Anesthesiology
81:1350–1355, 1994

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

Richard B. Weiskopf, M.D., Edmond I. Eger II, M.D.,† Mariam Noorani, B.A.,‡ Malcolm Daniel, M.B., Ch.B.§*

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 β-adrenergic antagonist, and an α_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 ± 1 yr (mean ± 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 μg/kg and on another day 4.5 μg/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 μg/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 ± 2 to 118 ± 6 beats/min at peak, mean ± standard error) and mean arterial blood pressure (from 66 ± 2 to 118 ± 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 ± 6 to 339 ± 83 pg/ml and from 205 ± 19 to 283 ± 30 pg/ml, respectively). Fentanyl 1.5 and 4.5 μg/kg attenuated the heart rate increase by 61 ± 14% and 70 ± 7% and the mean arterial blood pressure increase by 31 ± 16% and 46 ± 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,[1–5] vasopressin secretion,[2,3] and heart rate and arterial blood pressure.[1–7] These responses might increase the risk of myocardial ischemia in patients with coronary artery disease. Helman *et al.*[8] 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[2,4] and the decreased response with repeated increases in desflurane concentration[4] 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 β-adrenergic antagonist, and an α_2-adrenergic agonist.

* Professor, Department of Anesthesia and Department of Physiology; Staff, Cardiovascular Research Institute.

† Professor and Vice Chair for Research, Department of Anesthesia.

‡ Staff Research Associate, Department of Anesthesia.

§ Visiting Assistant Professor, Department of Anesthesia.

Received from the Department of Anesthesia and the Department of Physiology and The Cardiovascular Research Institute, University of California, San Francisco, California. Accepted for publication August 8, 1994. Supported by Ohmeda, Pharmaceutical Products Division, and by the Anesthesia Research Foundation. R.B.W. and E.I.E. are paid consultants to Ohmeda, Pharmaceutical Products Division.

Address correspondence to Dr. Weiskopf: Department of Anesthesia, University of California, San Francisco, 521 Parnassus Avenue, San Francisco, California 94143-0648.

Materials and Methods

We studied ten healthy male volunteers (age 25 ± 1 yr; weight 73 ± 4 kg; height 177 ± 2 cm; mean ± 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°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,[4] 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 μg/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 μg/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°C until thawed for analysis. Plasma catecholamine concentrations were determined by high-performance liquid chromatography,[5] 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 ± 2 mmHg to 118 ± 5 mmHg ($P < 0.001$; mean ± SE for all volunteers), and heart rate from 57 ± 2 beats/min to 118 ± 6 beats/min ($P < 0.001$). Plasma epinephrine concentration increased from 22 ± 6 to 339 ± 83 pg/ml ($P < 0.01$) and plasma norepinephrine concentration increased from 205 ± 19 to 283 ± 30 pg/ml ($P < 0.05$) at the time of peak cardiovascular changes.

Intravenous fentanyl 1.5 or 4.5 μg/kg decreased the heart rate response by 61 ± 14% ($P < 0.02$) and 70 ± 7% ($P < 0.01$), and the mean arterial blood pressure response by 31 ± 16%; ($P < 0.01$) and 44 ± 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 ± 6% ($P < 0.02$), but did not statistically alter

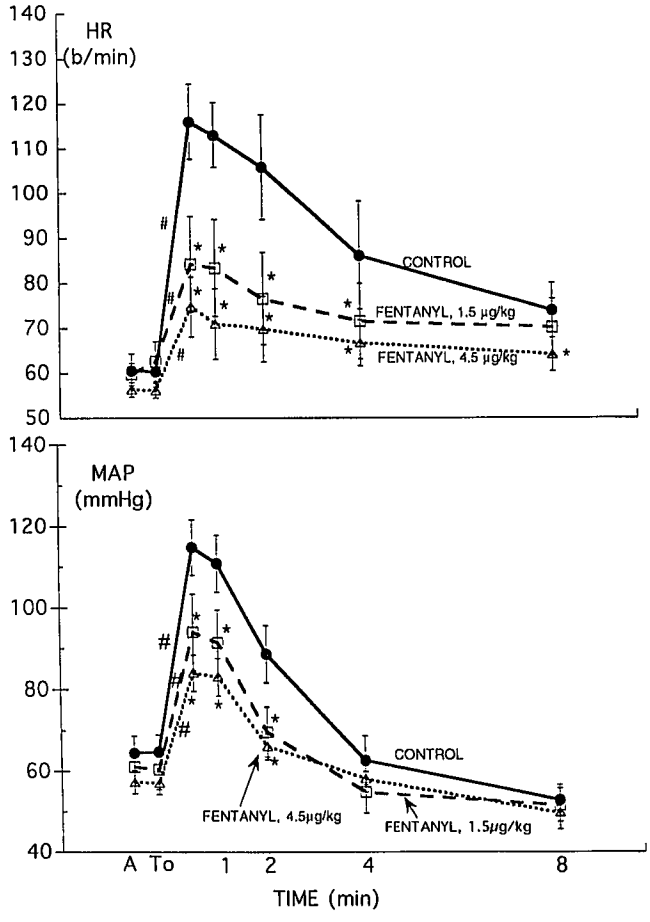

Fig. 1. Fentanyl 1.5 and 4.5 μg/kg attenuated the increase in heart rate (HR) and mean arterial blood pressure (MAP) that followed a rapid increase of end-tidal desflurane concentration from 4% to 8%. A = value at 32 min of 0.55 MAC; time 0 = time of first breath of increased anesthetic concentration. #$P <$ 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.

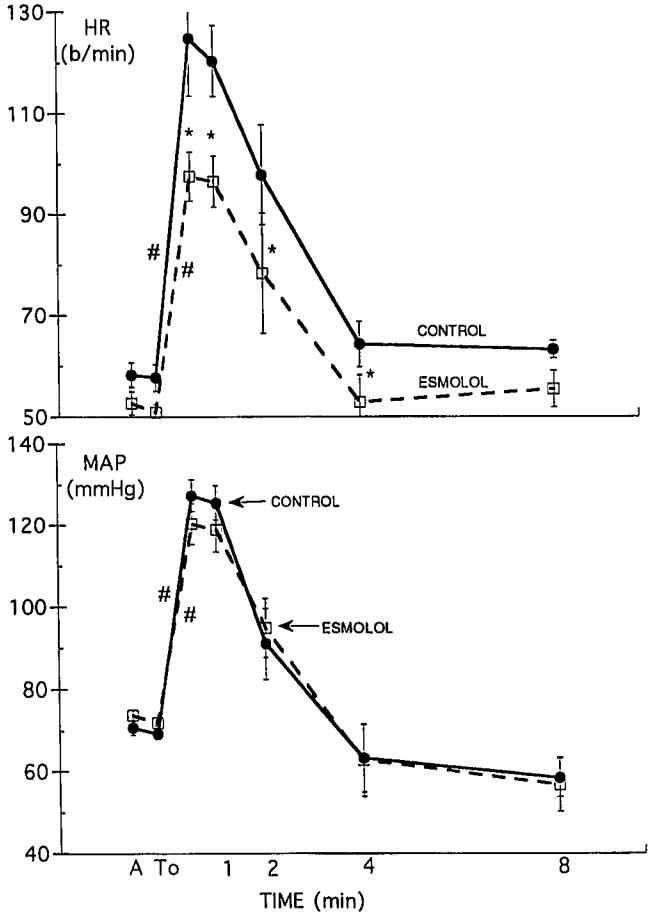

Fig. 2. Esmolol 0.75 mg/kg attenuated the increase in heart rate (HR) but not the increase in mean arterial blood pressure (MAP) associated with a rapid increase in end-tidal desflurane concentration from 4% to 8%. A = value at 32 min of 0.55 MAC; time 0 = time of first breath of increased anesthetic 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.

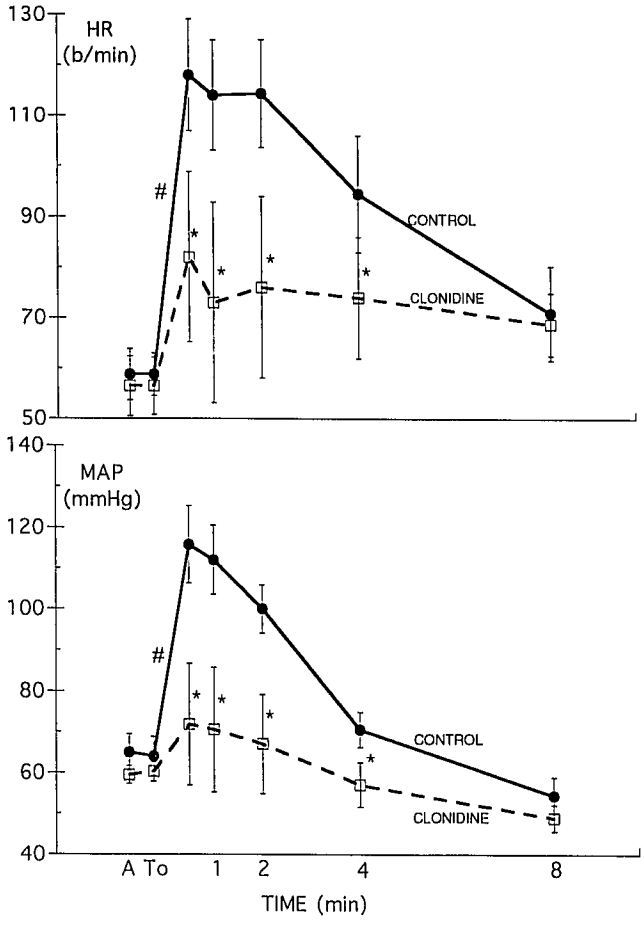

Fig. 3. Clonidine 4.3 μg/kg given by mouth attenuated the increase in heart rate (HR) and mean arterial blood pressure (MAP) associated with a rapid increase of end-tidal desflurane concentration from 4% to 8%. A = value at 32 min of 0.55 MAC; time 0 = time of first breath of increased anesthetic concentration. #$P < 0.05$ 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% ± 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 ± 12% ($P < 0.02$), the mean arterial blood pressure response by 80 ± 21% ($P < 0.05$) (figs. 3 and 4), and the plasma epinephrine response by 79% ± 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-

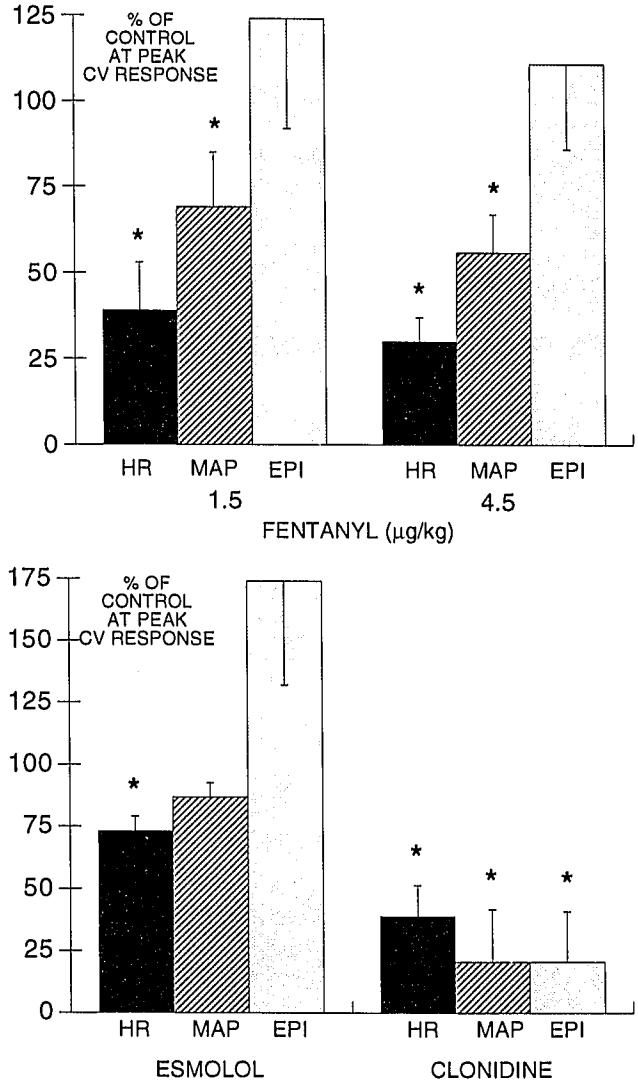

Fig. 4. Fentanyl, esmolol, and clonidine decreased the peak heart rate (HR) and mean arterial blood pressure (MAP) responses to a rapid increase in end-tidal desflurane from 4% to 8%. *$P < 0.05$ *versus* control (no drug). Only clonidine also attenuated the associated increase in plasma epinephrine 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[1–4] (and the current study) or isoflurane[2,6,7] 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%,[2] 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[9] and dogs[10,11] has vagomimetic properties[12,13] in dogs and decreases heart rate during inhalation anesthesia.[14] 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.[15] 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.[16] Systemically administered fentanyl in the dog does not alter the cardiovascular or sympathetic response to splanchnic nerve stimulation,[17] suggesting that peripheral effects would not be blocked in the current study. Alternatively, the increase to 8% desflurane without fentanyl could have caused supramaximal 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 β-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 α_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 μg/kg decreased desflurane MAC by an insignificant amount, whereas 4.5 μg/kg decreased MAC by more than 20%.[18] The effect in the current study may exceed those of Ghouri *et al.*[18] 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%,[4] and provided less blunting of the increase in arterial blood pressure than did fentanyl or clonidine. Furthermore, although 4.5 μg/kg of fentanyl decreases MAC of desflurane more than does 1.5 μg/kg,[13] 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, α_2-adrenergic agonists increase the depth of other inhaled anesthetics.[19,20] However, the dose we used did not affect blood pressure (clonidine: 60 ± 2 mmHg, control: 64 ± 5 mmHg; $P > 0.2$), or heart rate (clonidine: 57 ± 6 mmHg, control: 59 ± 4 mmHg; $P > 0.2$), at 4.0% end-tidal desflurane, before the concentration of desflurane was increased.

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 ≤ 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 ≤ 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 α_2-adrenergic agonists. Thus, although administration of 4.3 μg/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 μg/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.

The authors thank Dennis M. Fisher, M.D. for his assistance with statistical issues.

References

1. Ebert TJ, Muzi M: Sympathetic hyperactivity during desflurane anesthesia in healthy volunteers: A comparison with isoflurane. ANESTHESIOLOGY 79:444–453, 1993

2. Weiskopf RB, Moore MA, Eger EI II, Noorani M, McKay L, Chortkoff B, Hart P, Damask M: Rapid increase in desflurane concentration is associated with greater transient cardiovascular stimulation than with rapid increase in isoflurane concentration in humans. ANESTHESIOLOGY 80:1035–1045, 1994

3. Moore MA, Weiskopf RB, Eger EI II, Noorani M, McKay L, Damask M: Rapid 1% increases of end-tidal desflurane concentrations above 5% transiently increase heart rate and blood pressure in humans. ANESTHESIOLOGY 81:94–98, 1994

4. Weiskopf RB, Eger EI II, Noorani M, Daniel M: Repetitive rapid increases in desflurane concentration blunt transient cardiovascular stimulation in humans. ANESTHESIOLOGY 81:843–849, 1994

5. Goldstein DS, Feuerstein G, Izzo JL Jr, Kopin IJ, Keiser HR: Validity and reliability of liquid chromatography with electrochemical detection for measuring plasma levels of norepinephrine and epinephrine in man. Life Sci 28:467–475, 1981

6. Yli-Hankala A, Randell T, Seppala T, Lindgren L: Increases in hemodynamic variables and catecholamine levels after rapid increase in isoflurane concentration. ANESTHESIOLOGY 78:266–271, 1993

7. Ishikawa T, Nishino T, Hiraga K: Immediate responses of arterial blood pressure and heart rate to sudden inhalation of high concentrations of isoflurane in normotensive and hypertensive patients. Anesth Analg 77:1022–1025, 1993

8. Helman JD, Leung JM, Bellows WH, Pineda N, Roach GW, Reeves JD 3d, Howse J, McEnany MT, Mangano DT: A comparison of desflurane and sufentanil in patients undergoing coronary artery surgery. ANESTHESIOLOGY 77:47–62, 1992

9. Daskalopoulos NTH, Laubie M, Schmitt H: Localization of the central sympatho-inhibitory effect of a narcotic analgesic agent, fentanyl, in cats. Eur J Pharmacol 33:91–97, 1975

10. Flacke JW, Flacke WE, Bloor BC, Olewine S: Effects of fentanyl, naloxone, and clonidine on hemodynamics and plasma catecholamine levels in dogs. Anesth Analg 62:305–313, 1983

11. Flacke JW, Davis LJ, Flacke WE, Bloor BC, Van Etten AP: Effects of fentanyl and diazepam in dogs deprived of autonomic tone. Anesth Analg 64:1053–1059, 1985

12. Laubie M, Schmitt H, Canellas J, Roquebert J, Demichel P: Centrally mediated bradycardia and hypotension induced by narcotic analgesics: Dextromoramide and fentanyl. Eur J Pharmacol 28:66–75, 1974

13. Laubie M, Schmitt H, Drouillat M: Central sites and mechanisms of the hypotensive and bradycardic effects of the narcotic analgesic agent fentanyl. Naunyn Schmiedebergs Arch Pharmacol 296:255–261, 1977

14. Cahalan MK, Lurz FW, Eger EI 2d, Schwartz LA, Beaupre PN, Smith JS: Narcotics decrease heart rate during inhalational anesthesia. Anesth Analg 66:166–170, 1987

15. Weiskopf RB, Reid IA, Fisher DM, Holmes MA, Rosen JI, Keil LC: Effects of fentanyl on vasopressin secretion in human subjects. J Pharmacol Exp Ther 242:970–973, 1987

16. Wang C, Chakrabarti MK, Whitwam JG: Specific enhancement by fentanyl of the effects of intrathecal bupivacaine on nociceptive afferent but not sympathetic efferent pathways in dogs. ANESTHESIOLOGY 79:766–773, 1993

17. Jordan D, Miller ED Jr: Isoflurane-induced splanchnic sympathectomy. Anesth Analg 77:291–296, 1993

18. Ghouri AF, White PF: Effect of fentanyl and nitrous oxide on the desflurane anesthetic requirement. Anesth Analg 72:377–381, 1991

19. Bloor BC, Flacke WE: Reduction in halothane anesthetic requirement by clonidine, an alpha-adrenergic agonist. Anesth Analg 61:741–745, 1982

20. Savola MKT, MacIver MB, Doze VA, Kendig JJ, Maze M: The alpha-2-adrenoceptor agonist dexmedetomidine increases the apparent potency of the volatile anesthetic isoflurane in rats in vivo and in hippocampal slice in vitro. Brain Res 548:23–28, 1991