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## Fentanyl, Esmolol, and Clonidine Blunt the Transient Cardiovascular Stimulation Induced by Desflurane in Humans

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**Background:** A rapid increase in the end-tidal concentration of desflurane to greater than 1 MAC transiently increases heart rate, arterial blood pressure, and circulating epinephrine and vasopressin concentrations. We hypothesized that drugs that block sympathetic activity or decrease sympathetic outflow (an opioid, a  $\beta$ -adrenergic antagonist, and an  $\alpha_2$ -adrenergic agonist) would blunt these responses.

**Methods:** After induction of anesthesia with intravenous propofol 2 mg/kg in ten healthy male volunteers age  $25 \pm 1$  yr (mean  $\pm$  standard error), anesthesia was maintained with 4% end-tidal desflurane in oxygen (0.55 MAC) via an endotracheal tube for 32 min. Controlled ventilation provided normocapnia. We then increased the end-tidal desflurane concentration within 1 min to 8% (1.1 MAC) and maintained this concentration for 10 min. On separate days, five of these volunteers were similarly anesthetized except that 5 min before the increase to 8% desflurane, we administered intravenous fentanyl 1.5  $\mu$ g/kg and on another day 4.5  $\mu$ g/kg (dose randomly assigned). On 2 separate days, intravenous esmolol 0.75 mg/kg was given to five volunteers 1.5 min before, or clonidine 4.3  $\mu$ g/kg by mouth to four volunteers 90 min before, the increase from 4% to 8% desflurane.

**Results:** Without pretreatment, the increase to 8% desflurane increased heart rate (from  $57 \pm 2$  to  $118 \pm 6$  beats/min at peak, mean  $\pm$  standard error) and mean arterial blood pressure (from  $66 \pm 2$  to  $118 \pm 5$  mmHg). At the time of peak hemodynamic changes (within 1–2 min of the increase in desflurane concentration), plasma epinephrine and norepinephrine concentrations increased (from  $22 \pm 6$  to  $339 \pm 83$  pg/ml and from  $205 \pm 19$  to  $283 \pm 30$  pg/ml,

respectively). Fentanyl 1.5 and 4.5  $\mu$ g/kg attenuated the heart rate increase by  $61 \pm 14\%$  and  $70 \pm 7\%$  and the mean arterial blood pressure increase by  $31 \pm 16\%$  and  $46 \pm 11\%$  but did not alter the epinephrine or norepinephrine response at the time of peak cardiovascular changes. Esmolol attenuated the heart rate response but no other response. Clonidine attenuated all responses except that of norepinephrine and also caused postanesthesia sedation.

**Conclusions:** Fentanyl, esmolol, and clonidine blunt the transient cardiovascular response to a rapid increase in desflurane concentration. Fentanyl may be the most clinically useful of these drugs because it blunts the increase in heart rate and blood pressure, has minimal cardiovascular depressant effects, and imposes little postanesthetic sedation. (Key words: Anesthetics, volatile: desflurane. Blood pressure. Heart: heart rate. Opioid: fentanyl. Sympathetic nervous system, catecholamines: epinephrine; norepinephrine. Sympathetic nervous system, sympatholytic agents: clonidine; esmolol.)

RAPID increases in the concentrations of desflurane and isoflurane, to greater than 1 minimum alveolar concentration (MAC) can transiently increase sympathetic activity,<sup>1–5</sup> vasopressin secretion,<sup>2,3</sup> and heart rate and arterial blood pressure.<sup>1–7</sup> These responses might increase the risk of myocardial ischemia in patients with coronary artery disease. Helman *et al.*<sup>8</sup> found a greater incidence of myocardial ischemia in patients undergoing coronary artery bypass surgery but not given any opioid, when the desflurane concentration was increased rapidly, than in patients given only sufentanil. Ability to blunt or block this response might be beneficial for those patients with coronary artery disease. The transient nature of the cardiovascular response<sup>2,4</sup> and the decreased response with repeated increases in desflurane concentration<sup>4</sup> suggest a site of stimulation immediately accessible to the anesthetic and one that rapidly adapts to the stimulation, such as the rapidly adapting receptors in the airway. In the current report, we test the hypothesis that drugs that decrease sympathetic activity or action would blunt this response, and perhaps provide a useful therapeutic modality. These include an opioid, a  $\beta$ -adrenergic antagonist, and an  $\alpha_2$ -adrenergic agonist.

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## BLUNTING OF DESFLURANE-INDUCED STIMULATION

**Materials and Methods**

We studied ten healthy male volunteers (age  $25 \pm 1$  yr; weight  $73 \pm 4$  kg; height  $177 \pm 2$  cm; mean  $\pm$  standard error) after obtaining informed consent and with approval of the protocol by the University of California, San Francisco Committee on Human Research. No volunteer had general anesthesia within 6 months of this study, medications within 7 days, alcohol for at least 2 days, or food or drink within 9 h of each study. After skin infiltration with less than 1 ml 1% lidocaine, a peripheral venous cannula was inserted. An arterial cannula was inserted at this time (after skin infiltration with less than 1 ml 1% lidocaine) or after induction of anesthesia. Mean systemic arterial blood pressure measured by transducer (calibrated with a mercury manometer before and after each study; 23XL, Gould Statham, Oxnard, CA) and heart rate were recorded continuously by a digital polygraph (ES 2000, Gould, Cleveland, OH).

One minute after induction of anesthesia with intravenous propofol 2 mg/kg, desflurane in oxygen was administered to produce and sustain an end-tidal concentration of 0.55 MAC (4.0%). Anesthetic concentration was measured continuously at the proximal orifice of the endotracheal tube by an infrared spectrometer (Datex Ultima, Helsinki, Finland). The end-tidal sample was protected from contamination with expired gas by insertion of a 20-ml dead space. We calibrated the spectrometer before and after each study by secondary (tank) standards, which in turn were calibrated against primary (volumetric) standards using gas chromatography. We intubated the trachea after administration of intravenous vecuronium 0.1 mg/kg. Mechanical ventilation of the volunteers' lungs maintained normocapnia, and surface warming with heated air maintained normothermia throughout the study. Study days in any volunteer were separated by at least 1 week.

Desflurane anesthesia was maintained at 0.55 MAC for 32 min, at which time arterial blood was sampled for measurement of pH, oxygen tension, carbon dioxide tension (by standard electrodes), and plasma catecholamines (collected in heparin, immediately placed in wet ice, separated and frozen at  $-70^{\circ}\text{C}$  until measured by high performance liquid chromatography). Mean arterial blood pressure and heart rate were recorded. We then increased the end-tidal desflurane concentration within 1 min to 1.1 MAC (8%) and maintained this concentration for 10 min. Because subsequent similar step increases to 8% desflurane

evoke much smaller cardiovascular and sympathetic responses than the initial increase,<sup>4</sup> only one step change was imposed during each anesthetic. Five volunteers were anesthetized again, and given, in random order (on separate days), intravenous fentanyl 1.5 and 4.5  $\mu\text{g}/\text{kg}$  5 min before the increase to 8% desflurane. Five volunteers were given intravenous esmolol 0.75 mg/kg 1.5 min before the increase to 8% desflurane, and five volunteers were given clonidine 4.3  $\mu\text{g}/\text{kg}$  by mouth 90 min before the increase to 8%. We originally intended to study the effects of larger doses of the latter two drugs but did not because the smaller doses produced significant cardiovascular depression in some volunteers. We selected doses of these drugs that are within the common range of clinical use.

Arterial blood was sampled and cardiovascular measurements repeated 1, 2, 4, and 8 min after reaching an end-tidal concentration of 8% desflurane, after which the effects of vecuronium were antagonized and the volunteer was allowed to awaken.

*Catecholamine Analyses*

Plasma for analysis of epinephrine, norepinephrine, and vasopressin concentrations was stored at  $-70^{\circ}\text{C}$  until thawed for analysis. Plasma catecholamine concentrations were determined by high-performance liquid chromatography,<sup>5</sup> with limits of detection of 14 pg/ml for epinephrine and 25 pg/ml for norepinephrine. Within-run coefficients of variation were 2% for epinephrine and 1% for norepinephrine; between-run coefficients of variation were 7% for epinephrine and 3% for norepinephrine. Sample values less than the limit of detection were considered to have a concentration just less than the limit of detection.

*Statistical Analyses*

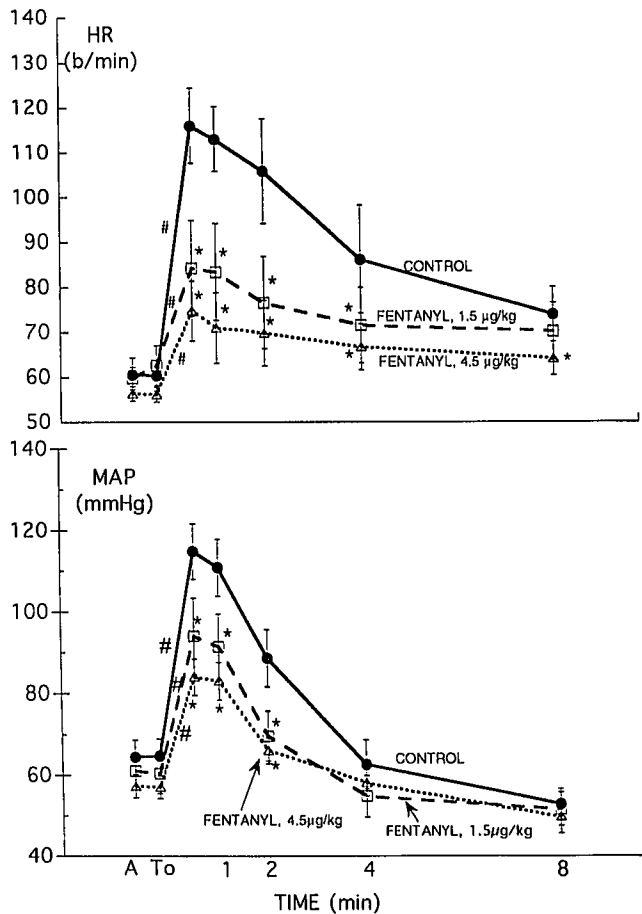
Data before and during 8% desflurane administration were compared for clonidine and esmolol against the data obtained without drugs in the same volunteers by paired *t* test with Bonferroni correction; and for the two doses of fentanyl against each other and against the data obtained without fentanyl in the same volunteers by analysis of variance with repeated measures and Student-Newman-Keul's test for multiple comparisons. Statistical significance was accepted at  $P < 0.05$ .

**Results**

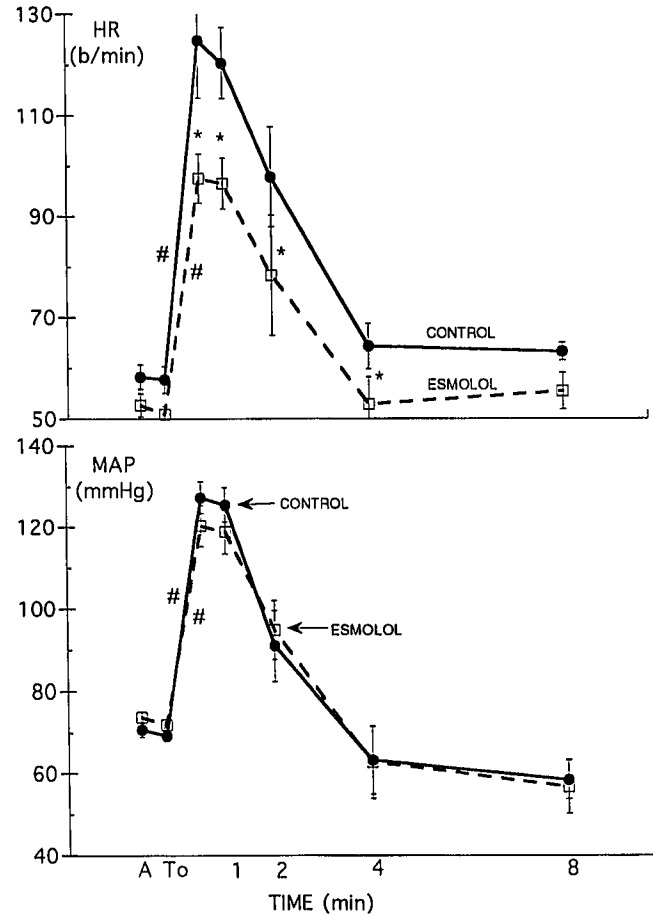
The increase to 8% desflurane transiently but consistently increased heart rate, mean arterial blood pressure

(figs. 1-3). Mean arterial blood pressure increased from  $66 \pm 2$  mmHg to  $118 \pm 5$  mmHg ( $P < 0.001$ ; mean  $\pm$  SE for all volunteers), and heart rate from  $57 \pm 2$  beats/min to  $118 \pm 6$  beats/min ( $P < 0.001$ ). Plasma epinephrine concentration increased from  $22 \pm 6$  to  $339 \pm 83$  pg/ml ( $P < 0.01$ ) and plasma norepinephrine concentration increased from  $205 \pm 19$  to  $283 \pm 30$  pg/ml ( $P < 0.05$ ) at the time of peak cardiovascular changes.

Intravenous fentanyl 1.5 or 4.5  $\mu$ g/kg decreased the heart rate response by  $61 \pm 14\%$  ( $P < 0.02$ ) and  $70 \pm 7\%$  ( $P < 0.01$ ), and the mean arterial blood pressure



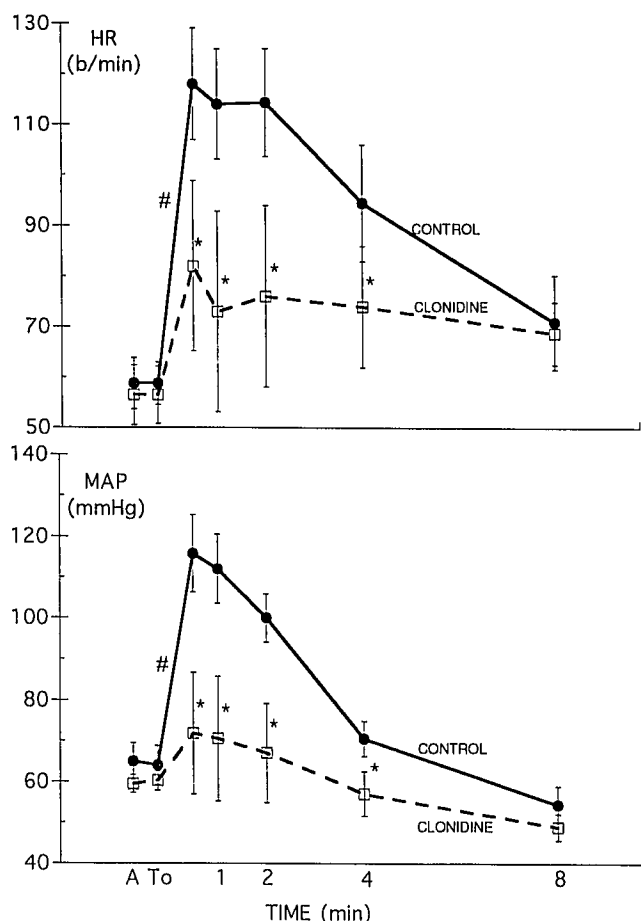
**Fig. 1.** Fentanyl 1.5 and 4.5  $\mu$ g/kg attenuated the increase in heart rate (HR) and mean arterial blood pressure (MAP) that followed a rapid increase of end-tidal desflurane concentration from 4% to 8%. A = value at 32 min of 0.55 MAC; time 0 = time of first breath of increased anesthetic concentration. # $P < 0.05$  between the peak value and the value at 32 min of 4% desflurane; \* $P < 0.05$  for the indicated value versus the value when desflurane concentration was increased similarly without administration of fentanyl.



**Fig. 2.** Esmolol 0.75 mg/kg attenuated the increase in heart rate (HR) but not the increase in mean arterial blood pressure (MAP) associated with a rapid increase in end-tidal desflurane concentration from 4% to 8%. A = value at 32 min of 0.55 MAC; time 0 = time of first breath of increased anesthetic concentration. # $P < 0.05$  between the peak value and the value at 32 min of 4% desflurane; \* $P < 0.05$  for the indicated value versus the value when desflurane concentration was increased similarly without administration of esmolol.

response by  $31 \pm 16\%$  ( $P < 0.01$ ) and  $44 \pm 11\%$  ( $P < 0.05$ ) (figs. 1 and 4). Fentanyl did not affect the increase of plasma catecholamines (fig. 4). The effect of the two doses of fentanyl on any variable did not differ. This finding for heart rate and blood pressure, in part, could have been a result of our small sample size. We have calculated that a sample two- to sevenfold larger than the sample we studied would have been required to detect a difference in the cardiovascular responses between the two doses of fentanyl we administered. Esmolol decreased the heart rate response by  $37 \pm 6\%$  ( $P < 0.02$ ), but did not statistically alter

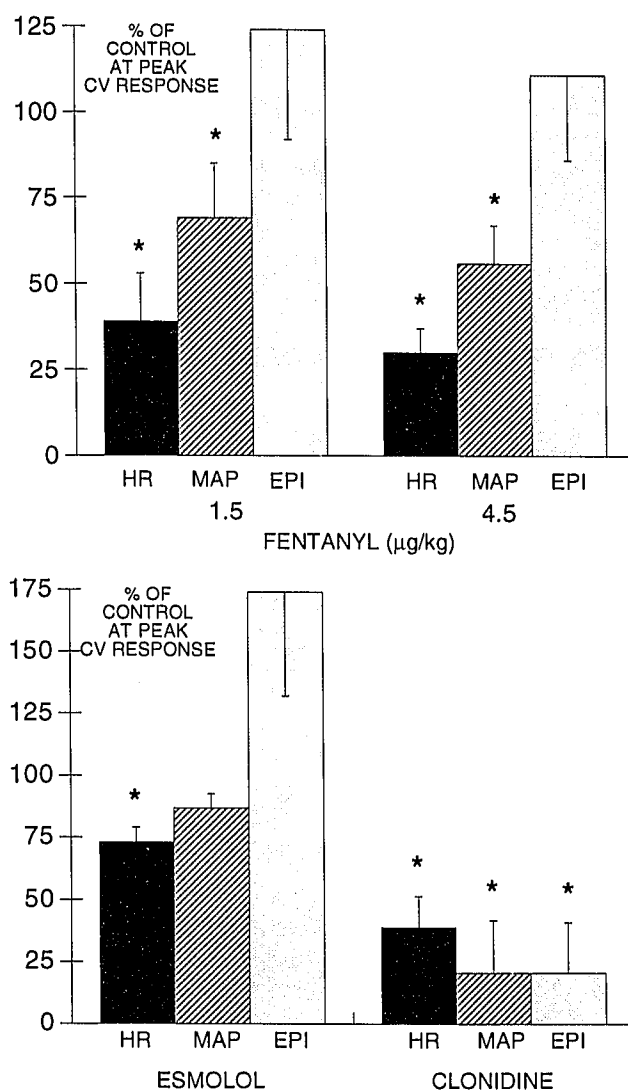
## BLUNTING OF DESFLURANE-INDUCED STIMULATION



**Fig. 3.** Clonidine 4.3  $\mu\text{g}/\text{kg}$  given by mouth attenuated the increase in heart rate (HR) and mean arterial blood pressure (MAP) associated with a rapid increase of end-tidal desflurane concentration from 4% to 8%. A = value at 32 min of 0.55 MAC; time 0 = time of first breath of increased anesthetic concentration. # $P < 0.05$  between the peak value and the value at 32 min of 4% desflurane; \* $P < 0.05$  for the indicated value versus the value when desflurane concentration was increased similarly without administration of clonidine.

the mean arterial blood pressure response ( $P = 0.1$ ) (figs. 2 and 4) or the plasma epinephrine response (fig. 4). We have calculated that a sample approximately twofold larger than the sample we studied would have been required to detect an effect of esmolol on mean arterial blood pressure. Esmolol did not affect the increase of plasma norepinephrine concentration at the time of peak increases of heart rate and mean arterial blood pressure ( $P > 0.25$ ). The increase in plasma norepinephrine was  $73\% \pm 13\%$  greater 8 min after the increase of desflurane concentration with esmolol than without esmolol ( $P < 0.05$ ). We used data from four

of the five volunteers given clonidine because one coughed during the rapid increase of desflurane concentration. Clonidine decreased the heart rate response by  $61 \pm 12\%$  ( $P < 0.02$ ), the mean arterial blood pressure response by  $80 \pm 21\%$  ( $P < 0.05$ ) (figs. 3 and 4), and the plasma epinephrine response by  $79\% \pm 21\%$  ( $P < 0.05$ ) (fig. 4), but did not alter the change of the plasma norepinephrine response. Although we did not quantitate the rapidity or quality of postanesthetic re-



**Fig. 4.** Fentanyl, esmolol, and clonidine decreased the peak heart rate (HR) and mean arterial blood pressure (MAP) responses to a rapid increase in end-tidal desflurane from 4% to 8%. \* $P < 0.05$  versus control (no drug). Only clonidine also attenuated the associated increase in plasma epinephrine concentration.

covery, it was evident that when given clonidine before the anesthetic, the volunteers had a protracted period of postanesthetic drowsiness.

## Discussion

A rapid increase of desflurane<sup>1-4</sup> (and the current study) or isoflurane<sup>2,6,7</sup> to concentrations greater than 1 MAC elicits a transient sympathetic response with attendant increases in heart rate, blood pressure, and plasma catecholamine concentrations. The magnitude and manner of response to a rapid increase from 4% to 8% end-tidal desflurane was similar to that produced by a rapid increase from 4% to 12%,<sup>2</sup> suggesting that the stimulus provided by 8% produced a maximum response. Thus the changes effected by fentanyl, esmolol and clonidine may be viewed as representative of the limits that may result in volunteers.

As hypothesized, we find that drugs that interfere with sympathetic responses attenuate the increase in mean arterial blood pressure, heart rate, and plasma epinephrine resulting from a rapid increase in desflurane that exceeds 1 MAC. Multiple mechanisms may interact to produce these effects. For example, fentanyl decreases central sympathetic outflow in cats<sup>9</sup> and dogs<sup>10,11</sup> has vagomimetic properties<sup>12,13</sup> in dogs and decreases heart rate during inhalation anesthesia.<sup>14</sup> However, in the current study, although fentanyl decreased the cardiovascular response to a rapid increase of desflurane, it did not alter the concentrations of circulating catecholamines. Perhaps under the circumstance of our study, fentanyl has a predominantly peripheral (cardiac and vascular), rather than central, effect. However, no evidence indicates that the doses of fentanyl we administered cause significant cardiovascular depression or vascular relaxation, although high doses may have these effects. However, small doses of fentanyl can have indirect vascular effects; for example, fentanyl increases vasopressin secretion.<sup>15</sup> In dogs, intrathecal fentanyl has a synergistic effect with intrathecal local anesthetics in causing modest decrease in C-fiber reflexes from the affected dermatomes but not other dermatomes.<sup>16</sup> Systemically administered fentanyl in the dog does not alter the cardiovascular or sympathetic response to splanchnic nerve stimulation,<sup>17</sup> suggesting that peripheral effects would not be blocked in the current study. Alternatively, the increase to 8% desflurane without fentanyl could have caused supra-maximal sympathetic stimulation, (as suggested by the lack of difference in response between 8% and 12%

desflurane), and fentanyl could have reduced the efferent sympathetic activity to the heart and vessels sufficiently to have noticeable cardiovascular effects, but insufficiently to alter adrenal secretion of epinephrine.

Similarly, multiple mechanisms may explain the results obtained with esmolol and clonidine. Esmolol, a potent  $\beta$ -adrenergic antagonist, has direct peripheral actions, and, as expected, decreased heart rate without altering epinephrine release. The greater increase of norepinephrine probably resulted as a response to the greater ensuing cardiovascular depression: two volunteers had mean arterial blood pressures below 45 mmHg. Clonidine, an  $\alpha_2$ -adrenergic agonist, directly suppresses the impulses arising from the brain that otherwise would lead to increases of plasma epinephrine concentration, heart rate, and mean arterial blood pressure, and likely blunted the norepinephrine response to the ensuing hypotension at 8% desflurane.

The increased depression (decrease in MAC) produced by fentanyl and clonidine may explain some of our results. Premedication with fentanyl 1.5  $\mu\text{g}/\text{kg}$  decreased desflurane MAC by an insignificant amount, whereas 4.5  $\mu\text{g}/\text{kg}$  decreased MAC by more than 20%.<sup>18</sup> The effect in the current study may exceed those of Ghouri *et al.*<sup>18</sup> because of the closer proximity of the time of injection to the time of testing in our study (*i.e.*, the cerebral concentration of fentanyl resulting from a given dose should have been higher in our study). However, other considerations may limit this explanation. Data from a previous study indicate that the MAC level has, at most, a limited effect on the response to increasing desflurane concentration. The addition of 0.5 MAC nitrous oxide (60%) to 4% desflurane did not alter the increase in heart rate or plasma catecholamine concentrations resulting from an increase in desflurane to 8%,<sup>4</sup> and provided less blunting of the increase in arterial blood pressure than did fentanyl or clonidine. Furthermore, although 4.5  $\mu\text{g}/\text{kg}$  of fentanyl decreases MAC of desflurane more than does 1.5  $\mu\text{g}/\text{kg}$ ,<sup>13</sup> the absence of a difference of effect between the two doses of fentanyl suggests that alteration of anesthetic depth was not an important issue.

Although their influence on the MAC of desflurane has not been reported,  $\alpha_2$ -adrenergic agonists increase the depth of other inhaled anesthetics.<sup>19,20</sup> However, the dose we used did not affect blood pressure (clonidine:  $60 \pm 2$  mmHg, control:  $64 \pm 5$  mmHg;  $P > 0.2$ ), or heart rate (clonidine:  $57 \pm 6$  mmHg, control:  $59 \pm 4$  mmHg;  $P > 0.2$ ), at 4.0% end-tidal desflurane, before the concentration of desflurane was increased.

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The implications of our results with esmolol and clonidine are limited by our use of only one dose of these drugs, as well as the use of healthy volunteers without cardiovascular disease. We chose not to give larger doses of esmolol because the dose given caused subsequent hypotension (mean arterial blood pressure  $\leq$  45 mmHg in two volunteers after increasing the desflurane concentration to 8%) without altering the peak pressor response. Similarly, we did not use a larger dose of clonidine because of the cardiovascular effects (three of five volunteers had mean arterial blood pressure  $\leq$  45 mmHg after increasing the desflurane concentration to 8%) and because we did not wish to increase postanesthesia sedation. We noted that volunteers given clonidine took longer to emerge from anesthesia and remained sleepy for a longer period of time, a result consistent with the well-known sedative property of  $\alpha_2$ -adrenergic agonists. Thus, although administration of 4.3  $\mu$ g/kg clonidine diminishes the effect of sympathetic stimulation caused by rapid increases in desflurane, it also diminishes an important clinical advantage of desflurane: rapid emergence from anesthesia. However, a smaller dose might have produced useful results, particularly if the current dose had a ceiling effect.

In summary, we find that several pharmacologic approaches can blunt the transient cardiovascular response to an increase in desflurane concentration to greater than 1 MAC. The absent (or at most limited) difference between the effect of the two doses of fentanyl suggests that the clinician who wishes to blunt the cardiovascular response to a rapid increase of desflurane above 1 MAC, may provide a substantial blunting with 1.5  $\mu$ g/kg fentanyl and incur lesser residual opioid effects. A larger dose may provide additional effect. Other considerations also recommend the use of fentanyl over other drugs such as esmolol or clonidine.

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