Oxygen Uptake during Recovery Following Naloxone

Relationship with Intraoperative Heat Loss

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The increased metabolic and respiratory demand during naloxone recovery from opioid-based anesthesia could be related to the return of thermoregulation in hypothermic patients and thus be avoided by preventing intraoperative hypothermia. In this study, we measured \( \dot{V}_O_2 \) uptake (\( \dot{V}_O_2 \)) during naloxone-induced recovery in two groups of patients to determine the effect of intraoperative heat loss on postoperative \( \dot{V}_O_2 \) changes. In seven patients, intraoperative hypothermia was prevented (normothermic group), whereas hypothermia was allowed to develop in seven other patients (hypothermic group). Core and skin temperatures were measured throughout the study to calculate changes in body heat content. Before naloxone antagonism of fentanyl-supplemented anesthesia, core temperature (mean ± SEM) was 36.8 ± 0.1°C in the normothermic group and 34.2 ± 0.2°C in the hypothermic group (\( P < 0.001 \)). After titrated administration of naloxone during recovery, \( \dot{V}_O_2 \) and minute ventilation (\( \dot{V}_E \)) increased in the hypothermic group, by 114 ± 37% and 97 ± 52% respectively (\( P < 0.05 \)), with a three-fold increase in four patients. In the normothermic group, \( \dot{V}_O_2 \) increased significantly less (25 ± 5%), without any significant change in \( \dot{V}_E \). The change in \( \dot{V}_O_2 \) and \( \dot{V}_E \) was significantly greater in patients who were hypothermic. \( \dot{V}_O_2 \) was integrated throughout the recovery period to calculate recovery energy expenditure. Recovery energy expenditure and intraoperative heat loss were highly correlated (\( r = 0.88; P < 0.01 \)). This study demonstrates that the metabolic and respiratory stresses associated with naloxone-induced recovery from opioid-based anesthesia depend on the intraoperative heat loss and can therefore be prevented by reducing intraoperative hypothermia. (Key words: Antagonists, opioid: naloxone. Metabolism: oxygen consumption. Recovery: Temperature: hypothermia; rewarming.)

Recovery after Anesthesia and surgery is associated with an increase in \( O_2 \) uptake (\( \dot{V}_O_2 \)), leading to increased cardiac output and minute ventilation (\( \dot{V}_E \)). This change in \( \dot{V}_O_2 \) is observed during spontaneous rewarming with shivering, following intraoperative hypothermia. Other factors of increased metabolic demand, such as pain or awareness, may also be involved.

Naloxone antagonism of opioid-based anesthesia induces an acute increase in \( \dot{V}_O_2 \), which may be deleterious in patients with poor cardiorespiratory reserve. This has been attributed to increasing pain perception and restlessness. Since opioids may inhibit the thermoregulatory response, it can be hypothesized that naloxone administration during recovery may trigger spontaneous rewarming and shivering in hypothermic patients. Thus, the changes in \( \dot{V}_O_2 \) induced by naloxone depend, in part, on the intraoperative thermal status.

This study was therefore designed to evaluate: 1) the effective role of intraoperative heat loss on changes in \( \dot{V}_O_2 \) after antagonism of opioid anesthesia by naloxone; and 2) the effects of intraoperative prevention of hypothermia on these metabolic changes.

Materials and Methods

Patients

After obtaining informed consent, 14 patients (ASA physical status 1 or 2) scheduled for elective abdominal surgery, lasting at least 3 h, were included in this study, which was approved by the local Ethics Committee. The patients were randomly divided into two groups, according to the intraoperative management of the temperature. In 7 patients (3 men and 4 women), no special precautions were taken to avoid hypothermia. In 7 other patients (4 men and 3 women), hypothermia was actively prevented: they were covered up to the shoulders with a warming blanket before the induction of anesthesia; they then lay on a warming mattress, and their lower limbs were covered up to the pubis with a warming blanket during surgery.

Anesthesia

Patients received flunitrazepam (1 mg intramuscularly) and atropine sulfate (0.5 mg intramuscularly) 1 h before surgery. Anesthesia was induced with flunitrazepam (0.04 mg kg\(^{-1}\)), fentanyl (5 \( \mu \)g kg\(^{-1}\)), and pancuronium (0.1 mg kg\(^{-1}\)) and maintained with the same drugs as required and nitrous oxide 60% in \( O_2 \) under mechanical ventilation. Ringer's solution was infused at a mean rate of 9.2 ± 0.7 ml kg\(^{-1}\) h\(^{-1}\). Nitrous oxide was discontinued at the end of surgery, and patients were immediately transferred to the recovery room. The patient's lungs were mechanically ventilated with air, and the patients were covered with a warming blanket during recovery. Muscle

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60
relaxation was reversed with neostigmine (0.04 mg·kg⁻¹) and atropine sulfate (0.015 mg·kg⁻¹). Tracheal extubation was performed when the patients were able to open their eyes and breathe on demand. Naloxone was then administered in increments of 40 µg until the respiratory rate was greater than 12 breaths·min⁻¹, without any apneic episode. The patients were discharged from the recovery room when normothermic, at least 90 min after naloxone administration.

**MEASUREMENTS**

Core temperature (Tcore) was measured using a probe inserted 10 cm into the rectum before induction of anesthesia, and a second was placed into the lower esophagus after induction. Four skin thermistors were fixed with adhesive plaster on the chest, the upper arm, the lateral midthigh and midcalf; mean skin temperature was calculated, according to the formula given by Ramanathan, as 0.3 (Tchest + Tarm) + 0.2 (Tthigh + Tcalf), where T = temperature. Mean body temperature was calculated as 0.66 Tcore + 0.34 MST, where MST = mean skin temperature. Changes in total body heat content were expressed in kilojoules, as: ΔMBT (°C) × weight (kilograms) × 3.48 (body specific heat; kJ·kg⁻¹·°C⁻¹). Where ΔMBT = the change in mean body temperature during the same period.

\[ V_{O_2} (ml·min⁻¹·m⁻², at standard temperature and pressure, dry), CO₂ output (V_{CO₂}, ml·min⁻¹·m⁻², at standard temperature and pressure, dry), V_E (ml·min⁻¹·kg⁻¹, at body temperature and pressure, saturated), and end-tidal partial pressure of CO₂ (PETCO₂, mmHg) were measured using a Beckman Metabolic Measurement Cart⁶ (Sensormedics, Fullerton, CA), and displayed every 30 s, as previously described by Giofolo et al. When spontaneously breathing, patients were connected to the Beckman apparatus via an anesthetic face mask, tightly held to the patient’s face to prevent leaks. During controlled ventilation, the apparatus was connected to the outlet of the ventilator. The O₂ and CO₂ analyzers were automatically calibrated before each period of measurement, with a zero gas (100% N₂) and a calibration gas (CO₂ 4.78 ± 0.08% and O₂ 16.0 ± 0.4% in N₂, as defined by mass spectrometry). Temperature, pressure, and volume transducers were calibrated before the beginning of measurements. The inspired fraction of O₂ was measured after each calibration. At the end of each measurement, the stability of calibration was checked by reading calibration gas O₂ and CO₂ partial pressures. Therefore, within the conditions of the study, an accuracy of ±5% in the measurement of \( \dot{V}_{O_2} \) could be expected.

During recovery, metabolic and respiratory measurements began at least 20 min after N₂O discontinuation and then were continuously recorded, with the exception of transient periods due to extubation and calibrations. Four periods of measurements were analyzed: 1) the basal period, before induction of anesthesia, during at least 20 min of steady state (assessed by variations of \( \dot{V}_{O_2} \), \( \dot{V}_{CO_2} \), and \( \dot{V}_{E} \) less than 10%); 2) before naloxone administration and during mechanical ventilation, just before extubation; 3) immediately after naloxone administration, for at least 20 min; and 4) before discharge from the recovery room. The values retained for analysis were averaged over each period from data displayed every 30 s.

\( V_{O_2} \) was integrated over the recovery period up to normothermia to calculate total \( V_{O_2} \) (liters); basal \( V_{O_2} \) (liters) was calculated as the integration of \( V_{O_2} \) below a straight line drawn from the preoperative \( V_{O_2} \) to the \( V_{O_2} \) recorded at normothermia, as previously described by Rodriguez et al.⁹ Recovery energy expenditure, expressed in kilojoules, was calculated for each patient as (total \( V_{O_2} \) – basal \( V_{O_2} \)) × 20.65, where 20.65 kJ·l⁻¹·O₂ approximates the energy liberated per liter of O₂ utilized in standard conditions.

The occurrence of shivering was noted by an independent observer and classified as absent, mild (when detected only by ECG artifacts), or severe (when clinically obvious).

**STATISTICS**

All values are expressed as means ± standard errors of the mean. Statistical analysis was performed using two-way analysis of variance between periods, modified t test, Fisher’s exact test or unpaired t test between groups, and linear regression as required. P < 0.05 was considered significant.

**Results**

The two groups of patients did not differ significantly in age, weight, sex ratio, duration of surgery, or dosage of drugs, including naloxone (table 1). Basal values of

| Table 1. Physical Characteristics and Anesthesia in Hypothermic and Normothermic Patients |
|-----------------------------------------------|----------------|----------------|----------------|----------------|----------------|
| Hypothermic (n = 7)                           | 56 ± 5         | 62 ± 1         | 229 ± 16       | 1.36 ± 0.18    | 0.20 ± 0.06    |
| Normothermic (n = 7)                          | 49 ± 6         | 66 ± 2         | 264 ± 36       | 1.19 ± 0.20    | 0.17 ± 0.04    |

Mean ± SEM.
Table 2. Core Temperature, Oxygen Uptake, Carbon Dioxide Output, and Minute Ventilation in Hypothermic and Normothermic Patients

<table>
<thead>
<tr>
<th></th>
<th>Basal</th>
<th>Before Naloxone</th>
<th>After Naloxone</th>
<th>Discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_{core}$ ($^\circ$ C)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypothermic</td>
<td>36.7 ± 0.2</td>
<td>34.7 ± 0.2*</td>
<td>35.1 ± 0.4*</td>
<td>37.1 ± 0.2</td>
</tr>
<tr>
<td>Normothermic</td>
<td>37.1 ± 0.1</td>
<td>37.2 ± 0.2</td>
<td>37.4 ± 0.1</td>
<td>37.5 ± 0.2</td>
</tr>
<tr>
<td>$V_O_2$ (ml·min$^{-1}$·m$^{-2}$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypothermic</td>
<td>98 ± 5</td>
<td>123 ± 15</td>
<td>269 ± 60*†</td>
<td>129 ± 12</td>
</tr>
<tr>
<td>Normothermic</td>
<td>101 ± 6</td>
<td>112 ± 9</td>
<td>141 ± 9†</td>
<td>113 ± 10</td>
</tr>
<tr>
<td>$\dot V_{CO_2}$ (ml·min$^{-1}$·m$^{-2}$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypothermic</td>
<td>70 ± 8</td>
<td>81 ± 5</td>
<td>224 ± 62*†</td>
<td>76 ± 4</td>
</tr>
<tr>
<td>Normothermic</td>
<td>77 ± 4</td>
<td>85 ± 9</td>
<td>106 ± 13</td>
<td>83 ± 7</td>
</tr>
<tr>
<td>$\dot V_E$ (ml·min$^{-1}$·kg$^{-1}$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypothermic</td>
<td>75 ± 4</td>
<td>98 ± 7</td>
<td>193 ± 57*†</td>
<td>71 ± 6</td>
</tr>
<tr>
<td>Normothermic</td>
<td>83 ± 4</td>
<td>108 ± 7</td>
<td>109 ± 11</td>
<td>84 ± 7</td>
</tr>
</tbody>
</table>

Mean ± SEM. Hypothermic: n = 7; normothermic: n = 7.

$T_{core}$ = core temperature; $V_O_2$ = oxygen uptake; $\dot V_{CO_2}$ = carbon dioxide output; $\dot V_E$ = minute ventilation.

* $P < 0.05$ versus group of normothermic patients.
† $P < 0.05$ versus period before naloxone.

$T_{core}$, $V_O_2$, $\dot V_{CO_2}$, and $\dot V_E$ were also similar between groups (Table 2).

Intraoperatively, total body heat content markedly decreased in the patients without intraoperative prevention of hypothermia (449 ± 220 kJ), whereas it slightly increased in the others (+151 ± 20 kJ; $P < 0.001$ between groups). At the end of surgery, $T_{core}$ was 34.2 ± 0.4$^\circ$ C in patients without a warming blanket, versus 36.8 ± 0.1$^\circ$ C in the others ($P < 0.001$). As a consequence, the former group will be subsequently referred to as the "hypothermic group" and the latter as the "normothermic group."

Before naloxone administration, $V_O_2$ was slightly greater than basal values in both hypothermic (+26 ± 13%) and normothermic (+13 ± 8%) patients, without any significant difference between groups (Fig. 1). One patient of each group displayed mild shivering.

After naloxone administration, $V_O_2$ increased significantly in both groups, as compared to its value before naloxone administration. The $V_O_2$ increase was significantly greater in the hypothermic group (+114 ± 37%) than in the normothermic group (+25 ± 5%; $P < 0.05$ between groups). $\dot V_{CO_2}$ and $\dot V_E$ significantly increased only in the hypothermic group. $\dot V_{CO_2}$ and $\dot V_E$ were significantly greater in the hypothermic than in the normothermic group. PetCO$_2$ was similar in the two groups (34.8 ± 1.6 mmHg in hypothermic and 32.1 ± 1.9 mmHg in normothermic groups, respectively). No shivering was observed in the normothermic group. Severe shivering, lasting up to 45 min, occurred in five hypothermic patients ($P < 0.05$ vs. the normothermic group). In four of these patients, $V_O_2$ increased more than threefold, as compared to the basal period. When they stopped shivering, hypothermic patients had a mean $T_{core}$ of 36.5 ± 0.2$^\circ$ C.

At discharge from the recovery room, all patients were normothermic, and none displayed shivering; $V_O_2$, $\dot V_{CO_2}$, and $\dot V_E$ did not significantly differ from basal values.

Recovery energy expenditure was greater in the hypothermic than in the normothermic group (438 ± 93 vs. 54 ± 22 kJ; $P < 0.001$) and was correlated with $T_{core}$ at the end of surgery ($r = 0.90; P < 0.01$) and with both intraoperative heat loss ($r = 0.88; P < 0.01$; Fig. 2) and recovery heat gain ($r = 0.95; P < 0.001$).

Discussion

Administration of naloxone per se has little effect on the metabolic response of the body.14 By contrast, reversal of opioid-supplemented anesthesia with naloxone is usually associated with major metabolic, respiratory, and hemodynamic changes.7,8 These changes may result from many factors, including 1) return of pain with subsequent restlessness and metabolic consequences; 2) restoration

![Fig. 1. Oxygen uptake (expressed as a percentage above basal value; mean ± SEM) is significantly higher after naloxone (NLX) administration in hypothermic patients (n = 7; hatched bars) than in normothermic patients (n = 7; solid bars) (*P < 0.05 between groups).](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931334/ on 08/06/2018)
of thermoregulation in hypothermic patients; 3) increase in respiratory work with spontaneous ventilation; and 4) reversal of the $\dot{V}_{O_2}$ decrease due to opioid anesthesia.\cite{Tigerstedt1976} Tigerstedt et al observed a significant increase in $\dot{V}_{O_2}$ cardiac output, and $\dot{V}_E$ after the administration of 0.16 mg naloxone during recovery.\cite{Tigerstedt1976} Unfortunately, the temperature of the patients was not specified either in this study or in other studies concerning the cardiorespiratory changes induced by naloxone.\cite{Tigerstedt1976,Sugerman1976} Since the restoration of thermoregulation after naloxone may be a major cause of increase in $\dot{V}_{O_2}$ during hypothermic patients’ recovery, we compared the effect of naloxone administration on $\dot{V}_{O_2}$ in two groups of patients, differing by their intraoperative heat loss.

The two groups of patients had similar physical status and underwent similar surgery and anesthesia. They differed significantly only with regard to the intraoperative prevention of hypothermia: the patients without a warming blanket did indeed have an important heat loss and were thermoregulated at the time of naloxone administration, while the others displayed a moderate intraoperative heat gain and were normothermic. In normothermic patients, naloxone-induced recovery was associated with a mild increase in $\dot{V}_{O_2}$ whereas hypothermic patients displayed a dramatic increase in $\dot{V}_{O_2}$. Since there is little storage of $O_2$ in the body, $\dot{V}_{O_2}$ as measured by indirect calorimetry, is an accurate estimate of the body $O_2$ consumption; thus, the changes in $\dot{V}_{O_2}$ can be attributed to changes in metabolic demand. CO$_2$, in contrast, can be stored or released. Thus, the interpretation of acute $\dot{V}_{CO_2}$ changes is more difficult. Nevertheless, two points should be emphasized:

1) $\dot{V}_{CO_2}$ significantly increased only in the group of patients with the greatest $\dot{V}_{O_2}$ changes, i.e. in hypothermic patients, suggesting that $\dot{V}_{CO_2}$ changes were related to an increased cellular CO$_2$ production; 2) the changes in $\dot{V}_E$ were adapted to the changes in $\dot{V}_{CO_2}$ since PET$_{CO_2}$ remained within a normal range in all patients. Naloxone-induced recovery was indeed associated with an abrupt increase in $\dot{V}_E$ in hypothermic patients and not in normothermic patients. This difference may be clinically relevant in patients with poor respiratory reserve.

The difference in postoperative metabolic and respiratory demand could not be attributed to differences in residual anesthetics or in naloxone reversal efficiency: 1) The intraoperative dose of anesthetics was similar, and residual muscle paralysis had been antagonized in all patients. Of course, the remaining effects of anesthetics, such as opioids and muscle relaxants, could differ between groups, because of decreased elimination and metabolism in hypothermic patients.\cite{Sugerman1976,McKean1976} However, this effect would result in sustained anesthesia and a subsequent decreased metabolic demand in hypothermic patients: the reverse situation was observed. 2) Naloxone dosage was not different between groups and in the range of previously published data.\cite{Sugerman1976,Tigerstedt1976,Sugerman1976,Sugerman1976} Moreover, after naloxone administration, PET$_{CO_2}$ was similar and within a normal range in both groups, suggesting an equally efficient opioid reversal in both normothermic and hypothermic patients.

$\dot{V}_{O_2}$ during recovery is the sum of basal resting energy expenditure, energy spent for spontaneous rewarming (including shivering), and energy expended for recovery $per se$ (related to spontaneous ventilation, pain, return of consciousness, restlessness, etc.). The basal energy expenditure was measured in preoperative resting conditions: it was within a normal range for such patients. The energy spent during recovery, apart from a thermoregulatory function, can be estimated as the energy expended above basal value during recovery (defined as recovery energy expenditure) in normothermic patients: it approximates 50 kJ within 100 min (i.e., $\approx$ 8 W), produced with a mean $\dot{V}_{O_2}$ increase of 25%. Assuming that the two groups of patients differed only in their thermal status, the energy spent on rewarming can be estimated as the difference in recovery energy expenditure between the normothermic and the hypothermic groups, and approximates 400 kJ within 3 h (i.e., $\approx$37 W). In hypothermic patients, this energy was produced as a result of a dramatic $\dot{V}_{O_2}$ increase, up to fourfold its basal value in some shivering patients.

During recovery, hypothermic patients produced as much energy above basal expenditure as they had lost in the operating room. This finding is unlikely to be a methodological bias, since recovery energy expenditure and intraoperative heat loss were independently measured, using indirect calorimetry for recovery energy expenditure and Burton’s formulas for changes in total body heat content.\cite{Burton1976} Although Burton’s computation has not been established in unsteady anesthetized or recovering pa-
patients, its use for estimating body heat content changes seems suitable for the clinical situations we studied, as suggested by the equivalence during the recovery period between calculated heat gain and energy expenditure. A regulation of heat body content cannot yet be inferred from these results, and there is no evidence for such a regulation in humans. In most physiologic models, thermoregulatory responses are triggered by variations in integrated body temperature. The precise contribution of various tissues to the integrated body temperature during anesthesia and recovery is unknown, yet $T_{core}$ is the determining factor in the integrated body temperature. $T_{core}$ is thus frequently substituted in clinical studies. Before naloxone administration, hypothermic patients had a $T_{core}$ of 34.2°C without obvious thermoregulatory response. This finding is consistent with the 2.5°C decrease in thermoregulatory threshold found by Sessler et al. in patients anesthetized with fentanyl–nitrous oxide. The present study demonstrates that naloxone reverses opioid inhibition of thermoregulation. Naloxone administration might result in resetting the thermoregulatory threshold near its normal value, allowing thermoregulatory responses in hypothermic patients. These patients stopped shivering near core normothermia: $\dot{V}_{\text{O}_2}$ had then returned close to its basal preoperative value.

This study shows that the $\dot{V}_{\text{O}_2}$ changes during recovery are mainly influenced by the thermal status of patients. The nonthermoregulatory factors have little metabolic effect when compared to the increased demand induced by spontaneous rewarming following intraoperative hypothermia. In addition, this study emphasizes the importance of preventing intraoperative hypothermia to minimize postoperative metabolic and respiratory changes. These findings may be especially important for those patients with poor respiratory and/or circulatory reserve.

References