

# Effects of Clonidine on Narcotic Requirements and Hemodynamic Response during Induction of Fentanyl Anesthesia and Endotracheal Intubation

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The effects of clonidine, a centrally acting  $\alpha_2$ -adrenergic receptor agonist, on depth of fentanyl anesthesia and on cardiovascular response to laryngoscopy and intubation were studied. Twenty-four patients undergoing aortocoronary bypass surgery (ACBS) with a history of arterial hypertension, coronary artery disease (NYHA class 3-4), and well-preserved left ventricular function were assigned randomly to either Group 1 (n = 12), who received standard premedication, or Group 2 (n = 12), who received clonidine  $5 \mu\text{g} \cdot \text{kg}^{-1}$  po in addition to standard premedication 90 min before estimated induction time. Depth of anesthesia was assessed by on-line aperiodic computerized analysis of the electroencephalogram (Lifescan EEG Monitor®). Fentanyl was administered in 250- $\mu\text{g}$  increments to shift the EEG to the 0.5-3-Hz frequency range (delta activity) in all subjects. In both groups, the anesthetic regimen effectively prevented hyperdynamic cardiovascular responses to laryngoscopy and intubation. No significant differences in measured or derived hemodynamic variables were observed between the two groups during the awake control period, except for stroke volume index (SVI), which was significantly greater in Group 1,  $44 \pm 9 \text{ ml} \cdot \text{beat}^{-1} \cdot \text{m}^{-2}$  compared with Group 2,  $35 \pm 3.3 \text{ ml} \cdot \text{beat}^{-1} \cdot \text{m}^{-2}$  ( $P < 0.05$ ). By contrast, fentanyl requirements in Group 2 were significantly reduced by 45% when compared with Group 1, *i.e.*, from  $110 \pm 23$  to  $61 \pm 19 \mu\text{g} \cdot \text{kg}^{-1}$  ( $P < 0.001$ ). The authors conclude that at a similar anesthetic depth, as assessed by the EEG shift into the lower frequency range (0.5-3 Hz), a markedly reduced fentanyl dose effectively prevented the hyperdynamic cardiovascular response to laryngoscopy and intubation in the group of patients premedicated with clonidine. This is likely explained by the known synergistic inhibitory action of opiates and  $\alpha_2$ -adrenoceptor agonists on central sympathetic outflow. (Key words): Anesthetics intravenous: fentanyl. Pharmacology: clonidine. Premedication: clonidine. Sympathetic nervous system: alpha-adrenergic agonist, clonidine.)

LARYNGOSCOPY AND ENDOTRACHEAL INTUBATION are potent stimuli that can induce increased sympathetic activity, tachycardia, and hypertension. Patients with coronary artery disease (CAD) are particularly prone to have

these hyperdynamic cardiovascular responses develop.<sup>1</sup> If there is a hypertensive history, blood pressure responses are amplified.

High-dose fentanyl anesthesia is a widely employed technique for patients undergoing aortocoronary bypass surgery (ACBS).<sup>2</sup> However, the dose range of fentanyl required to achieve stable hemodynamics is quite wide ( $30 \mu\text{g} \cdot \text{kg}^{-1}$  to  $200 \mu\text{g} \cdot \text{kg}^{-1}$ ). Lower dosages may result in hemodynamic breakthrough and myocardial ischemia.<sup>3-5</sup> By contrast, very high dosages are reported to totally blunt the hyperdynamic responses<sup>6</sup> at the cost of a need for prolonged postoperative ventilatory and hemodynamic support.<sup>6,7</sup> The wide dose range of fentanyl recommended to obtain stable hemodynamics is likely due to individual variability in central sympathetic tone and to a lack of objective criteria to adequately assess depth of anesthesia.

Clonidine, an antihypertensive agent known to reduce sympathetic outflow *via*  $\alpha_2$ -adrenergic receptor stimulation,<sup>8</sup> has been shown to decrease MAC of halogenated agents<sup>9,10</sup> and prevent autonomic mass reflex secondary to bladder catheterization in tetraplegic patients.<sup>11</sup> It also has been shown to be analgesic in humans.<sup>12</sup>

The present study was designed to assess the following, in a homogeneous subset of patients prone to develop hyperdynamic cardiovascular responses (*i.e.*, hypertensive subjects): 1) fentanyl dosage necessary to achieve stable hemodynamics during induction and endotracheal intubation when depth of narcotic anesthesia is assessed by objective criteria using frequency shift (left shift) of the on-line computerized electroencephalogram (EEG); 2) the effect of clonidine pretreatment on fentanyl requirement to achieve hemodynamic stability at similar anesthetic depth.

## Methods

This study was approved by the Ethics Committee of the University of Manitoba and the Winnipeg Health Sciences Centre and the Institutional Review Board of the Texas Tech University Health Sciences Center. Subject material consisted of 24 hypertensive patients scheduled for elective ACBS. The hypertension of at least 5 years duration was documented in their outpatient record in

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Received from the Department of Anesthesia, University of Manitoba, Health Sciences Centre, Winnipeg, Manitoba, the Department of Anesthesiology, Texas Tech University, Health Sciences Center, School of Medicine, Lubbock, Texas, and the Department of Anesthesia, Hôpital Cardiologique, Lyon, France. Accepted for publication August 21, 1985.

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TABLE 1. Patients' Characteristics (mean  $\pm$  SD, with range in parentheses)

	Group 1	Group 2
Age (yr)	58 $\pm$ 4.7 (53-68)	60 $\pm$ 8.8 (44-70)
Sex		
Male	6	7
Female	6	5
Weight (kg)	77 $\pm$ 10.7 (66-91)	70 $\pm$ 5.3 (64-80)
CABG	2.7 $\pm$ 1 (2-4)	2.5 $\pm$ 1.2 (2-4)
NYHA functional class	III-IV	III-IV
EF	0.62 $\pm$ 0.1 (0.55-0.77)	0.58 $\pm$ 0.08 (0.5-0.7)
Antianginal therapy		
Nifedipine (mg $\cdot$ day <sup>-1</sup> )	70 $\pm$ 35 (30-120)	65 $\pm$ 40 (20-120)
Isorbide dinitrate (mg $\cdot$ day <sup>-1</sup> )	60 $\pm$ 30 (30-120)	65 $\pm$ 35 (30-120)
Nitropaste (cm $\cdot$ day <sup>-1</sup> )	4 $\pm$ 2 (2-6)	3.5 $\pm$ 1 (2-6)
Propranolol* (mg $\cdot$ day <sup>-1</sup> )	140 $\pm$ 80 (120-240)	140 $\pm$ 60 (100-220)

\* Six patients in Group 1; four patients in Group 2.

at least two subsequent visits, when the average of multiple diastolic blood pressure (BP) measurements was 90 mmHg or higher and/or the systolic pressure was greater than 160 mmHg. Thiazide diuretics were the initial drug therapy. All patients (13 men and 11 women) had severe CAD and well-preserved left ventricular function (ejection fraction  $\geq$  0.5) and were NYHA functional class III-IV. All drugs were continued up to the time of surgery; diuretics were discontinued the previous day. The patients randomly were assigned to one of two groups, according to preanesthetic regimen. Twelve subjects (Group 1) received a standard premedication with morphine 0.15 mg  $\cdot$  kg<sup>-1</sup> im and oral lorazepam 0.03 mg  $\cdot$  kg<sup>-1</sup> 90 min before surgery. Twelve other subjects (Group 2) received the above premedications plus clonidine 5  $\mu$ g  $\cdot$  kg<sup>-1</sup> po. The peak antihypertensive effect of clonidine occurs 90 min after oral administration.<sup>13</sup> All antianginal regimens included isorbide dinitrate po, nitropaste and nifedipine po. Propranolol was used in 10 patients, six of whom were assigned to Group 1 and four to Group 2. Patient characteristics and drug therapy are reported in table 1. There were no significant differences between the two groups with respect to sex distribution, weight, age, ejection fraction, antianginal medication, and number of bypass grafts (CABG), as assessed by chi-square for discreet variables and by two sample *t* tests for continuous variables.

All patients received nasal oxygen during the insertion of intravenous, intraarterial, and thermoluted pulmonary artery catheters under local anesthesia. Electrocardiographic leads V<sub>5</sub> and II were monitored throughout the study and the operative period.

On-line computerized aperiodic analysis of the EEG by Lifescan EEG Monitor<sup>®</sup> (Neurometrics, San Diego, California) was used to assess depth of anesthesia. Characteristically, with high-dose fentanyl, there is a shift of the processed EEG signal toward lower frequencies of the

spectrum (0.5-3 Hz: delta range) and an increase in its amplitude (voltage).<sup>14,15</sup>

Before induction of anesthesia, patients were given pancuronium, 0.8 mg, and metocurine, 3.2 mg, to retard truncal rigidity induced by high-dose narcotics. Fentanyl was administered in 250- $\mu$ g increments to obtain a progressive shift toward  $\delta$  frequencies and increase amplitude of the EEG signal every 30 s up to the loss of verbal response, then every 20-30 s. The end point for drug administration was the assessment by an independent observer of a stable shift of the processed EEG to the delta range frequencies ( $\leq$ 3.5 Hz) and no further increase in signal amplitude. Full muscle relaxation was produced by the administration of an ED<sub>95</sub>  $\times$  2 (1:4 mixture) of pancuronium-metocurine 0.05 mg  $\cdot$  kg<sup>-1</sup> and 0.2 mg  $\cdot$  kg<sup>-1</sup> to all subjects upon loss of verbal response. The EEG frequency at this point showed predominance of  $\theta$  and  $\delta$  activity and a marked reduction of  $\beta$  activity. Patients were ventilated with 100% oxygen at an appropriate minute ventilation to produce eucapnia.

Measurements of the hemodynamics and processed EEG recordings were performed at the following times: 1) at control condition 15 min after insertion of all invasive monitoring lines; 2) after completion of induction (*i.e.*, stable frequency shift of the EEG into the delta range), which occurred over a period of 8-12 min in Group 1 and 4-8 min in Group 2; and 3) three minutes after endotracheal intubation. Pressure measurements and ECG signals were continuously displayed on a HP 8-channel recorder monitor (Model 7758B Hewlett Packard<sup>®</sup>). Cardiac output determinations were done in triplicate and averaged.

All measured hemodynamic variables were entered in a programmable pocket computer (TRS-80<sup>®</sup>) interfaced with a printer; derived indices were calculated according to standard formulae.

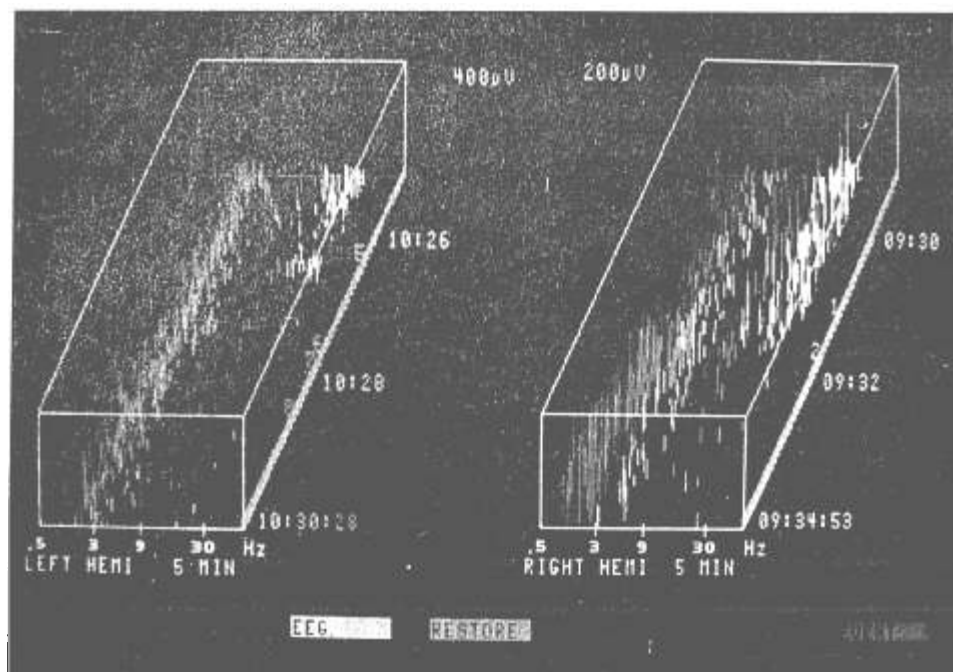


FIG. 1. Recordings of real-time aperiodic frequency analysis of the EEG from a representative patient of Groups 1 (right panel) and 2 (left panel). The tridimensional display reports frequency (Hz) on the x-axis, amplitude (V) on the y-axis, and time on the z-axis. At intubation similar anesthetic depth is indicated by the gradual and progressive shift of the EEG signal toward lower frequencies (0.5–3 Hz), despite significantly different doses of fentanyl  $100 \mu\text{g} \cdot \text{kg}^{-1}$  (right panel) and  $45 \mu\text{g} \cdot \text{kg}^{-1}$  (left panel), respectively (see text).

### STATISTICAL ANALYSIS

Analysis of variance repeated measurement studies were performed, and the Bonferroni inequality correction for *t* test was applied to hemodynamic data for simultaneous multiple comparison.<sup>16</sup> The differences between control values and values between each of the three conditions of the two groups were considered significant when *P* was less than 0.05. The two sample *t* test was applied to the fentanyl requirements for intubation between the two groups, and *P* < 0.05 was considered significant.

### Results

Loss of verbal response occurred after administration of  $1,000 \pm 250 \mu\text{g}$  of fentanyl in Group 1 and  $500 \pm 250 \mu\text{g}$  in Group 2. Induction was completed within 8–12 min ( $9.5 \pm 1$ ) in Group 1 and within 4–8 min ( $5.5 \pm 1.0$ ) in Group 2 (*P* < 0.05). Before intubation, the processed EEG signal indicated similar anesthetic depth (fig. 1) in the two groups. The total dose of fentanyl required to produce the same degree of spectral shift into the low-frequency EEG range (delta) was significantly different when comparing Group 1 with 2, i.e.,  $110 \pm 23$  versus  $61 \pm 19 \mu\text{g} \cdot \text{kg}^{-1}$  (*P* < 0.001). Hemodynamic data are shown in figure 2 and table 2. Blood pressure changes in both groups were similar, with the lowest mean value occurring in Group 1 after induction (72 mmHg) and in Group 2 after intubation (72 mmHg). Heart rate changes below  $55 \pm 5$  beats  $\cdot \text{min}^{-1}$  in both groups required no treatment. One patient in Group 1, whose antianginal therapy did not include propranolol, experienced an increase in heart rate to 115 beats  $\cdot \text{min}^{-1}$  after intubation. In general, pro-

pranolol-treated patients did not differ from the other patients assigned to the same experimental group. In addition, the Group 2 subjects showed less hemodynamic variability of stroke volume index (SVI) throughout the study and of heart rate (HR) after intubation; SVI coefficient of variation was 19% in Group 1 versus 9% in Group 2, while HR coefficient of variation at postintubation was 32% and 14%, respectively.

Throughout the study, there was no evidence of ischemia in either group, as assessed by changes in S-T and T waves, the appearance of v waves in the pulmonary capillary wedge pressure (PCWP) tracing or episodic elevation of PCWP. The only hemodynamic changes that achieved statistical significance were as follows: in Group 1 there was an increase in PCWP from  $9.2 \pm 1.2$  to  $12 \pm 2.4$  mmHg when comparing postintubation to control measurements (*P* < 0.05); Group 1 patients had a significantly greater SVI than those in Group 2 when the two groups were compared in the preinduction period ( $44.5 \pm 9.2$  vs.  $35 \pm 3.3$  ml  $\cdot \text{beat}^{-1} \cdot \text{m}^{-2}$ , *P* < 0.05). However, the SVI decreased in Group 1 to reach the same value observed in Group 2 after intubation. This 22% decrease is significant when control and postintubation SVI values are compared within Group 1 (*P* < 0.05). The addition of clonidine to the premedication regimen consistently caused marked sedation and dryness of mouth in our patients.

### Discussion

The employment of on-line EEG monitoring as a useful technique in assessing the depth of narcotic anesthesia

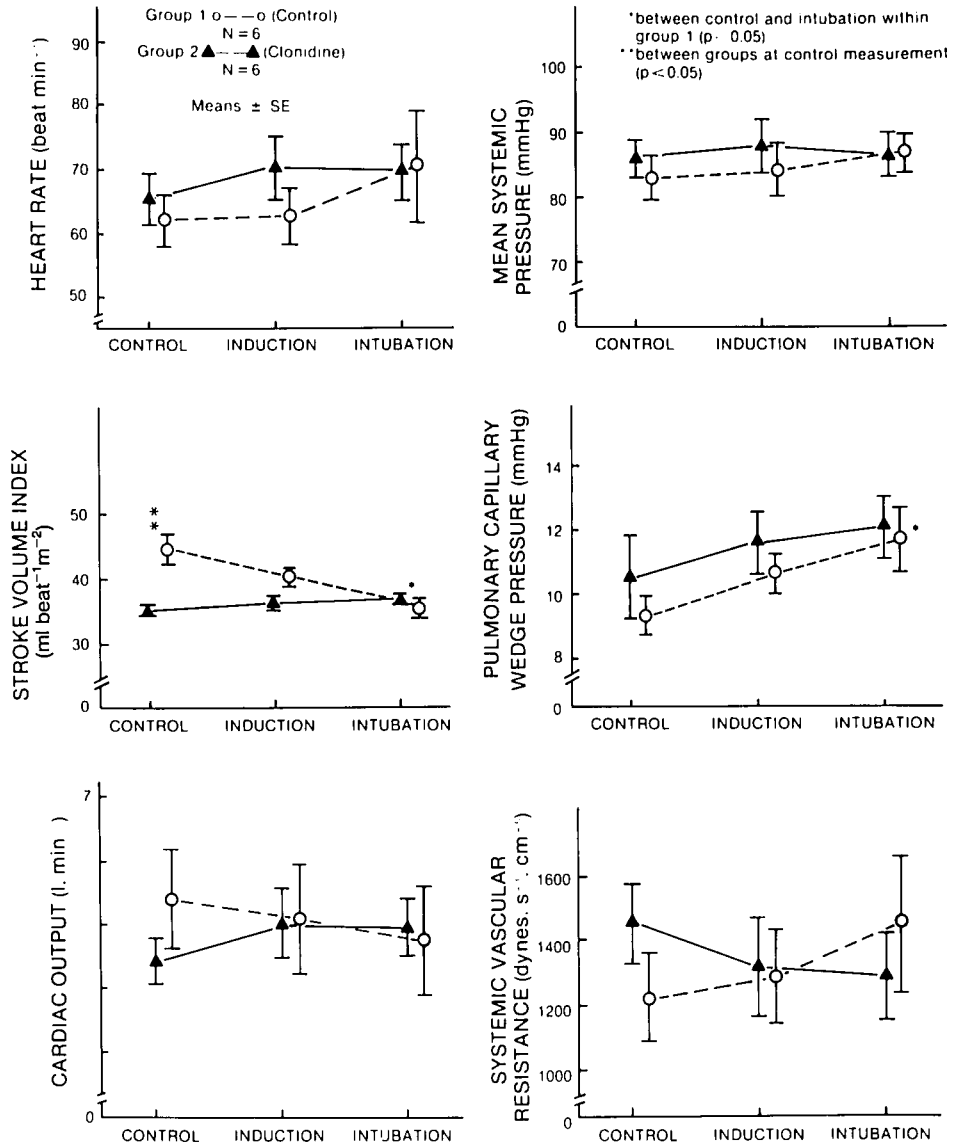


FIG. 2. Hemodynamic data ( $\pm$ SE). Measurements were taken as follows: 15 min after invasive monitoring (Control), when stable frequency shift of the EEG appeared (Induction), 3 min after laryngoscopy and endotracheal intubation (Intubation).

has been reported previously.<sup>14,15</sup> In our study, adequate control of the sympathetically mediated hyperdynamic cardiovascular responses during laryngoscopy and intubation correlated well with depth of narcotic anesthesia as assessed by the shift of the processed EEG signal toward the delta range (0.5–3 Hz). This would provide an objective criterion to titrate anesthetic requirements in a given patient, rather than through empirical administration of a fixed dose based on body weight. The fact that a similar anesthetic depth and hemodynamic stability were observed in the clonidine-premedicated group, despite a 45% reduction in fentanyl dosage, is of considerable significance.

Tachycardia and hypertension resulting from laryngoscopy and endotracheal intubation may lead to myocardial ischemia and prolonged regional myocardial dysfunction in patients with reduced coronary vascular re-

serve due to severe CAD.<sup>5,17</sup> Particularly prone to have this hyperdynamic cardiovascular reaction develop are patients with history of hypertension, CAD, and well-preserved LV function.<sup>1,6</sup>

High-dose fentanyl has been reported to effectively blunt the hemodynamic response to laryngoscopy and intubation without cardiovascular depression,<sup>2</sup> but breakthrough does occur.<sup>3–5</sup> Recent work suggests that very high doses of fentanyl (150–200  $\mu\text{g} \cdot \text{kg}^{-1}$ ) may be necessary to achieve cardiovascular stability in patients with CAD and well-preserved left ventricle (LV) function, but this may be complicated by a rapid decrease in cardiovascular function with the attending need of vasopressor support.<sup>7</sup>

The lack of objective criteria to establish depth of anesthesia and the variability of the sympathetic drive in individual patients are likely to account for the wide vari-

TABLE 2. Hemodynamic Data (mean  $\pm$  SD)

	Control		Induction		Intubation	
	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2
HR (beat $\cdot$ min <sup>-1</sup> )	62 $\pm$ 10	65 $\pm$ 10	62 $\pm$ 11	70 $\pm$ 12	70 $\pm$ 22	69 $\pm$ 10
BP (mmHg)	83 $\pm$ 8	85 $\pm$ 6	84 $\pm$ 13	88 $\pm$ 10	88 $\pm$ 8	86 $\pm$ 10
CO (l $\cdot$ min <sup>-1</sup> )	5.4 $\pm$ 2	4.5 $\pm$ 0.9	5.1 $\pm$ 2.1	5 $\pm$ 1.3	4.8 $\pm$ 1.8	4.9 $\pm$ 1.1
PCWP (mmHg)	9.2 $\pm$ 1.25	10.5 $\pm$ 3.3	10.6 $\pm$ 1.5	11.6 $\pm$ 2.4	12 $\pm$ 2.4*	12.1 $\pm$ 2.7
SVI (ml $\cdot$ beat <sup>-1</sup> $\cdot$ m <sup>-2</sup> )	44.5 $\pm$ 9.2†	35.0 $\pm$ 3.3	40.1 $\pm$ 6.2	36.6 $\pm$ 3.5	35.0 $\pm$ 6.1*	36.4 $\pm$ 3.4
SVR (dyn $\cdot$ s $\cdot$ cm <sup>-5</sup> )	1227 $\pm$ 330	1452 $\pm$ 315	1293 $\pm$ 371	1318 $\pm$ 387	1455 $\pm$ 524	1295 $\pm$ 330
PA (mmHg)	16.0 $\pm$ 2.0	16.8 $\pm$ 3.6	16.2 $\pm$ 2.6	17.3 $\pm$ 2.6	17.8 $\pm$ 3.6	17.1 $\pm$ 2.5
CVP (mmHg)	7.7 $\pm$ 1.5	8.5 $\pm$ 3.1	8.3 $\pm$ 1.9	9.2 $\pm$ 1.6	9.3 $\pm$ 1.6	9.7 $\pm$ 1.6
PVR (dyn $\cdot$ s $\cdot$ cm <sup>-5</sup> )	112 $\pm$ 54	120 $\pm$ 50	99 $\pm$ 57	96 $\pm$ 37	106 $\pm$ 30	93 $\pm$ 46

\*  $P < 0.05$  between control and intubation within Group 1.†  $P < 0.05$  at control measurements between Groups 1 and 2.

ations in dosages recommended in the literature. Because of the limits of pure narcotic anesthesia,<sup>†</sup> supplementation with agents devoid of detrimental effects on the cardiovascular system may be necessary. The hemodynamic stability of the Group 1 subject who required a mean dose of fentanyl of 110  $\mu\text{g} \cdot \text{kg}^{-1}$  is in agreement with previous clinical findings.<sup>6</sup> Moreover, this study shows that similar hemodynamics and anesthetic depth as assessed by real time EEG processing can be obtained with a mean dose of fentanyl of 61  $\mu\text{g} \cdot \text{kg}^{-1}$ , *i.e.*, a 45% reduction in patients premedicated with clonidine. At this dose, hemodynamic breakthroughs have been reported in a similar patient population who did not receive clonidine.<sup>3-5</sup>

Lack of significant changes in heart rate and mean blood pressure in both groups during induction of anesthesia and endotracheal intubation suggests that the myocardial supply/demand ratio was well preserved. The greater awake control SVI in the Group 1 subjects compared with the Group 2 subjects likely reflects greater sympathetic drive to the heart. This is supported by the significant decrease in SVI and increase in PCWP in Group 1 subjects when control and postintubation measurements were compared and by the larger variability of the hemodynamic variables (*i.e.*, SVI, HR) during the study period in Group 1 when compared with Group 2 subjects.

Volume loading resulting in an increase in left ventricular filling pressure was unlikely in this study, since both groups received approximately 700 ml of crystalloid

iv during anesthetic induction. The increase in PCWP associated with a reduction of SVI therefore indicates a mild depression of myocardial performance possibly due to the reduction in central sympathetic drive and/or circulating catecholamines produced by fentanyl anesthesia.<sup>18</sup> Such changes were not observed in the clonidine-premedicated group where stabilization of sympathetic drive was likely to have occurred before the induction of anesthesia. The greater the sympathetic activity, the greater the possibility for cardiovascular depression and precipitous decrease in the blood pressure upon anesthetic induction. This response has been observed, although infrequently with fentanyl.<sup>19</sup>

The hemodynamic stability observed with clonidine and fentanyl contrasts with reports of myocardial depression or significant hypotension when fentanyl anesthesia is supplemented with nitrous oxide or diazepam<sup>2,20</sup> and appears superior to low-dose droperidol,<sup>21</sup> since no volume expansion is required. Furthermore, the hemodynamic results with the acute administration of clonidine in this study are comparable to that obtained in a similar group of patients under narcotic anesthesia after chronic treatment with propranolol.<sup>22</sup> Thus, clonidine may well represent an alternative to propranolol when there is no time to institute chronic treatment or when there is a contraindication to the use of propranolol.

The safety of the clonidine dose (5  $\mu\text{g} \cdot \text{kg}^{-1}$  po) administered in the present study in terms of stable BP, HR, and cardiac pump performance is in agreement with clinical results observed in patients with chronic angina pectoris and with acute myocardial infarction.<sup>23,24</sup> It is further supported by experimental work showing no drug depression of the indices of contractility in a papillary

† DeCastro J, Parmentier P, Andrieu S: Les limites de l'anesthésie analgésique pure. *Ann Anesthesiol Franc* 17:1071-1086, 1976.

muscle preparation.<sup>25</sup> These data suggest that clonidine, by stabilizing and reducing sympathetic nervous system tone, has beneficial effects in ischemic heart disease by its ability to produce a slower HR, while minimally altering coronary perfusion pressure or systolic performance.

The interaction between an opiate and an  $\alpha_2$ -adrenoceptor agonist shown in this study is supported by several experimental and clinical findings. Clonidine has been shown to have potent analgesic properties<sup>12,26</sup> to reduce MAC halothane in experimental animals<sup>9,10</sup> and to suppress central noradrenergic hyperactivity induced by immobilization stress.<sup>27</sup> Furthermore, it has been shown to normalize the sympathetic hyperactivity observed in patients during opiate withdrawal syndrome.<sup>28</sup> The interaction of  $\alpha_2$ -adrenoceptor agonists and opiates is explained on the basis of their interplay at central noradrenergic neurons, resulting in reduced excitability<sup>29,30</sup> and reduced noradrenaline release at their central or peripheral terminals.<sup>31,32</sup> A close relationship exists between somatosensory function and autonomic regulation. The anatomic bases of this integrated response have been shown recently by the close overlap of the location of  $\alpha_2$  adrenoceptors and opiate binding sites in the brain stem and spinal cord in animals and humans.<sup>33</sup> The potentiation of fentanyl analgesia and anesthesia by clonidine can be explained by a preferential effect of these drugs on the coeruleo-spinal noradrenergic pathway<sup>34,35</sup> thought to be involved in the regulation of vigilance,<sup>36</sup> as well as in processing of nociceptive stimuli, both centrally<sup>26,35</sup> and at the spinal cord level.<sup>37,38</sup>

The excellent control of the hemodynamics observed in this study, despite lower fentanyl dose, may be explained by an overall inhibitory action of clonidine and opiates on catecholaminergic areas of the lower brain stem and their projections involved in the central control of the cardiovascular system.<sup>39,40</sup> Regimens so far proposed to blunt this hyperdynamic cardiovascular response during laryngoscopy and intubation can be classified as specific—designed to prevent target organ response, *i.e.*, beta blockers<sup>41</sup> or vasodilators such as nitroprusside<sup>42</sup>—or nonspecific—designed to increase anesthetic depth, (*i.e.*, diazepam, narcotics, lidocaine<sup>2,20,43</sup>).

By contrast, we propose the use of a pharmacologic tool, such as the  $\alpha_2$ -adrenoceptor agonist clonidine, endowed with central and peripheral inhibitory effects on sympathetic activity, to produce adequate depth of anesthesia and stable hemodynamics, while reducing anesthetic requirements.

Concern might be expressed regarding the risk of clonidine withdrawal and associated hyperdynamic cardiovascular states. This is unlikely to occur, since no evidence for an overshoot of sympathetic activity was observed in human subjects after a single dose of clonidine.<sup>44</sup> However, when given on a regular basis for control of

arterial hypertension, clonidine should be continued to avoid withdrawal and improve cardiovascular stability.<sup>45</sup> It is also unlikely that the effect of clonidine would be additive to opiate induced ventilatory depression, since high-dose clonidine has been found to have no respiratory depressant effects.<sup>46</sup> Further study is warranted to corroborate the clinical impression that clonidine does not delay extubation in patients recovering from fentanyl anesthesia.

We conclude that, by using  $\alpha_2$ -adrenoceptor agonist to manipulate central monoaminergic pathways that are involved in the sympathetic response to noxious stimuli, one can effectively and specifically decrease anesthetic narcotic requirements and provide stable hemodynamic conditions during induction and intubation. This approach may be particularly useful in patients with ischemic heart disease and hypertension presenting for surgical procedures of short duration.

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