1.3</td>
<td>26.1 ± 1.2</td>
<td>26.8 ± 1.2</td>
<td>26.5 ± 1.9</td>
</tr>
<tr>
<td></td>
<td>PL</td>
<td>27.0 ± 0.7</td>
<td>27.3 ± 1.3</td>
<td>27.5 ± 1.6</td>
<td>27.5 ± 1.5</td>
<td>27.1 ± 1.9</td>
</tr>
<tr>
<td>In vitro</td>
<td>MPN</td>
<td>27.1 ± 1.8</td>
<td>28.0 ± 1.8</td>
<td>27.9 ± 1.9</td>
<td>28.5 ± 1.9</td>
<td>27.8 ± 2.3</td>
</tr>
<tr>
<td></td>
<td>PL</td>
<td>27.8 ± 1.5</td>
<td>27.9 ± 1.8</td>
<td>28.0 ± 2.6</td>
<td>28.3 ± 1.7</td>
<td>28.3 ± 1.9</td>
</tr>
<tr>
<td>Erythrocyte 2, 3 DPG</td>
<td>MPN</td>
<td>11.8 ± 2.6</td>
<td>11.9 ± 3.0</td>
<td>12.6 ± 2.6</td>
<td>11.9 ± 4.0</td>
<td>10.5 ± 3.1</td>
</tr>
<tr>
<td></td>
<td>(13.2 ± 1.9 μmol/g Hb) PL</td>
<td>13.2 ± 1.8</td>
<td>12.8 ± 2.4</td>
<td>13.0 ± 2.5</td>
<td>12.7 ± 2.3</td>
<td>14.3 ± 1.4</td>
</tr>
<tr>
<td>Rectal temperature (°C)</td>
<td>MPN</td>
<td>37.0 ± 0.5</td>
<td>37.1 ± 0.5</td>
<td>37.1 ± 0.5</td>
<td>37.0 ± 0.6</td>
<td>37.2 ± 0.5</td>
</tr>
<tr>
<td></td>
<td>PL</td>
<td>36.8 ± 0.5</td>
<td>37.7 ± 0.4</td>
<td>36.9 ± 0.7</td>
<td>37.1 ± 0.6</td>
<td>37.4 ± 0.7</td>
</tr>
<tr>
<td>pH, mixed venous 37°C</td>
<td>MPN</td>
<td>7.36 ± 0.03</td>
<td>7.36 ± 0.04</td>
<td>7.36 ± 0.04</td>
<td>7.35 ± 0.04</td>
<td>7.37 ± 0.04</td>
</tr>
<tr>
<td></td>
<td>PL</td>
<td>7.35 ± 0.04</td>
<td>7.36 ± 0.03</td>
<td>7.37 ± 0.03</td>
<td>7.38 ± 0.03</td>
<td>7.39 ± 0.03</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>MPN</td>
<td>16.4 ± 1.4</td>
<td>16.5 ± 1.4</td>
<td>16.7 ± 1.4</td>
<td>16.4 ± 1.4</td>
<td>16.4 ± 1.5</td>
</tr>
<tr>
<td></td>
<td>(12-16 g/100 ml) PL</td>
<td>15.1 ± 1.6</td>
<td>14.9 ± 1.8</td>
<td>14.9 ± 1.7</td>
<td>14.8 ± 1.6</td>
<td>14.3 ± 1.5</td>
</tr>
<tr>
<td>Carboxyhemoglobin</td>
<td>MPN</td>
<td>2.9 ± 1.6</td>
<td>2.6 ± 1.6</td>
<td>2.5 ± 1.6</td>
<td>2.9 ± 1.2</td>
<td>2.5 ± 1.2</td>
</tr>
<tr>
<td></td>
<td>(≤ 3%) PL</td>
<td>3.1 ± 1.2</td>
<td>2.6 ± 1.0</td>
<td>2.7 ± 1.2</td>
<td>2.7 ± 1.4</td>
<td>2.5 ± 1.0</td>
</tr>
</tbody>
</table>

Values are mean ± so; values in parentheses are normal values.

\*p < 0.05 (unpaired t test).

\( p < 0.02 \) (unpaired t test).

\( \cdot p < 0.01 \) (unpaired t test).

\$ p < 0.05 \) (paired t test).

\( \cdot \) p < 0.01 (paired t test).

Abbreviations: MPN = methylprednisolone; PL = placebo; 2,3 DPG = 2,3 diphosphoglycerate.

CaO₂, VO₂ind increased significantly after MPN, from 146 to 170 ml/min/m² (p < 0.05), but remained statistically unchanged in the control group.

**Discussion**

No significant increase in \( P_{50} \) occurred after either MPN or PL in our investigation of patients within 12 hours after the onset of acute myocardial infarction. This finding contrasts with previous reports on changes of \( P_{50} \) in patients after acute myocardial infarction.\(^{3, 16}\) However, in those reports, the progressive increase in \( P_{50} \) was associated with extensive myocardial infarction that led to cardiac failure and often death, and the change in \( P_{50} \) often occurred after the initial 24 hours of hospitalization. We cannot entirely exclude local, limited changes in the \( P_{50} \) of myocardial blood, as our determinations were performed on mixed venous, not coronary sinus, blood.\(^{18}\) Nevertheless, the absence of acute increases in \( P_{50} \) after pharmacologic doses of MPN in our patients is consistent with the recent finding of Farber and associates, who administered MPN every 6 hours for 24 hours to patients with chronic obstructive pulmonary disease and found no increase in \( P_{50} \).\(^{28}\)

The slight increase in 2,3 DPG at 12 and 24 hours in the patients who received PL may relate to the persistent reduction in CI and the more significant reduction in Hb concentration. In contrast, 2,3 DPG did not increase during the 24-hour observation period in the patients who received MPN or in the steroid-treated patients studied by Farber.\(^{28}\) Further, there was no statistical correlation between the changes in 2,3 DPG and the changes in \( P_{50} \) in either group. The lack of correlation between changes in 2,3 DPG and changes in \( P_{50} \) has been documented by other investigators.\(^{31, 18, 46}\)

Although the arterial oxygen saturation did not change significantly in either group, the mixed venous oxygen saturation decreased significantly in the PL group. This suggests a slightly greater increase in peripheral oxygen extraction that may have resulted from the persistently low CI and the decrease in the Hb concentration.

The decline in the Hb concentration affected both the arterial and the mixed venous oxygen contents; however, Ca-vO₂ remained remarkably constant in both groups of patients. We believe that the slight increase in the oxygen extraction ratio in the PL group primarily reflected the decline in the arterial oxygen content. The constant Ca-vO₂ and the slight increase or normalization of pH in both groups suggested that oxygen availability was adequate under the prevailing conditions of these patients with acute myocardial infarction.\(^{46}\)

The persistent increase in CO after the administration of MPN, compared with PL, may be related to primary myocardial and/or peripheral hemodynamic effects of corticosteroids.\(^{21, 28, 47-51}\) Our measurements do not permit us to state the exact mechanisms by which CO increases.

According to the Fick equation (CO = oxygen consumption divided by Ca-vO₂), when Ca-vO₂ remains constant, the CI is linearly related to the oxygen consumption index. The increase in the oxygen consumption index after administration of MPN in our
patients may be attributed, at least in part, to the significant increase in CI. In contrast, no changes in CI and oxygen consumption index were observed in patients who received PL.

We conclude that the administration of MPN within 12 hours after acute myocardial infarction increases CI but has no significant effect on the position of the ODC, the level of 2,3 diphosphoglycerate or Ca-vO₂.

Acknowledgment

The authors are grateful to the members of the Medical and Nursing Staffs, Sybil Michaels and the STAT Laboratory Department and the General Laboratory Department for their collaboration in the care of these patients.

Table 2. Oxygen Concentrations and Utilization

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Baseline</th>
<th>4.5 hr</th>
<th>24 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial oxygen saturation (%)</td>
<td>MPN</td>
<td>96.6 ± 1.9</td>
<td>95.4 ± 2.4</td>
</tr>
<tr>
<td></td>
<td>PL</td>
<td>96.3 ± 2.7</td>
<td>96.4 ± 2.0</td>
</tr>
<tr>
<td>Mixed venous oxygen saturation (%)</td>
<td>MPN</td>
<td>73.4 ± 6.5</td>
<td>73.4 ± 5.1</td>
</tr>
<tr>
<td></td>
<td>PL</td>
<td>72.5 ± 4.2</td>
<td>69.9 ± 5.9</td>
</tr>
<tr>
<td>Arterial oxygen content</td>
<td>MPN</td>
<td>22.4 ± 1.7</td>
<td>22.0 ± 1.9</td>
</tr>
<tr>
<td></td>
<td>PL</td>
<td>20.6 ± 2.2*</td>
<td>20.1 ± 2.3*</td>
</tr>
<tr>
<td>Venous oxygen content</td>
<td>MPN</td>
<td>16.9 ± 1.7</td>
<td>16.7 ± 2.0</td>
</tr>
<tr>
<td></td>
<td>PL</td>
<td>15.3 ± 1.8*</td>
<td>14.5 ± 2.2†</td>
</tr>
<tr>
<td>Arteriovenous oxygen content difference</td>
<td>MPN</td>
<td>5.5 ± 1.3</td>
<td>5.3 ± 1.2</td>
</tr>
<tr>
<td></td>
<td>PL</td>
<td>5.3 ± 1.2</td>
<td>5.6 ± 1.2</td>
</tr>
<tr>
<td>Oxygen extraction ratio</td>
<td>MPN</td>
<td>0.25 ± 0.06</td>
<td>0.24 ± 0.05</td>
</tr>
<tr>
<td></td>
<td>PL</td>
<td>0.25 ± 0.05</td>
<td>0.28 ± 0.05*§</td>
</tr>
</tbody>
</table>

Values are mean ± sd.

* p < 0.05 (unpaired t test).
† p < 0.02 (unpaired t test).
‡ p < 0.01 (unpaired t test).
§ p < 0.05 (paired t test).
¶ p < 0.02 (paired t test).
** p < 0.01 (paired t test).

Abbreviations: MPN = methylprednisolone; PL = placebo.

Table 3. Oxygen Transport and Consumption

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Baseline</th>
<th>4.5 hr</th>
<th>24 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac index (ml/min/m²)</td>
<td>MPN</td>
<td>2.76 ± 0.8</td>
<td>3.06 ± 0.7¶</td>
</tr>
<tr>
<td></td>
<td>PL</td>
<td>2.40 ± 0.4</td>
<td>2.39 ± 0.3</td>
</tr>
<tr>
<td>Oxygen transport index</td>
<td>MPN</td>
<td>621 ± 199*</td>
<td>670 ± 150†</td>
</tr>
<tr>
<td></td>
<td>PL</td>
<td>495 ± 82</td>
<td>480 ± 72</td>
</tr>
<tr>
<td>Oxygen consumption index (ml/min/m²)</td>
<td>MPN</td>
<td>146 ± 28*</td>
<td>158 ± 28*</td>
</tr>
<tr>
<td></td>
<td>PL</td>
<td>125 ± 25</td>
<td>136 ± 26</td>
</tr>
</tbody>
</table>

Values are mean ± sd.

* p < 0.05 (unpaired t test).
† p < 0.01 (unpaired t test).
‡ p < 0.001 (unpaired t test).
§ p < (paired t test).

Abbreviations: MPN = methylprednisolone; PL = placebo.

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