Morphine and postoperative rewarming in critically ill patients

JORGE L. RODRIGUEZ, M.D., CHARLES WEISSMAN, M.D., MICHAEL C. DAMASK, M.D., JEFFREY ASKANAZI, M.D., ALLEN I. HYMAN, M.D., AND JOHN M. KINNEY, M.D.

ABSTRACT Morphine sulfate (MSO₄) has been demonstrated to attenuate the stress response. MSO₄ might be useful in minimizing the stress associated with the perioperative period, particularly that due to awakening from anesthesia and rewarming. Two groups of critically ill patients who developed hypothermia (35.8°C) during a surgical procedure were studied. The control group was observed during routine medical management. Group II received 1 or 4 mg/kg MSO₄ followed by an infusion of 0.2 or 0.5 mg/kg/hr. During the postoperative rewarming period the control group patients demonstrated a major increase in metabolic demand and myocardial work. In group II patients the infusion of MSO₄ resulted in a lower metabolic rate. This was associated with a significantly longer rewarming time and a significant reduction in shivering, heat loss, heart rate, mean arterial pressure, and rate-pressure product. Infusion of MSO₄ in critically ill patients during the perioperative period suppressed metabolic demands and myocardial work while preserving cardiovascular function. 

Circulation 68, No. 6, 1238–1246, 1983.

IN THE MODERN intensive care unit maintenance of physiologic homeostasis is important; increasing attempts are being made to define, measure, and control stresses encountered by the critically ill. In recent years, prolonged intra-abdominal and thoracic procedures in patients with compromised cardiopulmonary function have become commonplace. However, the metabolic changes that accompany these procedures often place a major stress on the cardiovascular system. These surgical procedures are often performed in air-conditioned operating rooms on patients under general anesthesia. The combination of an open body cavity, a cool operating room, and general anesthesia (which abolishes the normal compensatory mechanisms such as peripheral vasoconstriction and shivering) has resulted in a greater number of such patients becoming hypothermic during the operative period. In the immediate postoperative period the simultaneous recovery from anesthesia, metabolic response to injury, and rewarming often result in marked increases of metabolic rate and myocardial work. Morphine sulfate (MSO₄) has become an integral part of therapy for critically ill patients and is used to facilitate mechanical ventilation and the control of pain. In a variety of dosages it has inhibited surgically induced increases in adrenocorticotropic hormone, cortisol, and growth hormone levels. After the administration of MSO₄ to hypermetabolic patients a decrease in oxygen consumption, temperature, and urinary catecholamine excretion has been demonstrated. Furthermore, it has been postulated that MSO₄ may induce a genuine "hemodynamic sedation" that can be beneficial.

The aim of this study was to determine a method to lessen the abrupt and large increases in metabolic demands that are the result of the three following simultaneous stress factors: (1) emergence from anesthesia, (2) response to injury, and (3) postoperative rewarming. We examined metabolic, hemodynamic, and biochemical parameter values in 18 patients during the immediate postoperative period after they had undergone intra-abdominal or intrathoracic procedures. The effects of MSO₄ were compared with those of routine medical management. All patients required, on medical grounds, admission to the surgical anesthesiological intensive care unit and mechanical ventilatory support for the first 24 hr after surgery.

Methods

Protocol. Two groups of patients who were admitted to the surgical-anesthesiological intensive care unit after surgery with esophageal temperatures less than 35.8°C were studied.
I consisted of eight patients who had been anesthetized with a variety of anesthetic techniques and observed during routine postoperative rewarming. These patients were sedated with MSO₄ (table 1A) to control minute ventilation (Vₐ) and, when needed, to ensure comfort. Group II consisted of 10 patients who received an MSO₄ anesthetic that was continued at a constant infusion rate during the postoperative period (table 1B). Patients 1 through 8 received 1 mg/kg MSO₄ for the first hour of anesthesia, and the drug was continued at a rate of 0.2 mg/kg/hr throughout the operative and postoperative rewarming periods. Patients 9 and 10 received a higher dose of MSO₄ (4 mg/kg/hr for the first hour of anesthesia), which was continued at a rate of 0.5 mg/kg/hr throughout the operative and postoperative rewarming periods. All patients were warmed with a thermal blanket. Sodium nitroprusside was started when mean arterial pressure exceeded 110 mm Hg and the dosage was titrated to maintain a mean arterial pressure (MAP) between 80 and 100 mm Hg. Fluids were administered to maintain cardiovascular filling pressures (central venous or pulmonary capillary wedge pressure [CVP, PCWP]) between 7 and 14 mm Hg and an adequate urine output (25 to 40 ml/hr). Systolic arterial blood pressure was maintained above 100 mm Hg. The study was terminated when the metabolic parameters and esophageal temperature were constant for 1 hr (indicating that a steady state had been achieved) and when body temperature was at least 37°C. This study was approved by the Institutional Review Board of the Health Sciences Center of Columbia University and written informed consent was obtained from study subjects.

**Measurements.** Temperature was recorded with a Yellow Springs 400 thermistor (Yellow Springs, OH). Separate electrodes were placed at the head of the bed and at the distal esophagus for measurement of ambient and esophageal temperatures, respectively.¹¹ ¹² The position of the esophageal electrode was confirmed by chest x-ray on admission to the intensive care unit. Esophageal temperature was used to approximate mean whole-body temperature. The thermistors had an error of 0.15°C (company specification) and were coupled to a Hewlett-Packard temperature module with a range of from 20° to 45°C for continuous display.

Oxygen consumption (V̇O₂ ml/min, STPD), carbon dioxide production (V̇CO₂ ml/min, STPD), and respiratory quotient were measured every 15 min with a Beckman Metabolic Measurement Cart (Beckman Instruments, Fullerton, CA). The air and oxygen intakes of the Bourns Bear 1 respirator were provided with gas blended with a single Bennet AO-1 air oxygen mixer to ensure a constant concentration of forced inspiratory oxygen (FIO₂).¹³ The O₂ and CO₂ analyzers, as well as the volume transducers, were calibrated before the recording of each measurement. The accuracy of the Beckman Metabolic Cart was validated as described by Damask et al.¹⁴ Under the conditions of the study, therefore, we expected an accuracy of ±5%.

Continuous direct monitoring of MAP and heart rate (HR) was performed via a No. 20–gauge radial artery catheter inserted before surgery and attached to a Hewlett-Packard pressure-amplifier module (82025-B). In six patients in group I CVP was measured with a No. 16–gauge catheter inserted via the internal jugular vein into the superior vena cava with the use of a Hewlett-Packard pressure-amplifier module (82025-B); the position was confirmed radiographically on admission to the intensive care unit. Patients 5 and 6 of group I and all patients in group II had a pulmonary artery catheter inserted after surgery; the position was confirmed on admission to the intensive care unit. In these patients, pulmonary artery, systemic, and diastolic pressures, MAP, PCWP, CVP, and cardiac output were measured every 15 min by the thermodilution method. Cardiac index (CI), stroke index (SI), left ventricular work index (LVWI), systemic vascular resistance (SVR), and pulmonary vascular resistance (PVR) were calculated.

Arterial blood gas (Corning 186 automatic pH/Blood Gas System, Medfield, MA) and serum lactate concentrations (DuPont's Instruments Automatic Clinical Analyzer, CA III, Wilmington, DE) were recorded on admission and hourly during the study. Arterial blood gas concentrations were corrected for temperature by the method of Astrup et al.¹⁵

---

**Table 1A**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Wt (kg)</th>
<th>BSA (m²)</th>
<th>Past medical history</th>
<th>Pathology</th>
<th>Surgical procedure</th>
<th>Operative time (hr)</th>
<th>Morphine dose (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>60</td>
<td>93</td>
<td>2.0</td>
<td></td>
<td>Hypertension</td>
<td>Bladder cancer</td>
<td>9:30</td>
<td>0.33</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>61</td>
<td>65.7</td>
<td>1.8</td>
<td></td>
<td>Hypertension; renal insufficiency</td>
<td>Aortic abdominal aneurysm</td>
<td>3:30</td>
<td>0.30</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>25</td>
<td>72</td>
<td>1.9</td>
<td></td>
<td>-</td>
<td>Multiple stab wounds; cardiac arrest</td>
<td>6:15</td>
<td>1.11</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>15</td>
<td>52.6</td>
<td>1.5</td>
<td></td>
<td>-</td>
<td>Stab wound to left chest; cardiac arrest</td>
<td>4:00</td>
<td>1.90</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>73</td>
<td>71.2</td>
<td>1.8</td>
<td></td>
<td>Hypertension</td>
<td>Aortic abdominal aneurysm</td>
<td>4:00</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>60</td>
<td>80</td>
<td>2.1</td>
<td></td>
<td>Hypertension; chronic obstructive pulmonary disease</td>
<td>Dissecting type I aortic aneurysm</td>
<td>6:30</td>
<td>0.62</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>81</td>
<td>72</td>
<td>1.8</td>
<td></td>
<td>Hypertension; fibrothorax</td>
<td>Aortic abdominal aneurysm</td>
<td>4:30</td>
<td>0.41</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>25</td>
<td>33.6</td>
<td>1.1</td>
<td></td>
<td>Asthma</td>
<td>Patent ductus arteriosus</td>
<td>3:15</td>
<td>0.23</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>50</td>
<td>67.6</td>
<td>1.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.62</td>
</tr>
<tr>
<td>± SE</td>
<td></td>
<td>8.7</td>
<td>6.3</td>
<td>0.11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.21</td>
</tr>
</tbody>
</table>
TABLE 1B
Patient data (group II)

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Wt (kg)</th>
<th>BSA (m²)</th>
<th>Past medical history</th>
<th>Pathology</th>
<th>Surgical procedure</th>
<th>Operative time (hr)</th>
<th>Morphine dose (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>78</td>
<td>72.9</td>
<td>1.75</td>
<td>Atrial premature contraction; adult-onset diabetes mellitus; chronic obstruction pulmonary disease; cerebral vascular accident; peripheral vascular disease</td>
<td>Aortic abdominal aneurysm</td>
<td>Resection of aortic aneurysm</td>
<td>5:30</td>
<td>2.22</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>68</td>
<td>68.0</td>
<td>1.75</td>
<td>Hypertension; congestive heart failure; cerebral vascular accident; myocardial infarction; peripheral vascular disease</td>
<td>Aortic abdominal aneurysm</td>
<td>Resection of aortic aneurysm</td>
<td>5:00</td>
<td>3.29</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>60</td>
<td>81.0</td>
<td>1.90</td>
<td>Hypertension; angina; cerebral vascular accident; chronic renal failure; peripheral vascular disease</td>
<td>Aortic abdominal aneurysm</td>
<td>Resection of aortic aneurysm</td>
<td>6:00</td>
<td>4.69</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>76</td>
<td>60.0</td>
<td>1.65</td>
<td>Hypertension; mitral regurgitation; ventricular arrhythmias; peripheral vascular disease</td>
<td>Aortic abdominal aneurysm</td>
<td>Resection of aortic aneurysm</td>
<td>6:30</td>
<td>2.60</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>70</td>
<td>85.0</td>
<td>1.86</td>
<td>Hypertension; angina; chronic renal failure; peripheral vascular disease</td>
<td>Aortic abdominal aneurysm</td>
<td>Resection of aortic aneurysm</td>
<td>8:00</td>
<td>4.14</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>78</td>
<td>57.3</td>
<td>1.70</td>
<td>Hypertension; angina; peripheral vascular disease</td>
<td>Aortic abdominal aneurysm</td>
<td>Resection of aortic aneurysm</td>
<td>5:00</td>
<td>4.20</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>78</td>
<td>60.0</td>
<td>1.75</td>
<td>Hypertension; angina; asthma; myocardial infarction; ventricular arrhythmias; chronic renal failure; peripheral vascular disease</td>
<td>Aortic abdominal aneurysm</td>
<td>Resection of aortic aneurysm</td>
<td>5:30</td>
<td>2.90</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>79</td>
<td>64.0</td>
<td>1.65</td>
<td>Angina; congestive heart failure; 6 months post myocardial infarction</td>
<td>Sigmoid cancer</td>
<td>Total sigmoid resection</td>
<td>3:00</td>
<td>2.60</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>72</td>
<td>70.0</td>
<td>1.80</td>
<td>Hypertension; angina; type III thoracic aortic aneurysm</td>
<td>Aortic abdominal aneurysm</td>
<td>Resection of aortic aneurysm</td>
<td>4:00</td>
<td>10.00</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>48</td>
<td>70.0</td>
<td>1.80</td>
<td>Hypertension; Leriche syndrome</td>
<td>Aortoiliac reconstruction</td>
<td>Aortoiliac reconstruction</td>
<td>6:00</td>
<td>8.57</td>
</tr>
<tr>
<td>Mean ± SE</td>
<td>71</td>
<td>69.0</td>
<td>1.76</td>
<td>3.0</td>
<td>0.03</td>
<td></td>
<td></td>
<td>6.34</td>
<td>4.52</td>
</tr>
</tbody>
</table>

*p < .05, compared with group I.

BSA = body surface area.

Neuromuscular blockade was evaluated on admission and at the end of the study with a Dupaco nerve stimulator, Model 54120 (San Marco, CA), with a twitch stimulus frequency of 2 Hz and, for tetany, a frequency of 100 Hz. Characteristics of fade and posttetanic facilitation of evoked twitch responses of the abductor muscle of the thumb were observed.

Data analysis. VO₂ and VCO₂ were corrected for body weight in kilograms. Mean ± SE was calculated for VO₂ and VCO₂ at every 0.25°C and these values were expressed graphically vs temperature (figure 1) and time of the study period.

A Neurometric Clinical Graphic Analyzer, model 1239 (Lansdale, PA), was used to perform graphic integration. Total O₂ consumption (TVO₂) and basal O₂ consumption (BVO₂) were calculated as shown in figure 1. The O₂ cost of rewarming (% CgV₀₂), metabolic heat production, heat loss, and change in body heat content were calculated as described in the Appendix.

Resting energy expenditure (REE, calories/day) was calculated from measurements of VO₂ and VCO₂. Nitrogen excretion was estimated with the use of principles of indirect calorimetry. The rate-pressure product (RPP), defined as the product of systolic blood pressure and HR, was calculated and interpreted to represent a measure of myocardial VO₂. Shivering was confirmed each time by the same two observers (J. R., C. W.), and was defined as gooseflesh skin associated with muscular fibrillations usually beginning at the neck, extending to the pectoral muscles, and at times involving the upper and lower extremities with irregular periods of relaxation.

Intergroup comparisons were made at three specific points:
Results

The clinical characteristics of the two groups of patients at the time of entry into the study are given in tables 1A and 1B. The patients in the two groups were comparable with respect to weight, body surface area, and operative time. Patients in group II were significantly (p < .05) older than those in group I.

Intraoperative fluids administered to patients in group I were (mean ± SE) colloids, 2.5 ± 0.41, and crystalloids, 4.07 ± 0.4. Fluid administration in the perioperative rewarming period consisted of 5% dextrose plus one-half normal saline at 113 ± 9.4 ml/hr infused at room temperature. The Bourns Bear 1 ventilator settings (mean ± SE) were V̇ₐ, 8.5 ± 0.63 l/min; tidal volume (Vₜ), 766 ± 39 ml; positive end-expiratory pressure (PEEP), 3 cm H₂O; frequency intermittent mandatory ventilation, 10.5 ± 0.33 beats/min, and FIO₂, 0.49 ± 0.01; temperature of the inspired oxygen was maintained between 26.5° and 32.5° C. Ambient temperature ranged from 21.8° to 26° C. Six of the eight patients had significant underlying systemic diseases. Patients 1, 2, 4, 5, 6, and 7 required sodium nitroprusside infusions throughout the rewarming period to control blood pressure. Evaluation of neuromuscular function revealed absence of fade and posttetanic facilitation in all patients on admission and at the end of the study, representing recovery from neuromuscular blockade. Shivering was observed in all of the patients, but was particularly marked in patients 1, 3, 4, 6, and 8, in whom both upper and lower extremities were involved.

Intraoperative fluids administered to group II patients were colloids, 2.7 ± 0.41, and crystalloids, 4.32 ± 0.51. Fluid requirements in the perioperative period were greater than those in group I (p < .005) and consisted of D₃/₂ NS at 150 ± 0 ml/hr infused at room temperature. The Bourns Bear 1 ventilator settings (mean ± SE) were V̇ₐ, 7.3 ± 0.1 l/min; Vₜ, 730 ± 16 ml; PEEP, 3 cm H₂O; IMV, 10 ± 0 beats/min; and FIO₂, 0.47 ± 0.06. Temperature of inspired oxygen was maintained between 26.5° and 32.5° C and ambient temperature ranged from 21.8° to 26° C. Patients 3, 6, 8, 9, and 10 required the infusion of a sodium nitroprusside drip throughout the rewarming period to control blood pressure. Evaluation of neuromuscular function of each patient on admission to the intensive care unit and at the end of the study revealed the absence of fade and posttetanic facilitation. All patients in group II were arousable within 2 hr after admission to the intensive care unit. Patient 9 required an additional 16 hr of mechanized ventilation secondary to the large dose of MSO₄. All other patients were extubated within the expected time frame of 18 to 30 hr after surgery. Shivering was observed in four of the patients (Nos. 4, 6, 8, and 10), but its manifestations were limited to fibrillations of the trapezius and pectoral muscles and gooseflesh skin (40%). The total dose of MSO₄ received by patients 1 through 8 was (mean ± SE) 3.3 ± 0.7 mg/kg while for patients 9 and 10 it was 9.3 ± 0.3 mg/kg.

The A, PS, and ES temperatures, along with the changes in temperature from A to ES revealed no significant differences between the two groups (table 2). Shivering occurred for 64% of the rewarming period in the control group, while there was a significant increase (p < .05) in REE from admission to the intensive care unit to PS (figure 2).

A comparison of group I and group II patients revealed that a constant MSO₄ infusion (0.2 or 0.5 mg/kg/hr) resulted in the following:

**TABLE 2**
Temperatures and changes therein (°C) for the two groups at A, PS (group I) MP (group II) and ES

<table>
<thead>
<tr>
<th></th>
<th>Group I</th>
<th>Group II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admission</td>
<td>35.2±0.2</td>
<td>34.6±0.2</td>
</tr>
<tr>
<td>PS/MP</td>
<td>36.7±0.2</td>
<td>36.3±0.2</td>
</tr>
<tr>
<td>ES</td>
<td>38.1±0.1</td>
<td>37.8±0.2</td>
</tr>
<tr>
<td>Δ°C</td>
<td>2.9±0.3</td>
<td>3.2±0.2</td>
</tr>
</tbody>
</table>
(1) Suppressed visible shivering in 60% of the patients; the four patients who visibly shivered did so for only 25% of the rewarming period.

(2) A marked reduction in $\dot{V}O_2$ and $\dot{V}CO_2$ (figure 3).

(3) A significant reduction in REE from perioperative level both on admission to the intensive care unit ($p < .001$) and at MP ($p < .05$; figure 2).

(4) Increased rewarming time ($p < .025$; figure 4).

(5) Reductions in $\dot{V}O_2$ ($p < .005$), $\dot{V}CO_2$ ($p < .005$), and amount of $\dot{V}O_2$ above baseline ($p < .05$) by 66%, 64%, and 72%, respectively ($%C_\dot{V}O_2$ was similar; figure 5, left).

(6) Decreased metabolic heat production and heat loss ($p < .005$) that resulted in a change in body heat content of a magnitude similar to that in the control group (figure 5, right).

(7) Reduced HR at MP ($p < .005$) and ES ($p < .025$; figure 6).

(8) Decreased MAP ($p < .005$) at MP (figure 6).

(9) Reduction in RPP on admission to the intensive care unit ($p < .05$) and at MP ($p < .01$; figure 6).

Table 3 illustrates the changes in the hemodynamic and biochemical parameter values during the rewarming period. CVP increased in group II while in group I it decreased. In both groups CI, SI, LVWI, and PCWP increased while PVR and SVR fell. $Paco_2$ increased significantly ($p < .05$) in both groups, which corresponded to an increase in $\dot{V}CO_2$ (figure 1) and the shift in pH from the alkalotic to the acidic range. Patients in both groups had elevated serum lactate concentrations on admission (normal, 2.0 mmol/l), which returned to normal at ES.

The significant decrease in metabolic parameter values observed in group II could have been secondary to the lower intrinsic metabolic rate in the elderly and not to the MSO$_4$ infusion. To evaluate this possibility, we compared two smaller ($n = 5$) age-matched groups. Patients 1, 2, 3, 6, and 7 (67 ± 9 years) from group I were compared with patients 2, 3, 5, 7, and 9 (69 ± 7 years) from group II. REE, $\dot{V}O_2$, $\dot{V}CO_2$, amount of $\dot{V}O_2$ above baseline, metabolic heat production, heat loss, HR, MAP, and RPP were significantly ($p < .05$) reduced in the smaller group II at the same points previously mentioned when compared with in the smaller group I. Hemodynamic and biochemical parameter values paralleled those of the two larger groups; $Paco_2$ significantly increased ($p < .05$) in both small groups.
FIGURE 4. A comparison of the rewarming time vs the change in body temperature for the two groups.

FIGURE 5. Left, TVO₂ (ml/kg/hr), BVO₂ (ml/kg/hr), and % C₅ BVO₂ in the two groups. Right, Metabolic heat production loss (HL, Kcal/hr). Statistical analysis by Student's t test (comparison with group I).
s during the operative period. An important component in the maintenance of homeostasis is the control of stress factors that may be detrimental. Three stress factors often affect patients simultaneously on admission to the intensive care unit: (1) awakening from anesthesia, (2) response to operative injury, and (3) postoperative rewarming. These stress factors have been demonstrated to increase $\dot{V}O_2$, $\dot{V}CO_2$, $\dot{V}E$, and cardiac output. Furthermore, when cardiac output does not meet the requirements for oxygen delivery, arterial hypoxemia may result. In a previous study by our group, total abolition of shivering with a neuromuscular blocking agent eliminated the rapid rise in $\dot{V}O_2$, $\dot{V}CO_2$, and RPP associated with shivering.

In this study the infusion of MSO$_4$ in hypothermic critically ill patients lowered $\dot{T}VCO_2$, $\dot{B}VO_2$, REE, metabolic heat production, and heat loss for a similar change in body heat content as the control group. Although $C_4$-$\dot{V}O_2$ was similar in both the control and morphine groups, it was accomplished at a lower metabolic expenditure in the morphine group. This reflects the greater economy of the rewarming system in patients on morphine: the metabolic generation of heat was conserved for rewarming instead of being lost.

The metabolic effects of MSO$_4$ observed in the present study were similar to that observed by Rouby et al. (a 21% decrease in $\dot{V}O_2$).

In contrast to the hemodynamic data obtained by Rouby et al. CI, LVWI, SI, and cardiac filling pressure increased as rewarming took place. At the same time, myocardial work (HR, MAP, RPP) was significantly lower. There are several possible explanations for these findings. First, the different patient populations in the two studies could be partially responsible for the different results. All of the patients studied by Rouby et al. were over the most acute phase of the disease process and were metabolically and hemody-

### Discussion

Increasing numbers of patients with systemic disease who undergo major surgery are being admitted to the intensive care unit on an elective basis. The routine use of invasive monitoring, cardiopulmonary drugs, and the greater appreciation of physiologic mechanisms has improved our ability to maintain homeosta-

### TABLE 3

Hemodynamic and biochemical parameters values (mean ± SE) at A, PS (group I) or MP (group II), and at ES

<table>
<thead>
<tr>
<th></th>
<th>CVP (mm Hg)</th>
<th>PCWP (mm Hg)</th>
<th>PVR (dynes sec/cm$^2$)</th>
<th>.SVR (dynes sec/cm$^2$)</th>
<th>CI (l/min/m$^2$)</th>
<th>SI (l/min/m$^2$)</th>
<th>LVWI (torr)$^2$</th>
<th>$Paco_2$ (mm Hg)</th>
<th>Lactic acid (mol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group I</td>
<td>7 ± 2</td>
<td>7 ± 1</td>
<td>149 ± 50</td>
<td>1917 ± 862</td>
<td>1.9 ± 0.3</td>
<td>24 ± 4</td>
<td>31 ± 8</td>
<td>31 ± 1</td>
<td>3.0 ± 0.8</td>
</tr>
<tr>
<td>Group II</td>
<td>7 ± 0.8</td>
<td>9 ± 0.9</td>
<td>193 ± 18</td>
<td>1716 ± 141</td>
<td>2.3 ± 0.2</td>
<td>33 ± 2</td>
<td>38 ± 5</td>
<td>33 ± 1</td>
<td>2.6 ± 0.3</td>
</tr>
<tr>
<td>Midstudy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group I (PS)</td>
<td>6 ± 2</td>
<td>8 ± 2</td>
<td>103 ± 50</td>
<td>1270 ± 330</td>
<td>2.3 ± 0.2</td>
<td>29 ± 2</td>
<td>34 ± 4</td>
<td>42 ± 2$^a$</td>
<td>2.5 ± 0.2</td>
</tr>
<tr>
<td>Group II (MP)</td>
<td>8 ± 0.9</td>
<td>10 ± 2</td>
<td>176 ± 21</td>
<td>1378 ± 560</td>
<td>2.6 ± 0.1</td>
<td>36 ± 2</td>
<td>41 ± 3</td>
<td>40 ± 2$^a$</td>
<td>1.9 ± 0.3</td>
</tr>
<tr>
<td>ES</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group I</td>
<td>6 ± 2</td>
<td>9 ± 2</td>
<td>70 ± 50</td>
<td>1126 ± 270</td>
<td>2.5 ± 0.5</td>
<td>31 ± 2</td>
<td>35 ± 6</td>
<td>51 ± 2$^a$</td>
<td>1.5 ± 0.3</td>
</tr>
<tr>
<td>Group II</td>
<td>9 ± 1</td>
<td>10 ± 0.8</td>
<td>161 ± 13</td>
<td>1186 ± 77</td>
<td>3.1 ± 0.2</td>
<td>36 ± 2</td>
<td>39 ± 3</td>
<td>45 ± 1$^a$</td>
<td>1.5 ± 0.3</td>
</tr>
</tbody>
</table>

$^a$$p < .05$ compared with A in group I and group II.
ynamically stable. The patients in the present study were in the “ebb” phase of the perioperative period during which metabolic and hemodynamic demands are rapidly rising. Thus, the physiologic state of the patient may influence the response to MSO₂. Second, in the present study the patients receiving MSO₂ had a significantly greater fluid requirement. When this was provided no significant deterioration in cardiovascular function was observed, in agreement with the findings of Stanley et al. Rouby et al. observed a decrease in transmural cardiac filling pressures, which could have resulted in the reduction of CI and arterial blood pressure. Maintenance of the intravascular space with fluids could account for the increase in right and left ventricular preload and, therefore, maintenance of cardiovascular function. Finally, in the present study ventilator support and vasodilator therapy was uniform in the two groups. However, there is the possibility that heterogeneity of care in the critically ill patients could have contributed to the differing results in the two groups.

This study suggests that the use of large doses of morphine in the critically ill during the dynamic phase of physiologic stress not only suppresses total body metabolic demand and myocardial work but maintains cardiovascular function when fluid requirements are met. This would be beneficial in the care of critically ill patients.

Previous studies have demonstrated that the high doses of MSO₂ used would be expected to block the hormonal response to operative stress. The recommendation by Reier et al. that doses larger than 2 mg/kg be avoided, especially if there is concern about the patient surviving a stressful situation, was not supported by our results. Furthermore, the use of exceptionally large doses in two of the patients studied produced the same metabolic and cardiovascular effects.

The mechanism for the suppression of shivering is not clear at the present time. There was no clinical evidence that neuromuscular blockade was present; yet it is not surprising that shivering was not observed. Narcotics (especially meperidine) have effectively suppressed the symptomatic shaking chills caused by granulocyte transfusion and amphotericin B administration in man. In animals, MSO₂ has impaired neuromuscular transmission both at peripheral muscarinic and neuromuscular nicotinic sites. In man, it has also been reported to diminish the posttetanic phase of neuromuscular transmission, and in spinal man morphine selectively depresses nociceptive spinal reflexes by a direct spinal mechanism. The mechanism of action is still unknown; however, it may be a

central effect or a local effect in the periphery or at the neuromuscular junction. It is important to emphasize that in the patients who received MSO₂ and shivered, metabolic rate and myocardial work were similar to those in patients who did not shiver.

In both groups, even though CO₂ production was markedly lower in group II, there was a rise in CO₂ production between A and ES. This was paralleled by an increase in Paco₂, while V̇E was constant throughout the study period. In clinical practice, if V̇E is regulated to maintain a Paco₂ of 40 to 45 torr, the clinician may encounter respiratory acidosis as rewarming takes place. As a result, frequent monitoring of arterial blood gas levels is mandatory; furthermore, it should be noted that ventilatory settings that are appropriate early in the rewarming period may not provide adequate V̇E for gas exchange later in the perioperative period.

In conclusion, using a noninvasive procedure for indirect calorimetry, routine hemodynamic monitoring, and laboratory chemistries, we have defined the immediate postoperative changes in metabolic rate and hemodynamic function that occur after major operative procedures, particularly those complicated by the development of intraoperative hypothermia. A MSO₂ infusion during this period was able to control the rapid increase in metabolic rate and circulatory demands associated with this period while preserving cardiovascular function. In critically ill patients, especially those with underlying cardiovascular disease, the rapid increases in metabolic and hemodynamic parameters that occur after major surgery may not be well tolerated. Serious consideration should be given to the use of MSO₂ during the immediate postoperative period. However, it should be noted that the period required to rewarm will be extended, that postoperative fluid requirements will increase, and that the patient will require mechanical ventilation.

We thank the surgical anesthesia intensive care unit nursing staff for their cooperation.

Appendix

\[ T_{\text{VO}_2} \text{ was calculated as } T_2 \left( \frac{\text{VO}_2}{T_1 - T_2} \right) \]

where \( T_2 \) = time at end of study; \( T_1 \) = initial time. \( B\text{VO}_2 \) was calculated as

\[ \int \frac{\text{VO}_2}{T_1 - T_2} \]
when a straight line was drawn from $\dot{V}_O_2$ to the last recorded $\dot{V}_O_2$. The integration, as illustrated in figure 1, was computed for both groups. Amount of $\dot{V}_O_2$ above baseline was calculated as the difference between $T\dot{O}_2$ and $B\dot{O}_2$.

The % $C_k\dot{O}_2$ was defined as

$$\frac{T\dot{O}_2 - B\dot{O}_2}{T\dot{O}_2} \times 100$$

Thermodynamic principles dictate that heat production ($M$) + heat loss (HL) = change in body heat content (BHC). Therefore, HL = M - BHC. It should be noted that HL and BHC are related to the validity of esophageal temperature as a measure of whole-body temperature and energy content. Alterations in perfusion that lead to the closing down of vascular beds will reduce the validity of this assumption. However, total metabolic heat production is related to whole-body gas exchange, not to esophageal temperature. The study duration in the two groups varied. Consequently, heat loss, metabolic heat production, and change in body heat content can be calculated:

$$M = \frac{T\dot{O}_2 \times 4.94}{\text{Rewarming time}} \text{ (expressed in Kcal/hr)}$$

$$\text{BHC} = \frac{0.83W (T_1 - T_2)}{\text{Rewarming time}} \text{ (expressed in Kcal/hr)}$$

where $W$ = patient’s weight (in kg); $T_1$ = initial temperature; $T_2$ = temperature at ES; and 0.83 = whole-body specific heat, assuming normal body composition.33

References

Morphine and postoperative rewarming in critically ill patients.
J L Rodriguez, C Weissman, M C Damask, J Askanazi, A I Hyman and J M Kinney

Circulation. 1983;68:1238-1246
doi: 10.1161/01.CIR.68.6.1238

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1983 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/68/6/1238

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/