Clinical evaluation of sufentanil/pancuronium versus halothane/pancuronium in patients undergoing coronary artery surgery[1]

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The authors prospectively studied 29 patients undergoing coronary artery surgery, with normal or mildly impaired ventricular function. Seventeen patients received sufentanil (15 to 20 μg/kg) and 100% O_2 (group 1); 12 received sodium thiopental/halothane (1% to 3%), 50% O_2, and 50% N_2O (group 2). Hemodynamic parameters were measured before induction (control levels), and at three-minute intervals after intubation, incision, sternotomy, and immediately before cannulation of the great vessels. In both groups, the heart rate increased from control levels during induction and remained increased at all measurements ($P < 0.01$). Nine patients in group 1, and 4 in group 2 required beta blockers to control tachycardia. The cardiac index was higher than the control level at three points in group 1 ($P < 0.01$); and lower at one point ($P < 0.01$) in group 2. Pulmonary capillary wedge pressure did not change from the control level in group 1, but increased at two points ($P < 0.05$) in group 2. Recovery time and time to extubation were significantly longer in the sufentanil group ($P < 0.01$), which was probably due to the large dose. Sufentanil provided adequate surgical anesthesia, without patient recall of intraoperative events. Unlike halothane, sufentanil did not cause myocardial depression. However, sufentanil/pancuronium caused undesirable rises in heart rate and blood pressure.

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Sufentanil, a new synthetic opioid structurally related to fentanyl, is five to 10 times more potent than fentanyl, and 2,300 times more potent than morphine.[1] Its safety margin is 90 times greater than fentanyl and 363 times greater than morphine.[2] Sufentanil is a short-acting drug, which

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has a rapid onset of action because of its strong lipophilic properties.[3]

Sufentanil has previously been evaluated as an anesthetic for patients undergoing coronary artery surgery.[4,5] Clinical evaluation in man has shown sufentanil to produce electroencephalographic patterns consistent with anesthesia,[6,7] cardiovascular stability, reduced myocardial O_2 consumption, and reduced hormonal responses to the stresses of anesthesia and surgery.[8–10] Because of these reports, sufentanil has been introduced as an anesthetic agent and recommended for patients with heart disease.

We performed this study to compare the hemodynamic effects of sufentanil and halothane anesthesia in patients undergoing coronary artery surgery.

Methods

With institutional approval, we prospectively studied 29 patients undergoing coronary artery surgery. All consented to participate in the study. All patients were between 30 and 65 years of age. None had had an operation for coronary artery disease. As confirmed by coronary angiography, ventricular function was normal to mildly impaired; and all patients were American Society of Anesthesiology (ASA) physical status 3 or 4. We excluded those who had diabetes, hypertension, or other major systemic disease. Patients receiving nitrates and beta adrenergic blocking agents for control of angina continued the drug until time of surgery. Premedication consisted of scopolamine (0.4 mg, intramuscularly) and morphine sulfate (0.12 mg/kg, intramuscularly) given 1½ hours preoperatively. Nitroglycerin paste (two inches) was applied to the posterior chest wall.

Before the induction of anesthesia, all monitoring lines were introduced after local anesthesia. We monitored the following variables: heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), central venous pressure (CVP), and pulmonary capillary wedge pressure (PCWP). We measured cardiac output (CO) by thermodilution (average of three measurements) and calculated cardiac index (CI) and systemic vascular resistance (SVR). Measurements were recorded before induction of anesthesia (control level), three minutes after intubation, three minutes after incision, three minutes after sternotomy, and immediately before cannulation of the great vessels.

The study population was divided randomly into two groups. Group 1 (17 patients) received sufentanil for anesthesia. With the patient breathing 100% O_2 by face mask, pancuronium (2.0 mg) was given intravenously. Sufentanil was given intravenously over three minutes to a total dose of 15 to 20 μg/kg. This dose range of sufentanil was selected to correspond to about 150 μg/kg of fentanyl. Ventilation was assisted when the patient failed to respond to the command "take a deep breath." At this point, the remaining total dose of pancuronium (0.12 to 0.15 mg/kg) was administered intravenously for muscle relaxation and to facilitate tracheal intubation. Pancuronium and sufentanil were given within the range quoted according to the anesthesiologist's assessment of the patient's clinical condition. Additional sufentanil was given in increments of 50 μg intravenously every 45 minutes throughout the operation for maintenance of anesthesia; sufentanil supplements were administered sooner if clinical signs associated with decreased level of anesthesia were observed, such as diaphoresis and increase in HR and/or BP of 20% above control. Group 2 (12 patients) received halothane for anesthesia. With the patient breathing 100% O_2 by face mask, 2.0 mg of pancuronium was administered intravenously. Sodium thiopental was slowly administered intravenously (range, 3 to 5 mg/kg) until the patient became unconscious. Ventilation was then assisted with 50% O_2 and 50% N_2O. Halothane was added to this mixture starting at 0.5% and increasing the concentration to 3%, stopping if BP decreased 20%. The remaining pancuronium of the total dose of 0.12 to 0.15 mg/kg was given after loss of consciousness for muscle relaxation to facilitate tracheal intubation. Anesthesia was maintained with N_2O/O_2 (50%/50%) and halothane (0.5% to 1%); however, the concentration of halothane was increased or decreased (0.5% to 3%) to control levels, and according to the change in blood pressure.

For both groups the trachea was intubated five to seven minutes after the start of anesthesia. All patients had an orogastric sump catheter and a urinary catheter inserted after tracheal intubation.

Ventilation was adjusted by arterial blood gas analysis so that $PaCO_2$ was 30 to 35 mm Hg; PaO_2, >100 mm Hg; and pH, 7.35 to 7.45.

For the group of patients given sufentanil, an increase in SBP or DBP of 20% from control levels was treated in this order: sufentanil (50 μg,

intravenously); nitroglycerin (0.2 mg, intravenously), repeated if the pressure elevation persisted, and (if these measures failed to control the BP); sodium nitroprusside infusion (10 to 300 μg/min) was started and continued to maintain the BP at ± 10% control level.

For the patients given halothane anesthesia, a rise in SBP or DBP of 20% was treated by increasing the concentration of halothane. If an inspired concentration up to 3% failed to control the increase of BP, then nitroglycerin and nitroprusside were used as described for the sufentanil group.

A decrease of SBP to <90 mm Hg or DBP to <60 mm Hg in the sufentanil group was first treated by placing the patient in a 15° head-down position. If this did not restore the pressure, then a rapid infusion of 100 to 200 mL of lactated Ringer's solution was administered. If this did not restore the arterial pressure, then phenylephrine (10 to 20 μg) was administered and repeated as necessary. The only difference in the management of hypotension for the halothane group was that the halothane concentration was reduced first.

An increase in HR to >110/min in both groups was evaluated in conjunction with an alteration in BP. If the increase in HR occurred with an increase in BP, the first treatment was additional anesthetic (sufentanil, 50 μg, intravenously) for the group given sufentanil and an increase in halothane concentration for the halothane group. If the increase in HR persisted or if the increase in HR occurred without increase in BP, then propranolol (1 to 3 mg, intravenously) was given.

Recovery time was considered as the time from the patients' arrival in the Intensive Care Unit until they responded to verbal commands by opening their eyes and moving their extremities. Time was recorded from the patient's arrival in the Intensive Care Unit.

Artificial ventilation was discontinued when the patient was able to generate a vital capacity of about 1,000 mL and an inspiratory pressure of −20 mm Hg and time to extubation was recorded. Postoperatively, all patients were questioned about awareness during surgery.

Differences between groups with respect to sex, ASA physical status, and beta adrenergic blockade use were tested by Fisher's exact test.[11]

Age, weight, and cardiovascular control parameters were evaluated using analysis of variance followed by the least significant difference test to make pairwise treatment group comparisons.

Calculation of percent change from control for subsequent measurements followed by analysis of variance followed by least significant difference test was used to compare hemodynamic variables within and between groups.

Results were reported as statistically significant if the two-tailed *P* value does not exceed 0.05. This level of significance is "protected" by a preliminary statistical test (analysis of variance), which must be significant at the 0.05 level before any pairwise treatment comparisons can be made.

Table 1. *Patient characteristics*

	Sufentanil	Halothane
Number of patients	17	12
Male	17	11
Female	0	1
Age (yr)	55.4 ± 6.6	53.9 ± 8.5
Weight (kg)	84.5 ± 12.3	83.3 ± 14.1
ASA class IV	17	12
Duration of anesthesia (hr)	3.8 ± 0.7	3.8 ± 0.7

Data presented as mean ± standard deviation.
No statistically significant difference between the two groups.
ASA = American Society of Anesthesiologists.

Results

Patient characteristics for the two groups are listed in *Table 1*. The results of hemodynamic changes at different measurement points are presented in *Table 2* and graphically in the *Figure*. Significant changes both within and between groups are noted for HR, SBP, DBP, PCWP, CI, and SVR.

Seven patients in the sufentanil group and 9 patients in the halothane group were receiving beta adrenergic blocking agents preoperatively. There was no significant difference in any of the measured cardiovascular variables when these patients were compared to others in their group not receiving beta adrenergic blocking agents.

The incidence of use of vasoactive agents in the two groups is listed in *Table 3*. None of the 9 patients given halothane who received preoperative beta adrenergic blocking drugs required vasopressors intraoperatively (compared with 2 of 3 patients given halothane who did not receive beta adrenergic blocking drugs preoperatively); this probably represents a chance finding because of the number of statistical tests performed and the small sample size.

Table 2. Hemodynamic changes during administration of sufentanil (SF)/pancuronium and halothane (HA)/pancuronium

		Control level	Intubation + 3 min	Postincision + 3 min	Sternotomy + 3 min	Precannulation
HR	HA	60.4 ± 11.1	82.9 ± 15.2†	78.2 ± 11.8†	76.3 ± 10.1†	80.3 ± 11.0†
	SF	63.5 ± 10.5	85.8 ± 20.3†	81.4 ± 15.6†	85.4 ± 21.5†	90.9 ± 17.7†
SBP	HA	129.9 ± 30.5	126.4 ± 15.1	114.7 ± 15.2	107.3 ± 15.5[b]*	112.0 ± 9.9
	SF	140.7 ± 18.7	138.8 ± 25.2	136.9 ± 18.8	137.8 ± 15.5[a]	129.9 ± 17.8
DBP	HA	68.5 ± 14.8	74.4 ± 11.7	70.8 ± 10.7	69.3 ± 10.1	64.0 ± 7.7
	SF	73.6 ± 8.5	75.8 ± 14.6	75.8 ± 13.1	78.6 ± 6.9*	70.0 ± 12.0
MAP	HA	84.8 ± 18.6	90.8 ± 12.3	85.4 ± 11.5	82.3 ± 12.1	80.3 ± 7.3
	SF	94.5 ± 9.6	95.5 ± 16.9	95.9 ± 14.2	97.1 ± 8.5	86.2 ± 8.1*
MRAP	HA	7.2 ± 3.9	10.5 ± 4.9	10.1 ± 4.4	10.7 ± 4.0	8.8 ± 3.3
	SF	6.2 ± 3.2	9.4 ± 3.7*	7.9 ± 2.5*	7.5 ± 3.0	6.7 ± 2.8
PCWP	HA	12.7 ± 5.0	16.2 ± 4.5*	16.6 ± 5.8*	14.5 ± 4.2	13.4 ± 5.1
	SF	9.8 ± 4.6	11.5 ± 4.0	10.8 ± 3.1	8.5 ± 2.9	8.7 ± 2.3
CO	HA	4.55 ± 1.11	4.92 ± 1.13	4.32 ± 1.12[a]	3.74 ± 0.84[a]†	5.19 ± 1.15
	SF	5.05 ± 1.25	6.21 ± 1.76†	6.04 ± 1.94[b]†	4.82 ± 1.70[b]†	5.26 ± 1.32
CI	HA	2.36 ± 0.60	2.56 ± 0.68	2.22 ± 0.53[a]	1.93 ± 0.39[a]†	2.71 ± 0.74
	SF	2.51 ± 0.54	3.12 ± 0.90†	3.03 ± 0.95[b]†	3.16 ± 0.90[b]†	2.63 ± 0.62
SVR	HA	1,414 ± 440	1,367 ± 404	1,469 ± 376	1,577 ± 327	1,157 ± 316
	SF	1,507 ± 554	1,207 ± 468	1,307 ± 510	1,238 ± 407	1,282 ± 341

[a,b] Different letters for means at the same observation point indicate a significant between-group difference, $P \leq 0.05$.
* Significantly different from control, $P \leq 0.05$.
† Significantly different from control, $P \leq 0.01$.
Data presented as mean ± SD.
HR = heart rate, *SBP* = systolic blood pressure, *DBP* = diastolic blood pressure, *MAP* = mean arterial pressure, *MRAP* = mean right arterial pressure, *PCWP* = pulmonary capillary wedge pressure, *CO* = cardiac output, *CI* = calculated cardiac index, *SVR* = systemic vascular resistance.

The median recovery time for the sufentanil group was 3.5 hours, significantly higher ($P < 0.01$) than the halothane group (2.7 hours). The median time to extubation in the sufentanil group was 16.5 hours, significantly higher ($P < 0.01$) than the halothane group (11 hours).

Discussion

The use of opioids for cardiovascular anesthesia has increased over the last decade.[12] This can be attributed to the development and use of fentanyl, which has several advantages compared to morphine. These include a higher safety margin, shorter duration of action, minimal cardiovascular effects, and attenuation of stress responses seen with operative stimuli.[13–16] The initial reports from Europe claimed that sufentanil, as an anesthetic for patients with cardiovascular disease, was superior to fentanyl in ability to minimize hemodynamic changes.[9,17–19] However, in this study, significant changes in HR and BP occurred within and between both groups. The significant increase in HR seen in both groups was surprising, since both halothane and sufentanil are known to decrease HR,[3,20] and particularly since about half the patients in both groups received beta adrenergic blocking agents preoperatively including the morning of surgery.

Increases in HR are known to occur during the induction of anesthesia and intubation.[21] Although narcotics can blunt this autonomic response, increases in HR were reported during fentanyl anesthesia even when large doses were used, especially when associated with the use of pancuronium for muscle relaxation.[22,23] Sebel and Bovill[17] reported increased HR in 16/30 patients they studied during sufentanil anesthesia. The increased HR seen in both groups of this study probably is related to the vagolytic and sympathetic stimulant effects of pancuronium.[24,25] Later studies by our group of similar patients demonstrated that the increase in HR and BP during sufentanil anesthesia was significantly less when metocurine was used as a muscle relaxant.[26] However, we cannot exclude the possibility that the early use of a vasodilator indirectly contributed to the increased HR by a reflex mechanism.

We could find little significant difference in the comparison between patients who received beta adrenergic blocking agents preoperatively and those who did not (*Table 3*). However, we

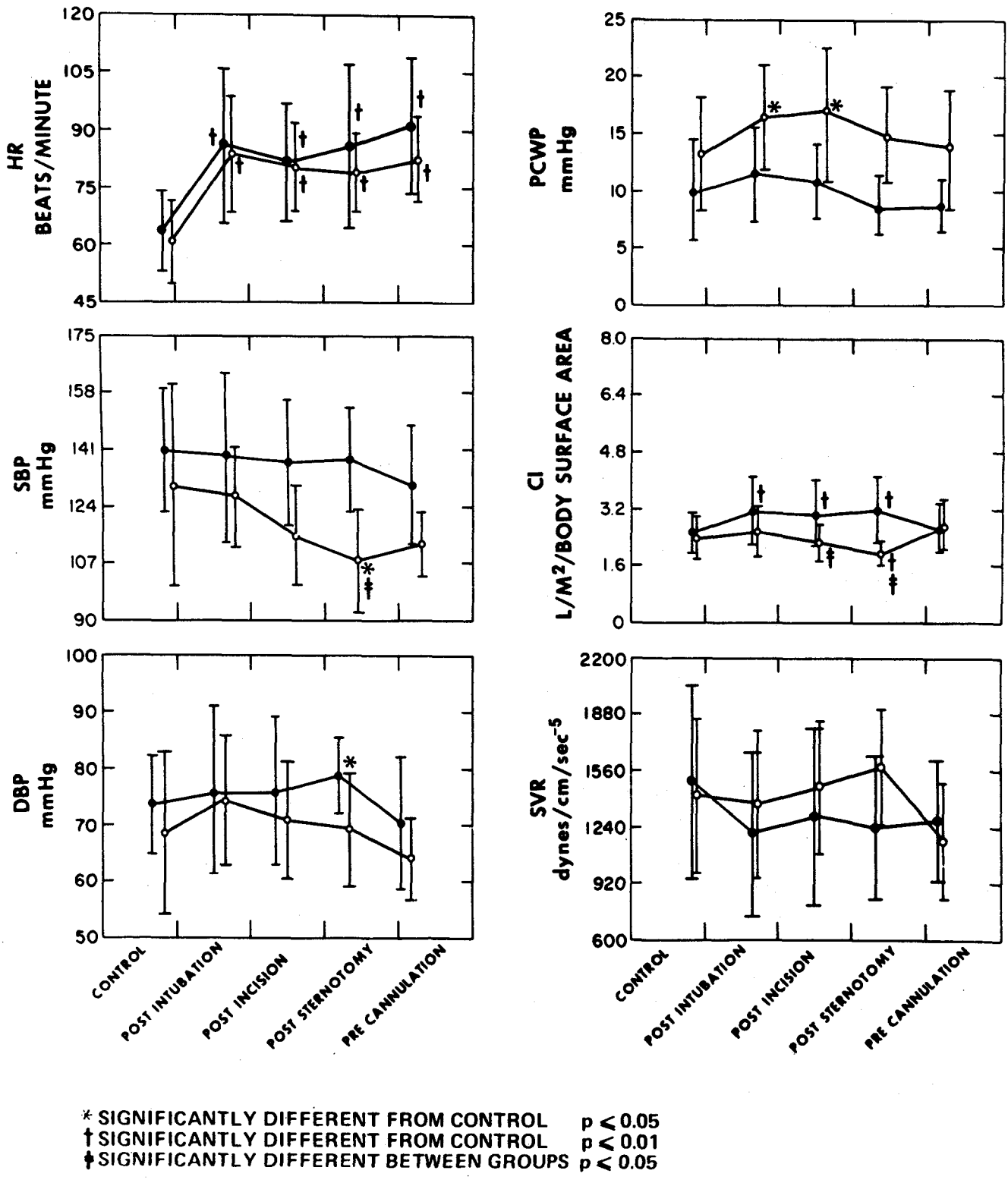

Fig. Changes in cardiovascular variables during sufentanil/pancuronium anesthesia (●) versus halothane/pancuronium anesthesia (○) in patients undergoing coronary artery surgery. *HR* = heart rate, *PCWP* = pulmonary capillary wedge pressure, *SBP* = systolic blood pressure, *CI* = cardiac index, *DBP* = diastolic blood pressure, *SVR* = systemic vascular resistance.

Table 3. Effect of preoperative beta adrenergic blockade on intraoperative vasodilators, vasopressors, and propranolol

	No. of patients	Vaso-dilator	Propran-olol	Vaso-pressor
Sufentanil	17			
Preoperative propranolol	7	7	2	1
None	10	9	6	1
Halothane	12			
Preoperative propranolol	9	9	3	0*
None	3	3	2	2

* The only statistically significant (p 0.05) finding of 16 tests, which may be a chance finding.

did not study the degree of beta adrenergic sympathetic blockade preoperatively, and the number of patients studied in each subgroup was small.

Increases in BP are not obvious from the measurements presented; however, they are inferred by the large numbers of patients in both groups treated with vasodilators (*Table 3*). Significant increases in BP during sufentanil anesthesia were also observed by Sebel and Bovill.[17] Clinically, sufentanil did not decrease the BP when administered as incremental doses on the assumption that an increase in BP was due to "light" anesthesia. In fact, increases in BP with narcotic anesthesia may be a poor indicator of the need for additional narcotic.[27]

In contrast, in the halothane group, the rise in BP could have been controlled by increasing the halothane concentration alone. However, the time required for halothane to decrease the BP was usually longer than what we accepted in this study. Also, although high halothane concentration (up to 3%) was used initially to induce anesthesia and/or to control the BP, lower concentrations were used (0.75% to 1.0%) for maintenance.

We emphasize that treatment of significant changes in HR and BP was initiated usually within a few seconds. This may explain why 90% of the patients in both groups received a vasodilator (nitroprusside, nitroglycerin, or both, intravenously), to control the BP, and about 30% of the halothane group and 50% of the sufentanil group received beta adrenergic blocking agents to control increases in the HR. However, it is obvious that neither sufentanil nor halothane completely blocked hemodynamic responses to stimuli.

With our protocol for halothane, there was a pronounced difference between the effect of halothane and sufentanil on the CI and PCWP. In the sufentanil group, the CI was significantly higher than control at the postintubation, postincision, and poststernotomy measurements, and significantly higher than the CI for the patients given halothane at the postincision and poststernotomy measurements. Nevertheless, in the halothane group the PCWP was only significantly higher than control at two measurement points (postintubation and postincision). However, the frequent use of vasodilators in both groups may have affected these results. Afterload reduction could have minimized the decrease in CI associated with halothane anesthesia, and may have emphasized the lack of myocardial depression seen in the sufentanil group.

None of the patients in either group had any recall of intraoperative events. However, because of the small number of patients studied, we cannot conclude that recall will not occur with sufentanil anesthesia.

In the sufentanil group, the median time to extubation was 16 hours, significantly longer than in the halothane group. Since sufentanil has a shorter half-life and faster elimination time than fentanyl,[4,5] we anticipated a shorter extubation time compared to that reported for fentanyl.[28] However, we used a large dose of sufentanil (15 to 20 μg/kg) that corresponded to the large doses of fentanyl we used in a previous study. Further evaluation by our group has demonstrated that smaller doses of sufentanil (10 μg/kg) provided adequate anesthesia, faster postoperative return of consciousness, and shorter time to extubation.[29]

The protocol of the study did not allow flexibility to demonstrate maximal differences in HR, BP, and other cardiovascular variables because of the rapid treatment and control of these variables by the use of vasoactive substances. The differences have thus been blunted. This highlighted a difference in clinical practice between anesthesiologists and cardiologists. While cardiologists, during stress testing, allow the HR to reach 150/min for three minutes,[30] anesthesiologists treat much lower HR after shorter durations. In this study, we treated a rise in HR above 110/min for less than one minute. It is possible that such aggressive management by the anesthesiologist may represent overtreatment.[31]

Conclusion

Sufentanil provided adequate surgical anesthesia without recall of intraoperative events. Neither sufentanil nor halothane blocked increases in HR and BP, both required frequent treatment with vasodilator drugs and beta adrenergic blocking agents. This probably was related to the use of pancuronium bromide. Further studies by our group of sufentanil anesthesia in which we compared metocurine with pancuronium for muscle relaxation revealed more hemodynamic stability with metocurine.[26] However, in patients given sufentanil for anesthesia, CI was preserved and, in fact, increased, and the PCWP did not increase. This can be an advantage for patients with more compromised cardiovascular status. Finally, the dose and method of administration that result in adequate sufentanil anesthesia and minimal postoperative respiratory depression still need to be determined.

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