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Concentration–Response Relationships for Fentanyl and Sufentanil in Patients Undergoing Coronary Artery Bypass Grafting

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Background: **Concentration–response relationships for sufentanil and fentanyl are undefined in patients undergoing coronary artery bypass grafting.**

Methods: **Separate studies of sufentanil and fentanyl were performed in lorazepam-premedicated patients undergoing coronary artery bypass grafting. Patients were assigned randomly to groups with different prebypass effect-site opioid concentrations targeted by computer-assisted infusion. The target sufentanil concentrations were 0.4 ng/ml (group L_S, n = 11), 0.8 ng/ml (group M_S, n = 10), and 1.2 ng/ml (group H_S, n = 11); the target fentanyl concentrations were 5 ng/ml (group L_F, n = 7), 10 ng/ml (group M_F, n = 7), and 15 ng/ml (group H_F, n = 6). Propofol at a dose of 1 mg/kg was administered at induction of anesthesia and isoflurane was used for hemodynamic control. Hemodynamics, end-tidal isoflurane concentration, and opioid concentration in arterial blood were measured at specific intervals.**

Results: **Intraoperative opioid concentrations were constant, averaging 0.71 ± 0.13, 1.25 ± 0.21, and 2.03 ± 0.46 ng/ml for groups L_S, M_S, and H_S, respectively, and 7.3 ± 1.1, 13.2 ± 2.2, and 24.4 ± 5.8 ng/ml for groups L_F, M_F, and H_F, respectively (all mean ± SD). Isoflurane requirements were significantly greater in group L_S than in groups M_S and H_S and greater in group L_F than in groups M_F and H_F. The serum opioid and end-tidal isoflurane concentrations were correlated significantly. There were no intergroup differences in hemodynamics.**

Conclusions: **Serum sufentanil and fentanyl concentrations of 0.71 ± 0.13 ng/ml and 7.3 ± 1.3 ng/ml, respectively, are on the steep parts of the concentration–response relationships and facilitate prebypass hemodynamic control in patients undergoing coronary artery bypass grafting with opioid–isoflurane anesthesia. Concentrations of sufentanil ≥ 1.25 ± 0.21 ng/ml and of fentanyl ≥ 13.3 ± 2.2 ng/ml minimize isoflurane requirements but do not improve hemodynamic control. (Key words: Cardiac anesthesia, dose response, minimum alveolar concentration reduction.)**

THE potent synthetic opioids fentanyl and sufentanil are used frequently during anesthesia for patients undergoing coronary artery bypass grafting (CABG). The analgesia provided by opioids attenuates the hemodynamic response to noxious surgical stimulation. However, the respiratory depressant effects of opioids tend to delay postoperative recovery. Current clinical trends emphasize reduced opioid doses to facilitate early postoperative extubation after CABG.[1] In this context, the minimum opioid dose compatible with effective hemodynamic control should be used. Precise opioid dosing necessitates definition of concentration–response relationships for suppression of hemodynamic responsiveness by the potent opioids. These relationships have not been defined for patients undergoing CABG.

Initial efforts to demonstrate concentration-related suppression of hemodynamic responsiveness by high doses of opioids in patients undergoing CABG yielded negative results.[2,3] These investigators concluded that no clinically applicable, unsupplemented opioid dose regimen would reliably abolish hemodynamic responses to surgical stimulation. Concentration–response relationships for fentanyl and sufentanil have been defined in terms of the reduction of the minimum alveolar concentration (MAC) of volatile anesthetics.[4–7] These studies show a plateau in the MAC-reducing properties of opioids, between 60–90% of MAC, occurring at relatively low serum opioid concentrations. However, the relevance of MAC reduction studies to the clinical management of patients undergoing CABG is unclear. The clinical MAC reduction studies were undertaken in relatively young, healthy, unpremedicated patients, and venous rather than arterial blood sampling was performed.[6,7] A single surgical event, skin incision, was studied. Patients undergoing CABG generally are older, less healthy, and

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premedicated. Furthermore, the clinical goal in patients undergoing CABG is provision of sustained hemodynamic control in 100% of patients, rather than prevention of movement in response to skin incision in only 50% of patients.

Therefore, we explored the concentration–response relationships for suppression of hemodynamic responsiveness by fentanyl and sufentanil in premedicated patients undergoing CABG. We used arterial rather than venous blood sampling. Our clinical goal was tight hemodynamic control throughout the prebypass period in all patients. We used a computer-driven infusion pump to produce stable intraoperative serum opioid concentrations. We supplemented the opioid with isoflurane and used the dose of isoflurane needed to maintain hemodynamic stability as our index of the effectiveness of various serum opioid concentrations.

Methods

These studies were approved by the Ethics Committee of the University of Manitoba, and all patients provided written informed consent. Fifty-two patients undergoing elective CABG participated in two sequential studies evaluating the concentration response to sufentanil and fentanyl. We excluded patients with left ventricular (LV) ejection fraction < 0.3 or "severe" LV dysfunction, as assessed by cineangiography, radionuclide ventriculography, or echocardiography. Other exclusion factors were previous heart surgery, unstable angina necessitating continuous electrocardiographic monitoring or intravenous nitroglycerin, planned awake intubation, body weight > 110 kg, long-term use of sedative-hypnotics, alcohol or drug abuse, or a previous adverse reaction to any of the study drugs. In each study, patients were assigned randomly to one of three groups, with different target effect-site opioid concentrations.§ The target sufentanil concentrations were 0.4 ng/ml (group L_S), 0.8 ng/ml (group M_S), and 1.2 ng/ml (group H_S); the target fentanyl concentrations were 5 ng/ml (group L_F), 10 ng/ml (group M_F), and 15 ng/ml (group H_F). The sufentanil target concentrations were chosen based on a previous, negative, concentration–response study that used higher target concentrations.[8] The fentanyl target concentrations and sample size were based on the results of the sufentanil study reported here and an assumed potency ratio of 1:12 for fentanyl compared with sufentanil.[9]

Resting heart rate (HR) and mean arterial pressure (MAP) were determined at least 1 day before operation. Heart rate and MAP were measured every 3 min for 15 min using an automated, noninvasive device. The three lowest HR and MAP measurements were averaged and used as a baseline for intraoperative hemodynamic management. Patients whose baseline MAP was > 100 mmHg were excluded from the study.

Patients received 150 mg ranitidine administered orally the night before surgery and again 75 min before operation. An oral dose of 0.06 mg/kg lorazepam was administered 75 min before operation with the patient's usual antianginal medication. After premedication, all patients received nasal oxygen at 4 l/min. Before induction of anesthesia, electrocardiograph leads II and V5 were applied and monitored thereafter. Venous, arterial, and central venous catheters were inserted during local anesthesia. Heart rate and systemic arterial pressure were monitored continuously. End-tidal carbon dioxide tension and the end-tidal isoflurane concentration (ET-ISO) were measured continuously at the y-connector of the anesthetic circle absorption system using a photoacoustic monitor (type 1304; Brüel & Kjær, Naerum, Denmark). The gas monitor was calibrated immediately before each study according to appropriate standards.

All patients received 7 ml/kg Ringer's lactate solution intravenously before anesthesia was induced. One hundred percent oxygen was administered by face mask. An intravenous opioid infusion was begun 1 min later using a computer-driven infusion system (STANPUMP‖). STANPUMP was programmed with pharmacokinetic parameters we derived previously in patients undergoing abdominal aortic surgery[10,11] and with values for the equilibration constants between plasma and the effect site (K_{e0}) obtained by Scott *et al.*[9] in healthy persons undergoing surgery.[9] The opioids were prepared by our pharmacy, in concentrations of 8, 16, or 24 μg/ml for sufentanil and 16.7, 33.3, or 50 μg/ml for fentanyl, and administered in a double-blinded manner. The attending anesthetist knew which opioid was being administered, but not the concentration. STANPUMP was programmed to rapidly achieve and maintain target concentrations of 1.2 ng/ml sufentanil or 15 ng/ml fentanyl. The program assumed an administered opioid concentration of 24 μg/ml for sufentanil or 50 μg/ml for fentanyl, thus effec-

§The effect site is the theoretical site of opioid effect in the central nervous system.

‖STANPUMP is freely available from the author, Steven L. Shafer, M.D., Anesthesiology Service (112A), PAVAMC, 3801 Miranda Avenue, Palo Alto, California 94304, and *via* the Worldwide Web at http://pkpd.icon.palo-alto.med.va.gov.

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tively targeting effect-site concentrations of 0.4, 0.8, or 1.2 ng/ml for sufentanil, and 5, 10, or 15 ng/ml for fentanyl, depending on the administered opioid concentration. Two minutes after the start of the opioid infusion, 1 mg/kg propofol was administered intravenously over 30 s. After loss of the eyelash reflex, 1 mg/kg succinylcholine was administered. One minute later, the trachea was intubated. In patients with significant gastroesophageal reflux, cricoid pressure was applied, and propofol and succinylcholine were administered as rapidly as possible. One hundred percent oxygen was continued, positive pressure ventilation was begun, and the end-tidal carbon dioxide tension was adjusted to 30–35 mmHg. The target opioid concentration was held constant throughout the study, and no other opioids or sedative-hypnotic agents were administered. Further muscle relaxation was achieved with vecuronium administered intravenously. Incomplete paralysis was used so that gross patient movement could be detected. A nerve stimulator was applied to the facial nerve, and two or more visible twitches during train-of-four stimulation were maintained at all times. Supplemental isoflurane was administered according to a protocol that will be described. In addition, all patients received a minimum ET-ISO of 0.25% for 5 min before skin incision to ensure adequate depth of anesthesia. The opioid infusion and the study were discontinued 2 min after placement of a stitch for aortic cannulation. After the study was discontinued, the attending anesthetist was given a sealed envelope from the pharmacy that revealed the infused opioid concentration and was informed by the investigators of the total volume of opioid infused. This permitted appropriate anesthetic management during the rest of the operation. Investigators remained blinded to the administered opioid concentration. Each patient was interviewed after operation and questioned about awareness of the surgical procedure.

After induction, our protocol necessitated that the anesthetist maintain patient MAP as close to baseline as possible and HR at 120% or less of baseline. Hemodynamics were controlled by up-and-down titration of the ET-ISO between 0–2.3% (except during the 5-min period before incision when a minimum ET-ISO of 0.25% was maintained). Isoflurane was administered reactively in response to changing hemodynamics, rather than proactively in anticipation of the changing intensity of surgical stimulation. A MAP greater than baseline was treated by increasing the ET-ISO. The protocol permitted the target effect-site opioid concentration to be doubled if an ET-ISO of 2.3% failed to reduce MAP to $<$ 120% of baseline. Failing this, intravenous nitroglycerin was to be administered. During surgery, MAP less than baseline was first treated by reducing the inspired isoflurane concentration, to zero if necessary. Hypotension (MAP $<$ 80% of baseline) was treated with intravenous phenylephrine. An HR $>$ 120% of baseline that did not respond to isoflurane was treated with an intravenous β-adrenergic blocking agent. Atropine was used to treat bradycardia (HR $<$ 35 beats/min).

Hemodynamic variables were acquired every 15 s, and ET-ISO was acquired every 30 s, by computers interfaced with the operating room monitors. The hemodynamic computer files were manually edited off-line to remove artifacts such as those related to blood sampling and flushing of the arterial catheter. For each patient, mean HR, MAP, and ET-ISO for the period between the start of opioid infusion and study discontinuation were obtained by averaging all data in the corresponding computer files. To determine the maximum isoflurane requirement associated with each study event, we determined the peak ET-ISO between each of the specified study intervals by visually inspecting the data files. The following times were specified for statistical analysis: (1) awake (the last minute before the start of opioid infusion); (2) intubation (the second minute after intubation); (3) skin incision (the second minute after skin incision); (4) sternotomy (the second minute after sternotomy); (5) sternal lift (the second minute after elevation of the hemisternum for dissection of the internal mammary artery); (6) sternal spread (the second minute after sternal spread); (7) aortic dissection (the second minute after periaortic dissection); and (8) aortic stitch (the second minute after placement of an aortic suture). The values reported at these times are the average of data collected during 1 min.

Arterial blood for serum opioid concentration was collected immediately before the specified study intervals. The clotted blood was centrifuged, and the serum was frozen for later analysis. Serum opioid concentrations were determined using commercially available radioimmunoassay kits (Janssen Biotech, Olen, Belgium) used according to manufacturer instructions. All samples were assayed in duplicate, and the mean value was reported. For sufentanil, the average intrasample coefficient of variation was 2.26%. The average percentage error of the assay was 1.29% at a sufentanil concentration of 0.2 ng/ml. For fentanyl, the average intrasample coefficient of variation was 2.66%. The average percentage error of the assay was 3.11% for standard samples in the range of 5–20 ng/ml.

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Table 1. Demographics

	Group L_S (n = 11)	Group M_S (n = 10)	Group H_S (n = 11)
Sufentanil study			
Age (yr)	63 ± 7	69 ± 7*	62 ± 5
Weight (kg)	76.2 ± 20.2	73.7 ± 9.0	83.2 ± 14.4
Male:female	9:2	5:5	8:3
β-Blocker	9	8	8
HR (beats/min)†	61 ± 12	66 ± 8	62 ± 9
MAP (mmHg)†	83 ± 9	87 ± 8	91 ± 8
	Group L_F (n = 7)	Group M_F (n = 7)	Group H_F (n = 6)
Fentanyl study			
Age (yr)	69 ± 8	66 ± 8	67 ± 4
Weight (kg)	92.1 ± 12.5	87.4 ± 13.3	78.8 ± 8.6
Male:female	5:2	6:1	5:1
β-Blocker	6	6	5
HR (beats/min)†	62 ± 10	55 ± 6	58 ± 9
MAP (mmHg)†	87 ± 2	91 ± 4	92 ± 7

HR = heart rate; MAP = mean arterial pressure.

* $P < 0.05$, group M_S *versus* groups L_S and H_S.

† Baseline values determined at least 1 day preoperatively and used to guide intraoperative hemodynamic management.

Data are presented as mean ± SD in the text and the tables. Demographic data were compared by analysis of variance (ANOVA) or ANOVA on ranks. Hemodynamic data, serum opioid concentration, and ET-ISO were subjected to ANOVA or two-way ANOVA for repeated measures. Nonlinear regression was used to seek correlations between serum opioid concentration and ET-ISO at all study intervals except intubation. A probability value < 0.05 was considered significant.

Results

Thirty-two patients participated in the sufentanil study: 11 in group L_S, 10 in group M_S, and 11 in group H_S. There were 20 participants in the fentanyl study: 7 in group L_F, 7 in group M_F, and 6 in group H_F. Within each study, the groups did not differ with respect to weight, gender, preoperative use of β-adrenergic blocking agents, or baseline hemodynamics (table 1). However, patients in group M_S were significantly older than those in groups L_S and H_S. The internal mammary artery was not harvested in one patient each in groups L_S, H_S, M_F, and H_F. These patients are included in the analysis, with missing data points at sternal lift.

The target effect-site sufentanil concentration was doubled in three patients from group L_S (between skin incision and sternotomy in two patients, and between sternotomy and sternal lift in one) but not in any patients from groups M_S or H_S ($P < 0.05$, by ANOVA on ranks). All three patients who required doubling of the target sufentanil concentration were taking β-adrenergic blocking agents before operation. Data from these three patients were retained in group L_S for purposes of statistical analysis. Serum sufentanil concentrations drawn within 6 min of doubling the effect-site concentration were excluded from statistical analysis. The target opioid concentration was not doubled in any patient in the fentanyl study. In one patient from group L_F, the ET-ISO transiently reached 2.65% at sternotomy, and the MAP was 15% above baseline.

The total dose of sufentanil administered in the prebypass period was 1.87 ± 0.44, 3.12 ± 0.51, and 4.93 ± 0.77 μg/kg for groups L_S, M_S, and H_S, respectively. The corresponding fentanyl doses were 18.8 ± 2.5, 33.9 ± 2.9, and 50.4 ± 3.0 μg/kg, in groups L_F, M_F, and H_F, respectively. STANPUMP maintained relatively constant opioid concentrations in most patients (fig. 1). The serum opioid concentration did not change significantly between skin incision and study discontinuation in either study (table 2). However, in both studies, the serum opioid concentration at intubation was significantly higher than that measured subsequently ($P < 0.05$). The average of all intraoperative sufentanil concentrations, excluding those at intubation, was 0.71 ± 0.13 ng/ml for group L_S, 1.25 ± 0.21 ng/ml for group M_S, and 2.03 ± 0.46 ng/ml for group H_S. Among the three patients who required doubling of the target sufentanil concentration because of inadequate MAP control, the serum sufentanil concentration before doubling was 0.54 ± 0.13 ng/ml. The average intraoperative fentanyl concentrations were 7.3 ± 1.1 ng/ml in group L_F, 13.2 ± 2.2 ng/ml for group M_F, and 24.4 ± 5.8 ng/ml for group H_F. In the patient in group L_F in whom the ET-ISO reached 2.65% at sternotomy, the corresponding serum fentanyl concentration was 4.75 ng/ml.

In both studies there were no intergroup differences in hemodynamics at the specified study intervals (table 3) or during the entire prebypass period. The mean prebypass HR was 53 ± 10, 48 ± 6, and 53 ± 8 beats/min; and the MAP was 82 ± 5, 81 ± 4, and 84 ± 6 mmHg in groups L_S, M_S, and H_S, respectively. The mean prebypass HR was 50 ± 7, 48 ± 4, and 46 ± 5 beats/min; the mean prebypass MAP was 81 ± 4, 81 ± 4, and 82 ± 5 mmHg for groups L_F, M_F, and H_F, respectively.

In both studies, the average prebypass ET-ISO in group L was significantly greater than that in groups M and H, with no difference between the latter two groups. The

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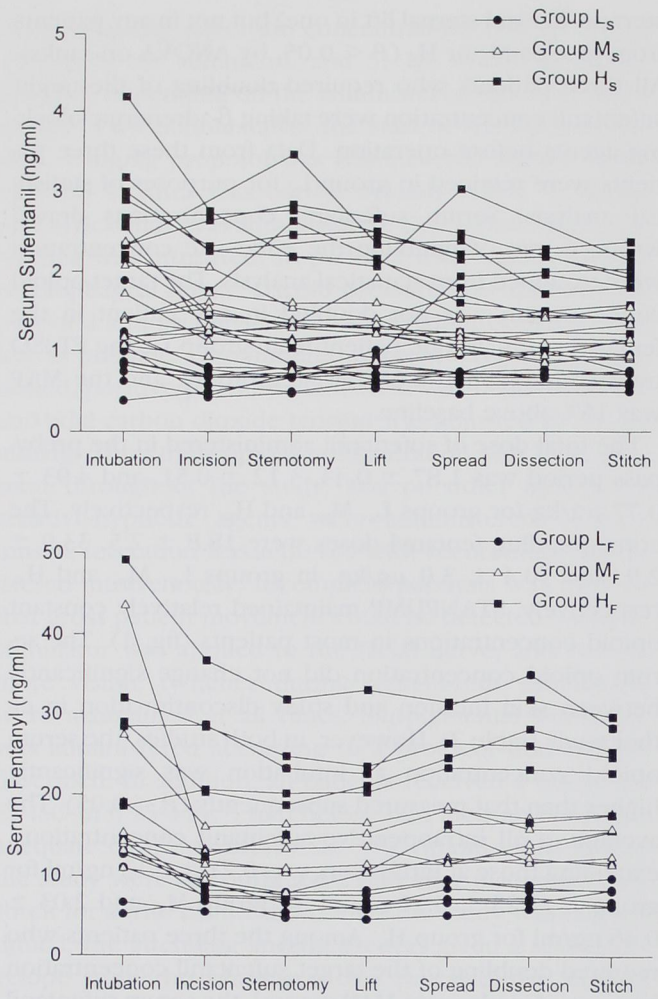

Fig. 1. Serum sufentanil (*top*) and fentanyl (*bottom*) concentrations (ng/ml) for each patient at the specified study intervals. Incision = skin incision; Lift = sternal lift; Spread = sternal spread; Dissection = aortic dissection; and Stitch = aortic stitch.

mean ET-ISO during sufentanil infusion was 0.50 ± 0.25% in group L_S, 0.27 ± 0.15% in group M_S, and 0.23 ± 0.07% in group H_S ($P = 0.002$). Similarly, the mean ET-ISO during the fentanyl infusion was 0.50 ± 0.15% in group L_F, 0.20 ± 0.08% in group M_F, and 0.25 ± 0.14% in group H_F ($P = 0.0009$). In both studies, the ET-ISO at the seven specified study intervals, and the peak ET-ISO between intervals, differed significantly between groups (table 4, fig. 2). For both studies, the ET-ISO and peak ET-ISO in group L were significantly greater than in either groups M or H, with no difference between the latter two groups. A MAP greater than baseline was invariably the indication for increasing the ET-ISO. When MAP was maintained at baseline with isoflurane, gross patient movement was not observed.

The power function ET-ISO = a × [serum opioid]^b described the relation between serum opioid concentration and ET-ISO. Nonlinear regression analysis revealed significant correlations between the serum opioid concentration and ET-ISO at most study intervals. Similar correlations were noted between the serum opioid concentration and the subsequent peak ET-ISO. The strongest correlations were between serum sufentanil concentration and peak ET-ISO at skin incision ($P < 0.0001$, $r^2 = 0.452$; fig. 3), and between serum fentanyl concentration and peak ET-ISO at sternal lift ($P = 0.0003$, $r^2 = 0.556$; fig. 3). There were no clear differences in the concentration–response relationships at various study intervals.

In each study, the three groups did not differ with respect to pharmacologic interventions. Fifty-seven of 59 patients required phenylephrine (97%), usually between induction and skin incision. One patient in group M_F received metoprolol, and one in group L_S required atropine. No patient received nitroglycerin. No patient recalled any intraoperative event.

Discussion

Our studies show concentration-related suppression of hemodynamic responsiveness by fentanyl and sufentanil during the prebypass period in patients undergoing CABG. In both studies, patients in group L required more isoflurane to achieve hemodynamic stability than patients in groups M and H. This difference was most striking after the intense stimuli of sternotomy and sternal lift. These data indicate the presence of inflections in the slopes of the concentration–response curves for suppression of hemodynamic responsiveness by the opioids. For sufentanil, a concentration of 0.71 ± 0.13 ng/ml (group L_S) was on a steep portion of the concentration–response relationship, whereas concentrations of 1.25 ± 0.21 ng/ml (group M_S) and 2.03 ± 0.46 ng/ml (group H_S) were on the plateau. Similarly, a fentanyl concentration of 7.3 ± 1.1 ng/ml was on a steep portion of the concentration–response relationship, whereas concentrations of 13.2 ± 2.2 ng/ml and 24.4 ± 5.8 ng/ml were on the plateau. The identical isoflurane requirements in groups L_F and L_S suggest a potency ratio of 1:10 for fentanyl compared with sufentanil that is compatible with previous studies using different methods.[6,7,9]

A strength of our study is that the effectiveness of various opioid concentrations was evaluated during typ-

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Table 2. Serum Opioid Concentrations (ng/ml)

	Intubation	Skin Incision	Sternotomy	Sternal Lift	Sternal Spread	Aortic Dissection	Aortic Stitch
Sufentanil study							
Group L_S	0.96 ± 0.39	0.62 ± 0.13	0.68 ± 0.12	0.71 ± 0.14	0.73 ± 0.19	0.81 ± 0.16	0.72 ± 0.18
Group M_S	1.51 ± 0.42	1.41 ± 0.33	1.25 ± 0.24	1.33 ± 0.28	1.23 ± 0.24	1.14 ± 0.27	1.18 ± 0.23
Group H_S	2.60 ± 0.77	2.06 ± 0.6	2.22 ± 0.78	2.10 ± 0.57	2.04 ± 0.52	1.87 ± 0.32	1.85 ± 0.36
Fentanyl study							
Group L_F	11.1 ± 3.8	7.6 ± 1.3	6.7 ± 1.2	6.5 ± 1.2	7.7 ± 1.6	7.5 ± 1.1	7.7 ± 1.3
Group M_F	19.8 ± 11.7	12.2 ± 2.2	12.0 ± 2.9	13.0 ± 2.6	14.3 ± 3.1	13.7 ± 2.1	14.3 ± 2.4
Group H_F	29.3 ± 11.1	24.5 ± 8.5	22.3 ± 5.8	24.1 ± 5.2	25.6 ± 5.6	26.8 ±6.5	24.7 ± 4.3

ical clinical circumstances. Specifically, clinicians used a volatile anesthetic to maintain hemodynamic control during varying levels of surgical stimulation. Therefore, the serum concentrations achieved in groups L_S and L_F may be clinically useful. When appropriately supplemented with isoflurane, serum concentrations of 0.71 ± 0.13 ng/ml sufentanil and 7.3 ± 1.1 ng/ml fentanyl provided effective intraoperative hemodynamic control without the need for supplemental vasodilators or β-adrenergic blocking agents. This was achieved with a total prebypass opioid dose (1.87 ± 0.44 μg/kg sufentanil or 18.8 μg/kg fentanyl) similar to that used in a recently published study of early extubation after CABG.[1] Targeting higher initial opioid concentrations is unnecessary in patients without severe LV dysfunction. Although the higher serum opioid concentrations in the other study groups (M_S, H_S, M_F, and H_F) minimized isoflurane requirements, they did not improve hemodynamic control. In patients with severe LV dysfunction, it may be important to minimize the requirement for volatile anesthetic by achieving near-maximal opioid effect. This could be accomplished by targeting the serum concentrations we achieved in groups M_S and M_F (1.25 ng/ml sufentanil or 13.2 ng/ml fentanyl).

Nonlinear regression confirmed the significant relationship between the ET-ISO necessary to maintain hemodynamic stability and serum opioid concentration. Serum sufentanil concentrations < 0.7 ng/ml and serum fentanyl concentrations < 7 ng/ml were associated with high isoflurane requirements in individual patients. In three patients, a serum sufentanil concentration of 0.54 ± 0.13 ng/ml did not permit adequate hemodynamic control with an ET-ISO of 2.3%. Similarly, in one patient with a serum fentanyl concentration of 4.75 ng/ml, an ET-ISO of $> 2.3\%$ failed to return MAP to baseline.

The concentration–response relations illustrated in figure 3 should be interpreted cautiously, because relatively few data points lie on the steep portions of these curves. We administered 0.25% isoflurane to all patients before skin incision to ensure adequate anesthesia in patients in group L. Subsequent to skin incision, the

Table 3. Hemodynamics

	Group	Awake	Intubation	Skin Incision	Sternotomy	Sternal Lift	Sternal Spread	Aortic Dissection	Aortic Stitch
Sufentanil study									
HR (beats/min)	L_S	59 ± 13	56 ± 14	64 ± 24	61 ± 26	57 ± 19	55 ± 19	56 ± 13	52 ± 9
	M_S	63 ± 9	53 ± 9	49 ± 12	51 ± 9	50 ± 9	47 ± 6	55 ± 14	49 ± 6
	H_S	65 ± 11	56 ± 8	52 ± 14	53 ± 9	51 ± 8	55 ± 13	60 ± 16	59 ± 14
MAP (mmHg)	L_S	101 ± 15	80 ± 13	91 ± 13	97 ± 8	87 ± 12	89 ± 12	82 ± 15	80 ± 9
	M_S	100 ± 12	68 ± 14	84 ± 7	86 ± 10	85 ± 10	83 ± 13	89 ± 7	78 ± 7
	H_S	99 ± 14	72 ± 10	83 ± 10	90 ± 10	92 ± 11	86 ± 11	89 ± 13	85 ± 8
Fentanyl study									
HR (beats/min)	L_F	58 ± 9	53 ± 10	48 ± 9	52 ± 9	56 ± 12	49 ± 6	51 ± 7	52 ± 7
	M_F	58 ± 7	50 ± 8	43 ± 5	45 ± 4	46 ± 5	47 ± 7	48 ± 4	48 ± 35
	H_F	57 ± 5	46 ± 4	43 ± 4	48 ± 4	45 ± 5	48 ± 7	47 ± 8	51 ± 4
MAP (mmHg)	L_F	103 ± 10	74 ± 14	86 ± 9	94 ± 12	87 ± 12	84 ± 17	93 ± 7	82 ± 6
	M_F	98 ± 6	68 ± 16	83 ± 8	87 ± 9	83 ± 10	93 ± 13	84 ± 10	81 ± 10
	H_F	103 ± 13	76 ± 14	89 ± 7	92 ± 14	90 ± 19	89 ± 19	85 ± 14	79 ± 9

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Table 4. End-tidal Isoflurane Concentration (ET-ISO)

	Intubation	Skin Incision	Sternotomy	Sternal Lift	Sternal Spread	Aortic Dissection	Aortic Stitch
Sufentanil study							
Group L_S*	0.13 ± 0.13	0.51 ± 0.36	1.03 ± 0.71	0.97 ± 0.58	0.48 ± 0.37	0.71 ± 0.37	0.49 ± 0.23
Group M_S	0.07 ± 0.05	0.28 ± 0.09	0.33 ± 0.20	0.45 ± 0.44	0.25 ± 0.26	0.38 ± 0.40	0.48 ± 0.44
Group H_S	0.04 ± 0.04	0.36 ± 0.16	0.33 ± 0.19	0.28 ± 0.16	0.20 ± 0.09	0.30 ±0.31	0.23 ± 0.13
Fentanyl study							
Group L_F*	0.11 ± 0.12	0.43 ± 0.12	1.02 ± 0.84	1.05 ± 0.57	0.53 ± 0.23	0.51 ± 0.19	0.94 ± 0.53
Group M_F	0.04 ± 0.03	0.28 ± 0.06	0.35 ± 0.41	0.37 ± 0.25	0.19 ± 0.10	0.18 ± 0.11	0.28 ± 0.24
Group H_F	0.09 ± 0.05	0.29 ± 0.09	0.36 ± 0.23	0.29 ± 0.16	0.30 ± 0.18	0.33 ± 0.23	0.32 ± 0.21

* For each study, ET-ISO was significantly greater in group L than in groups M and H ($P = 0.0011$ and $P = 0.0015$ for the sufentanil and fentanyl studies, respectively).

inspired isoflurane concentration was reduced to zero if MAP was less than baseline. However, incomplete washout of previously administered isoflurane inevitably affected the subsequently measured ET-ISO. For this reason, an ET-ISO of zero rarely was recorded, even in patients with high opioid levels. Therefore, the plateaus of these concentration–response curves may be elevated artifactually. However, the precise level of the plateau ET-ISO is relatively unimportant, compared with identification of the opioid concentration where the slope of the concentration–response relationship changes.

Premedication with 0.06 mg/kg lorazepam probably influenced our results. Benzodiazepines reduce the MAC of volatile anesthetics,[12] although the combined anesthetic-sparing effects of opioids and benzodiazepines are less than additive.[13] Subanesthetic serum concentrations of midazolam produce a 40% reduction in halothane MAC in humans.[14,15] Importantly, the effects of lorazepam should have been consistent among study groups because of its high bioavailability and rapid absorption in elderly patients.[16] However, differences in the effect of lorazepam between individuals may have affected the dose–response curves. The effect of 1 mg/kg propofol administered intravenously at induction would be expected to decrease rapidly. However, an interaction between propofol and fentanyl might have affected our results.[17] Therefore, our findings are strictly applicable only to patients without severe LV dysfunction, premedicated with 0.06 mg/kg lorazepam, and induced with 1 mg/kg propofol. However, because heavy premedication and administration of a sedative-hypnotic agent at induction are common practices in anesthesia for CABG, broader applicability may be possible. In this regard, we recently noted no difference in the prebypass isoflurane requirements between patients undergoing CABG who were premedicated with 0.06 mg/kg oral lorazepam, compared with those administered 0.1 mg/kg morphine plus 0.006 mg/kg scopolamine intramuscularly.[18]

The validity of our results depends on the reliability with which the attending anesthetist titrated the ET-ISO concentration in response to changing hemodynamics. Our protocol stipulated that clinicians maintain MAP as close to baseline as possible at all times after induction. This necessitated constant up-and-down titration of the ET-ISO, even in response to minor changes in MAP. The high isoflurane concentrations needed in individual patients (fig. 3) reflect real requirements for hemodynamic control, rather than careless overdosage or failure to down-titrate the ET-ISO. This is confirmed by the finding that the three patients in group L_S, with the highest isoflurane requirements, ultimately required doubling of the target sufentanil concentration because of failure to control MAP with ET-ISO $\leq$2.3%. These patients had relatively low serum sufentanil concentrations before doubling. Similarly, in the one patient in group L_F in whom the isoflurane concentration exceeded 2.3%, the corresponding MAP was still 15% above baseline, and the serum fentanyl concentration was relatively low.

Classic studies by Wynands *et al.*[2] and Philbin *et al.*[3] explored concentration–response relationships for unsupplemented high-dose fentanyl and sufentanil anesthesia in patients undergoing CABG. Using bolus plus constant-infusion dose regimens, these investigators concluded that no clinically applicable dose of fentanyl or sufentanil would, by itself, completely suppress the hemodynamic response to noxious stimulation in all patients undergoing CABG. Similarly, using computer-assisted sufentanil infusion, we found no evidence of concentration-related suppression of hemodynamic responsiveness in patients undergoing CABG, over a range of sufentanil concentrations of 2.3 ± 0.6 ng/ml to 6.9 ± 1.9 ng/ml.[8] The results presented here suggest that the

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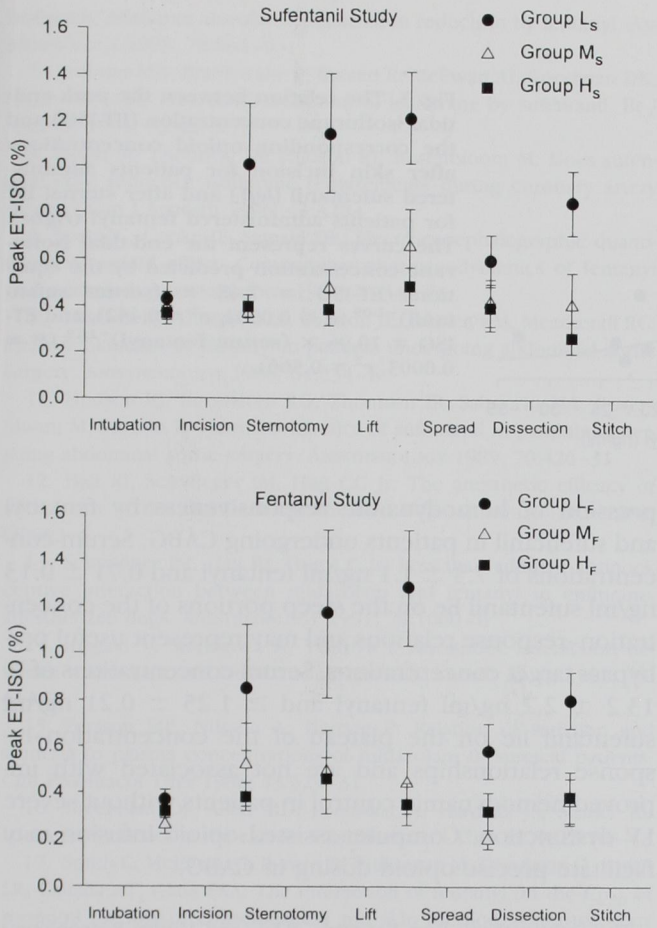

Fig. 2. Peak end-tidal isoflurane concentration (ET-ISO) (mean ± SEM) after each study interval for the sufentanil study (*top*) and the fentanyl study (*bottom*). The peak ET-ISO was significantly greater in group L than in groups M and H (P = 0.0019 and P = 0.0034 by repeated measures analysis of variance for the sufentanil and fentanyl studies, respectively). Incision = skin incision; Lift = sternal lift; Spread = sternal spread; Dissection = aortic dissection; and Stitch = aortic stitch.

absence of concentration-related hemodynamic suppression by opioids in these previous studies reflects the fact that all the opioid concentrations studied were on the plateaus of the concentration–response curves.

McEwan *et al.*[6] and Brunner *et al.*[7] previously defined concentration–response relationships for opioids in terms of the reduction of isoflurane MAC in healthy unpremedicated patients. A 50% reduction in isoflurane MAC was obtained at venous plasma concentrations of 1.67 ng/ml fentanyl and 0.145 ng/ml sufentanil. These concentration–response curves lie substantially to the left of those we defined, despite the expectation that anesthetic requirements would be reduced in our older, lorazepam-premedicated patients. Substantial differences in methods may explain these differences.

The MAC-reduction studies defined, for various plasma opioid concentrations, the ET-ISO concentration that prevented movement in 50% of patients.[6,7] In contrast, our goal was complete control of hemodynamic responsiveness in 100% of our patients. This end point was chosen to correspond to the usual clinical goal in patients undergoing CABG. More volatile anesthetic is needed to prevent hemodynamic responsiveness, as opposed to movement, in response to noxious stimulation,[19] and even higher isoflurane concentrations are needed to prevent a response in all patients. In addition, the MAC-reduction studies evaluated the response to the discrete stimulus of skin incision, whereas we studied the response to sustained, intense surgical stimulation, including sternotomy, and sternal elevation. Finally, the clinical MAC reduction studies used venous sampling, whereas we used arterial blood sampling. These various factors probably explain the differences between our results and those obtained in clinical MAC-reduction studies.

Our results are consistent with several other studies. These include (1) the concentration–response relationship for suppression of hemodynamic–autonomic responsiveness by fentanyl, with 70% nitrous oxide, in humans[20]; (2) the relationship between enflurane MAC and opioid concentration in dogs[4,5]; and (3) the opioid concentrations inducing half-maximal electroencephalographic slowing in humans.[9] Recently, Kazama *et al.*[21] evaluated the effect of fentanyl on the propofol concentration that prevented movement in response to various noxious stimuli in humans. The movement-preventing effects of fentanyl were near-maximal at a plasma concentration of only 2.6 ± 0.5 ng/ml. However, a fentanyl concentration of 5.5 ± 0.8 ng/ml was needed to completely suppress the systolic blood pressure response to intubation, at a serum propofol concentration that prevented movement in 95% of patients.[21] The latter observation is more consistent with our results.

As anticipated, STANPUMP produced stable intraoperative serum opioid concentrations that differed between the groups. The measured serum opioid levels generally were higher than predicted, with a median percentage error of 64.8% for sufentanil and of 40.5% for fentanyl. Clearly, pharmacokinetic parameters from patients undergoing abdominal aortic surgery do not describe accurately opioid kinetics in patients undergoing CABG.[10,11] When targeting the effect-site, STANPUMP administers an initial opioid bolus, followed by an exponentially

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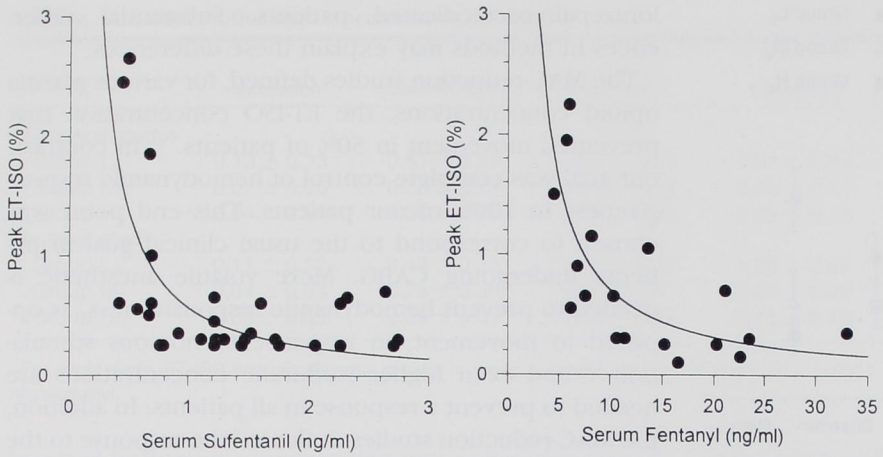

Fig. 3. The relation between the peak end-tidal isoflurane concentration (ET-ISO) and the corresponding opioid concentrations after skin incision for patients administered sufentanil (*left*) and after sternal lift for patients administered fentanyl (*right*). The curves represent the end-tidal isoflurane concentration predicted by the equations ET-ISO = 7.48 × (serum sufentanil)$^{-1.09}$ (P = 0.0001, r^2 = 0.452), and ET-ISO = 10.96 × (serum fentanyl)$^{-1.19}$ (P = 0.0003, r^2 = 0.566).

decreasing infusion. Equal concentrations in plasma and the effect-site are predicted 6 to 7 min after the infusion is started, with a pseudoequilibrium existing thereafter. Therefore, the intraoperative serum opioid concentrations we measured accurately reflect effect-site concentrations and can be used to define concentration–response relationships. Because intubation was performed before the presumed equilibrium between plasma and the effect-site, the significantly higher serum opioid concentrations observed at that time do not reflect effect-site concentrations. Similarly, serum sufentanil levels drawn within 6 min of doubling the target concentration were excluded from our concentration–response analysis.

Appropriately programmed computer-assisted infusion devices may facilitate opioid administration to patients undergoing CABG. We found that the pharmacokinetic parameters for sufentanil defined by Gepts *et al.*[22] accurately predict prebypass sufentanil concentrations in patients undergoing CABG.[23] Pharmacokinetics defined by McLain and Hug[24] appear to work well for fentanyl.[25,26] In practice, a computer-assisted infusion device could be used to target the steep-slope opioid concentrations we defined, with subsequent adjustment of the target based on each patient's response. Importantly, the target concentration could be decreased during less intense surgical stimulation. For clinicians who do not use computer-assisted infusion, manual infusion schemes can be used to target these concentrations, but with less precision and flexibility.[27] For example, based on Gepts' kinetics, a sufentanil bolus of 1 μg/kg, followed by an infusion of 0.01 $\mu g \cdot kg^{-1} \cdot min^{-1}$, would result in a serum sufentanil concentration $>$ 0.7 ng/ml, throughout the prebypass period, in an 85-kg patient undergoing CABG.

In conclusion, we defined concentration-related suppression of hemodynamic responsiveness by fentanyl and sufentanil in patients undergoing CABG. Serum concentrations of 7.3 ± 1.1 ng/ml fentanyl and 0.71 ± 0.13 ng/ml sufentanil lie on the steep portions of the concentration–response relations and may represent useful prebypass target concentrations. Serum concentrations of ≥ 13.2 ± 2.2 ng/ml fentanyl and ≥ 1.25 ± 0.21 ng/ml sufentanil lie on the plateau of the concentration–response relationships and are not associated with improved hemodynamic control in patients without severe LV dysfunction. Computer-assisted opioid infusion may facilitate precise opioid dosing in CABG.

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