Oxygen Uptake after Major Abdominal Surgery: Effect of Clonidine

L. Quintin, M.D., Ph.D.,* J. P. Viale, M.D., Ph.D.,† G. Annat, M.D., Ph.D.,‡ J. P. Hoen, M.D.,† E. Butin, M.D.,† J. M. Cottet-Emard, Ph.D.,§ J. C. Levron, Ph.D.,¶ D. Bussery, M.D.,† J. Motin, M.D.**

To examine the effect of an alpha-2 agonist, clonidine, on oxygen uptake and on the incidence of postoperative shivering, 28 patients presenting for major abdominal surgery were randomly assigned in a double-blind manner to one of two groups. Intraoperatively, 14 patients received 5 µg·kg⁻¹ clonidine infused over 3 h (clonidine group), and 14 patients received placebo (placebo group). Oxygen uptake was measured continuously over the first 3 postoperative hours with a mass spectrometer system. Circulatory variables, esophageal temperature, and skin temperature were measured over the first 6 postoperative hours. Heart rate, mean arterial pressure, rate pressure product, and norepinephrine concentration were decreased in the clonidine group (P < 0.05). There were no differences among groups in the incidence of shivering and in the rate of increase of esophageal temperature. By contrast, oxygen uptake was lower in the clonidine group (P = 4.10⁻⁴). This contrasting pattern may be secondary to a reduction in the intensity of mean muscular tremor in the clonidine group. (Key words: Measurement technique, mass spectrometry; oxygen uptake. Sympathetic nervous system; α-2 adrenergic agonist; clonidine; catecholamines. Temperature, thermoregulation; shivering.)

SHIVERING DURING RECOVERY from surgery may lead to an increase in oxygen uptake (VO₂) by as much as 200–500% of baseline.1,2,4 To satisfy the increase in VO₂ associated with shivering, an increase in oxygen delivery and by extension cardiac output are required. This increased cardiac output1 may or may not match the oxygen demand.1,4,†† Hence a greater arteriovenous oxygen difference and arterial hypoxemia may follow in patients with†† or without1 reduced cardiopulmonary reserve.

Thus, a reduction in postoperative VO₂ or shivering may be of clinical importance.

Experimentally, clonidine, an imidazoline with alpha-2 agonist properties, reduces shivering3 and VO₂.4 Furthermore, this drug reduces the intensity of muscular activity during thermoregulatory shivering induced by a cold environment.5 In addition, clonidine has been reported to reduce the incidence of postanesthetic shivering after coronary6 and aortic7 surgery. The current study was an attempt to determine whether clonidine, given at a dose intermediate between those previously administered,5,7 would modify the incidence of shivering after major abdominal surgery, a setting in which postoperative hypothermia is common, even when all possible countermeasures are taken to reduce heat loss. Since shivering is not easily quantitated, VO₂ was measured in order to estimate the intensity of shivering. In addition, plasma concentrations of clonidine, opioids, and catecholamines were measured to assess the possibility of an interaction between alpha-2 agonists and opioids and to provide an indirect index of sympathetic activity8 during the postoperative period.

Materials and Methods

Patients

After approval by the Ethics Committee of the Hospices Civils de Lyon, informed consent was obtained in 28 ASA Physical Status 1 or 2 patients presenting for colon or colorectal surgery lasting at least 3 h (table 1). Patients presenting with a coronary or respiratory pathology or treated chronically with beta-blockers or centrally acting antihypertensive agents were excluded from the trial.

After preanesthetic medication with hydroxyzine 1.5 mg·kg⁻¹ orally and chlorazepate 0.25 mg·kg⁻¹ orally, anesthesia was induced with thiopental 4 mg·kg⁻¹ and fentanyl 4 µg·kg⁻¹. Atracurium 500 µg·kg⁻¹ was followed by tracheal intubation. Anesthesia was maintained with N₂O (66%) and fentanyl 4 µg·kg⁻¹·h⁻¹. Atracurium 500 µg·kg⁻¹·h⁻¹ was given to maintain muscle paralysis until peritoneal closure. Supplemental fentanyl (2 µg·kg⁻¹) was injected upon increase of systolic blood pressure (SBP) by more than 30% of preinduction values. Tachycardia or bradycardia were defined as a heart rate (HR) above 110 or below 50 beats per min, respectively, for 5 min. Hypertension or hypotension were defined as
SBP above 170 or below 90 mmHg, respectively, for 5 min. The patients were randomized in a double-blind manner by means of a computer-generated random table and assigned to one of two groups: 1) placebo patients (n = 14), who received a placebo (saline) infusion over 3 h, beginning at the time of surgical incision, and 2) clonidine patients (n = 14), who received clonidine 5 μg·kg⁻¹ dissolved in a similar volume of saline, over an identical period of time.

**Protocol**

In all patients, upon arrival in the recovery room (RR), 1) morphine (100 μg·kg⁻¹ subcutaneously) was administered; 2) neuromuscular blockade was assessed; and 3) patients were covered with a sheet. The lungs were mechanically ventilated for 3 h postoperatively with a Dräger E-VA ventilator (tidal volume [Vₜ] = 8 ml·kg⁻¹; respiratory rate = 12 breaths per min). Gases were humidified and rewarmed throughout the study, including the intraperative period. OR and RR temperatures were 20 ± 1 and 23 ± 1°C, respectively. Warmed fluids were infused to keep the central venous pressure above 5 cmH₂O and diuresis above 1 ml·kg⁻¹·h⁻¹ throughout the study. Dextrose was infused at a constant rate (2 mg·kg⁻¹·min⁻¹) throughout the study. A 10-ml sample of venous blood was collected immediately after induction of anesthesia (baseline), at skin closure, upon arrival in the RR, and hourly for 3 h thereafter. Circulatory data were recorded at the following stages: 1) after induction; 2) every 5 min intraoperatively; 3) every 5 min postoperatively for 3 h; and 4) every 15 min for an additional 3 h after extubation. Temperatures were recorded at the same intervals except during the intraperative period. VₐO₂ was measured during the first 3 postoperative hours, after which the patients’ tracheas were extubated.

**Measurements**

Circulatory variables such as SBP, mean arterial pressure (MAP), and HR were measured noninvasively (with a Dynamap®). The rate–pressure product (RPP) was calculated as the product of HR and SBP. Temperatures were measured with NCC HiLo Temp 8200 thermocouples (Bailey, Saddle Brook, NJ) inserted in the esophagus and at four sampling sites—trunk, arm, thigh, and leg. Mean skin temperature was calculated as: 0.3 × (trunk temperature + arm temperature) + 0.2 × (thigh temperature + leg temperature). The intensity of visible spontaneous shivering was assessed, every 5 min, as: absent = no visible muscular fasciculations observed in the maseter muscle; present = minimal muscular fasciculations observed in the same muscle or vigorous continuous or violent tremor.

**Oxygen Uptake**

Description and validation of the mass spectrometer system used for the measurement of Vₒ₂ are summarized as follows. Vₒ₂ was calculated as: Vₒ₂ = VE (F吸入 O₂ × F吸入 N₂/F吸入 N₂ – F吸入 O₂), where F吸入 and F吸入 are the fractional concentrations of inspired and expired gases, respectively, and VE is the expired flow. This equation is valid even in the presence of anesthetic gases, and especially during washout of N₂O. Gas samples were drawn from the endotracheal tube for 60 s while F吸入 O₂ and F吸入 N₂ were measured by a mass spectrometer (model MGA1100, Perkin Elmer). The input valve of the mass spectrometer then was automatically switched on for another 60-s period to draw gas samples from a 4-l expiratory mixing chamber to measure F吸入 N₂ and F吸入 O₂. During these two sequences, flow rate signals from a pneumotachometer were sampled and integrated to compute expired minute volume. Corrections of the flow signal were made to take into account the composition of the expired gas and to convert the results into standard temperature and pressure, dry (STPD) conditions. At the end of this 2-min measurement cycle, Vₒ₂ (at STPD) was computed, and the result stored. The gas exchange data obtained during the 15 min after the withdrawal of nitrous oxide were discarded for analysis to take into account changes in body nitrogen stores after step changes in F吸入 N₂.

**Plasma Samples**

Blood was withdrawn with a chilled syringe, transferred to chilled lithium heparin tubes, and handled at 4°C. The plasma was separated within 30 min in a centrifuge (4°C, 1,000×g) and stored at −80°C. Concentrations of norepinephrine (NE) and epinephrine (E) were determined in duplicate with a validated high-pressure liquid chromatography–electrochemical detection technique. Limits of detection were 5 and 9 pg·ml⁻¹ for NE and E, respectively. Intra- and interassay coefficients of variations were 2.7 and 3.4%, respectively, for NE and 3 and 5.8%, respectively, for E. Clonidine concentrations were determined with a radioimmunologic assay. The detection limit for clonidine was 10 pg·ml⁻¹. Intra- and interassay coefficients of variation were 4 and 8.3%, respectively.
Concentrations of fentanyl were determined with a radioimmunoassay. The detection limit for fentanyl was 0.1 ng · ml⁻¹. Intra- and interassay coefficients of variation were 5.0 and 9.9%, respectively.

**DATA ANALYSIS**

Data are reported as means ± SEM. Demographic and clinical data were compared by the chi-squared test with Yates's correction and Wilcoxon's two-sample test when appropriate. Plasma, gas exchange, and circulatory variables were analyzed first at baseline for homogeneity by analysis of variance. A two-way analysis of variance for repeated-measurement testing for treatment and time and their interaction was performed between groups. A $P$ value of less than 0.05 was considered significant.

**Results**

Demographic, medical, and surgical data, as well as fluid management, were similar between groups (table 1).

Intraoperative circulatory side effects were minimal, and the number of anesthetic interventions was reduced in the clonidine group (table 2), as reported previously. Recovery from neuromuscular blockade was similar in all patients upon arrival in the RR. Fentanyl concentrations were similar between groups, whereas clonidine concentrations remained in the 1–1.5-ng · ml⁻¹ range in the treated group (table 3). Neither group demonstrated deleterious effects, such as delayed awakening or prolonged need for mechanical ventilation beyond the 3 h of mechanical ventilation.

Postoperatively, the number of episodes of tachycardia and hypertension was reduced in the clonidine group ($P < 0.01$, table 2). The clonidine group experienced a greater number of episodes of bradycardia ($P < 0.05$), although HR remained always above 40 beats per min. Furthermore, relative bradycardia was not accompanied by systolic hypotension in the clonidine group. Clonidine affected the extreme values for HR and SBP only minimally (table 2).

**TABLE 2.**

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo</th>
<th>$P$</th>
<th>Clonidine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraoperative events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tachycardia (episodes)</td>
<td>25</td>
<td>&lt;0.001</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension (episodes)</td>
<td>26</td>
<td>&lt;0.01</td>
<td>5</td>
</tr>
<tr>
<td>Bradycardia (episodes)</td>
<td>11</td>
<td>NS</td>
<td>7</td>
</tr>
<tr>
<td>Hypotension (episodes)</td>
<td>49</td>
<td>NS</td>
<td>46</td>
</tr>
<tr>
<td>Patients having received atropine</td>
<td>5</td>
<td>NS</td>
<td>5</td>
</tr>
<tr>
<td>Fentanyl rejections</td>
<td>4.2 ± 0.5</td>
<td>&lt;0.01</td>
<td>2.2 ± 0.5</td>
</tr>
<tr>
<td>Fentanyl injected (total µg)</td>
<td>468 ± 68</td>
<td>&lt;0.05</td>
<td>240 ± 59</td>
</tr>
<tr>
<td>Postoperative events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tachycardia (episodes)</td>
<td>104</td>
<td>&lt;0.01</td>
<td>52</td>
</tr>
<tr>
<td>Hypertension (episodes)</td>
<td>32</td>
<td>&lt;0.01</td>
<td>6</td>
</tr>
<tr>
<td>Bradycardia (episodes)</td>
<td>0</td>
<td>&lt;0.05</td>
<td>11</td>
</tr>
<tr>
<td>Hypotension (episodes)</td>
<td>0</td>
<td>NS</td>
<td>6</td>
</tr>
<tr>
<td>HR (range: lowest–highest, beats per min)</td>
<td>51–150</td>
<td>43–144</td>
<td></td>
</tr>
<tr>
<td>SBP (range: lowest–highest, mmHg)</td>
<td>71–205</td>
<td>82–195</td>
<td></td>
</tr>
</tbody>
</table>

HR = heart rate; SBP = systolic blood pressure.

**TABLE 3. Plasma Variables**

<table>
<thead>
<tr>
<th>Event</th>
<th>After Induction</th>
<th>Skin Closure</th>
<th>Arrival in RR</th>
<th>1st h</th>
<th>2nd h</th>
<th>3rd h</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>NE (pg · ml⁻¹)</td>
<td>Placebo</td>
<td>266 ± 46</td>
<td>695 ± 105</td>
<td>1002 ± 236</td>
<td>980 ± 184</td>
<td>845 ± 111</td>
<td>712 ± 106</td>
</tr>
<tr>
<td>E (pg · ml⁻¹)</td>
<td>Placebo</td>
<td>283 ± 51</td>
<td>320 ± 51</td>
<td>369 ± 91</td>
<td>764 ± 188</td>
<td>531 ± 102</td>
<td>471 ± 114</td>
</tr>
<tr>
<td>Fentanyl (ng · ml⁻¹)</td>
<td>Placebo</td>
<td>55 ± 7</td>
<td>95 ± 20</td>
<td>928 ± 71</td>
<td>321 ± 98</td>
<td>204 ± 67</td>
<td>158 ± 53</td>
</tr>
<tr>
<td>Clonidine (ng · ml⁻¹)</td>
<td>Placebo</td>
<td>60 ± 24</td>
<td>92 ± 22</td>
<td>138 ± 49</td>
<td>170 ± 41</td>
<td>147 ± 38</td>
<td>124 ± 46</td>
</tr>
<tr>
<td>Clonidine (ng · ml⁻¹)</td>
<td>Clonidine</td>
<td>1.2 ± 0.2</td>
<td>5.8 ± 1.1</td>
<td>6.3 ± 1.2</td>
<td>3.2 ± 0.4</td>
<td>2.6 ± 0.5</td>
<td>2.2 ± 0.3</td>
</tr>
<tr>
<td>Clonidine (ng · ml⁻¹)</td>
<td>Placebo</td>
<td>1.6 ± 0.2</td>
<td>7.3 ± 1.5</td>
<td>4.9 ± 1.5</td>
<td>2.7 ± 0.2</td>
<td>2.1 ± 0.2</td>
<td>1.9 ± 0.2</td>
</tr>
</tbody>
</table>

Data are means ± SEM.

Normal values are 245 ± 51 pg · ml⁻¹ for NE and 41 ± 6 pg · ml⁻¹ for E.

RR = recovery room; NE = norepinephrine; E = epinephrine; ND = below limit of detection.
POSTOPERATIVE OXYGEN UPTAKE AND CLONIDINE

Fig. 1. Circulatory and temperature changes during 6 h of the postoperative period after major abdominal surgery. Patients were treated with clonidine (closed circles, 5 μg·kg⁻¹ iv over 3 h beginning at skin incision, n = 14) and placebo (open circles, n = 14). Data are expressed as means ± SEM. HR = heart rate (P < 10⁻⁴ between groups); MAP = mean arterial pressure (P < 10⁻⁴ between groups); RPP = rate pressure product (P < 10⁻⁴ between groups). A difference for mean skin temperature progressively developed between groups (P = 10⁻⁴).

HR, MAP, and RPP were lower in the clonidine group (P < 10⁻⁴ for each variable, fig. 1). NE concentrations were reduced in this group (P = 2.10⁻⁴, table 3). The rate of increase in esophageal temperature was similar in both groups. By contrast, a difference in mean skin temperature progressively developed in the clonidine group (P < 10⁻⁴, fig. 1). Oxygen consumption was reduced in the clonidine group (P = 4.10⁻⁴, fig. 2). However, the incidence of shivering was the same in both groups: 6 patients in each group presented clinical evidence of visible shivering.

Discussion

Circulation

Postoperatively, the placebo group presented with circulatory variables at the upper limit of normal values, but with marked increased NE concentrations. This overall profile is compatible with an increased sympathetic nervous activity, bearing in mind the limitation of NE concentrations as an index of sympathetic activity.⁸ In contrast, circulatory variables were lower, as were NE concentrations, in the clonidine group. Since this profile was observed in the presence of opioid concentrations similar to those in the placebo group, the blunting of the circulatory and sympathetic hyperactivity observed in the treated group is likely to be a consequence of clonidine administration.

However, the reduction in the mean HR and MAP as well as the reduction in the number of episodes of hypertension and tachycardia should be contrasted with the minimal effect of clonidine on extreme values for HR and SBP, as seen in this study and as reported intraoperatively in another study.²⁰ Thus, after clonidine, the circulatory system appears to reset to a lower level while its reactivity is affected only minimally. This pattern may be explained by the finding that clonidine affects only the adrenergic component of the central circulatory command and leaves the other component intact.²¹

A partial circulatory blunting was obtained in this study with the dose of 5 μg·kg⁻¹ of clonidine and resulted in a concentration in the 1–1.5 ng·ml⁻¹ range. Similar partial circulatory blunting was reported after similar doses of clonidine (7 μg·kg⁻¹ clonidine intravenously over 4 h⁶; 7 μg·kg⁻¹ clonidine orally over 6 h⁹). In contrast, a

Fig. 2. Changes in oxygen consumption (VO₂, ml·min⁻¹, P = 4·10⁻⁴ between groups) measured with a mass spectrometer system during 3 h of postoperative mechanical ventilation after major abdominal surgery. The experimental protocol and the expression of the data are as in figure 1. Data represent the mean of values measured every 2 min and are averaged over 15-min periods for clarity.
near-total blunting of sympathetic responses has been observed after 7 μg·kg⁻¹ of intravenous clonidine over 2 h, a dosage that resulted in a concentration of 2 ng·ml⁻¹. Indeed, maximal circulatory effects were observed with a concentration of clonidine close to 1.5–2 ng·ml⁻¹. Thus, a dose of clonidine in the 5–7 μg·kg⁻¹ range infused over 2–3 h, or its bioequivalent, may result in a significant attenuation or suppression of the circulatory response after major surgery.

**Oxygen Uptake**

Study of VO₂ in the postoperative period necessitates extra care. The method used here was an open-collection technique. This was performed with equipment that allowed simultaneous multiple-gas analysis and computation of VO₂. VO₂ was measured continuously to ensure that measurement the peak increase in VO₂ in the postoperative period was obtained. The use of nitrogen as a tracer gas to calculate inspired volume from the measurement of expired volume is unreliable after step changes in F[sub]N₂ associated with the end of anesthesia. At this interval, nitrogen stores are in an unsteady state and the calculation of VO₂ with the equation given above (Materials and Methods) leads to a systematic error. When a dynamic model of nitrogen body stores is used, this error has been found to be negligible beyond the 15 min after abrupt changes in F[sub]N₂.

The absence of reduction in the incidence of visible shivering by clonidine after major abdominal surgery contrasts with previous observations after coronary or aortic surgery. Since the incidence of shivering was identical between groups and the VO₂ was reduced in the clonidine group, a possible explanation for this pattern is a reduction in the intensity of muscular tremor and of muscular heat production. Indeed, a difference in mean skin temperature progressively developed in the clonidine group, despite a similar rate of increase in core temperature, a finding reported previously. In this respect, clonidine reduces the mean muscular tremor, but leaves unaffected the maximal tremor in humans and reverses opioid-induced muscular rigidity in rats.

Postanesthetic tremor comprises tonic and phasic/clonic components. This clonic component may be secondary to the activation of a spinal reflex. In this regard, clonidine reduces the intensity of the electromyographic (EMG) activity in rats after transection of the spinal cord. However, in this experimental paradigm, the phasic component of the EMG is unaffected by clonidine. Thus, a reduction of mean muscular tremor and of VO₂ is compatible with a lack of effect of clonidine on either the phasic component of tremor or on the incidence of shivering. Lastly, supraspinal influences may contribute to an effect by clonidine.

The blunting of the circulatory instability and the absence of change in the incidence of shivering at lower VO₂ may bear clinical significance. Indeed, the lack of respiratory depression associated with the use of clonidine contrasts with such the possibility of respiratory depression when opioids or muscle relaxants are used to reduce VO₂ or to control shivering. Secondly, a reduction in tachycardia and hypertension and in total body oxygen consumption may be of importance in patients at risk of developing inadequate cardiac output or myocardial ischemia in the postoperative period. These potential advantages of clonidine remain to be established in patients with reduced cardiopulmonary or coronary reserve, bearing in mind the previous demonstrations of improved perioperative circulatory stability after the administration of clonidine in patients with coronary disease or hypertension, who present for major surgery.

M. Dhers and C. Hemery were instrumental in this study. Bioscience determined clonidine concentrations. M. Ghigione reviewed an earlier draft of this manuscript.

**References**


11. Aukburg SJ, Geer RT, Wollmann H, Neufeld GR: Errors in mea-
sessment of oxygen uptake due to anesthetic gases. ANESTHESIOLOGY 62:54–59, 1985
12. Sagnot M, Claustre J, Cochet-Emard JM, Pequiernot JM, Fellmann N, Coudert J, Peyrin L: Plasma free and sulphated catechol-
13. Arndts D, Stähle H, Förster HJ: Development of a RIA for clo-
idine and its comparison with the reference methods. J Phar-
15. Ghignone M, Quintin L, Duke PC, Kehler CH, Calvillo O: Effects of clonidine on narcotic requirements and hemodynamic re-
sponse during induction of fentanyl anesthesia and endotracheal intubation. ANESTHESIOLOGY 64:36–42, 1986
16. Helbo Hansen S, Fletcher R, Lundberg D, Nordström L, Werner O, Stähl E, Nordén N: Clonidine and the sympato-adrenal re-
18. Ghignone M, Noe C, Calvillo O, Quintin L: Anesthesia for ophthallic surgery in the elderly: The effects of clonidine on intraocular pressure, perioperative hemodynamics, and anes-
thetic requirement. ANESTHESIOLOGY 68:707–716, 1988
19. Engelmann E, Lipsycz M, Gilbart E, Van der Linden P, Bellens B, Van Romphey A, de Rood M: Effect of clonidine on anesthetic drug requirements and hemodynamic response during aortic sur-
25. Jerussi TP, Capechione JF, Benvenga MJ: Reversal of opioid-induced muscular rigidity in rats: Evidence for alpha-2 adren-
26. Sessler DI, Israel D, Pozos RS, Pozos M, Rubinstein EH: Spon-
taneous anesthetic tremor does not resemble thermoregulatory shivering. ANESTHESIOLOGY, 68:843–850, 1988
27. Tremblay LE, Bedard PJ: Effect of clonidine on motoneuron ex-