Drug Interactions with Sufentanil

Hemodynamic Effects of Premedication and Muscle Relaxants

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Induction of anesthesia with synthetic opioids is occasionally accompanied by undesirable hemodynamic changes such as tachycardia and hypertension, or bradycardia and hypotension. We hypothesized that drug interactions cause many of these adverse responses. Therefore, we conducted a randomized double-blind study to investigate the interactive effect of premedication and muscle relaxants on the hemodynamic response to induction with intravenous (iv) sufentanil 10 $\mu g \cdot kg^{-1}$. Eighty patients with left ventricular ejection fraction $\geq$ 0.40, undergoing elective coronary artery surgery, were premedicated with either morphine 0.1 mg·kg^{-1} and scopolamine 6 $\mu g \cdot kg^{-1}$ intramuscularly, or lorazepam 60 $\mu g \cdot kg^{-1}$ orally, and paralyzed with either pancuronium 0.1 mg·kg^{-1} or vecuronium 0.1 mg·kg^{-1} iv. The four treatment groups were SP (morphine–scopolamine + pancuronium), LP (lorazepam + pancuronium), SV (morphine–scopolamine + vecuronium), and LV (lorazepam + vecuronium). Hemodynamics were recorded at three time periods: 1) control, 2) induction, and 3) intubation. Premedication–relaxant interactions significantly affected hemodynamics. In group SP, mean heart rate (HR) increased significantly on induction (56 ± 11 to 69 ± 13 beats · min^{-1}), while mean arterial pressure (MAP) and cardiac index (CI) were unchanged. HR, MAP, and CI were significantly higher after induction in group SP compared to the other three groups. In group LP, mean HR increased less than in group SP (56 ± 8 to 62 ± 14 beats · min^{-1}), whereas MAP and CI declined significantly. In group SV, HR and CI were unchanged, but MAP declined significantly. In group LV, HR was stable, whereas both MAP and CI declined significantly. The incidence of pharmacologic interventions during the study period also differed significantly among groups. Intravenous β-adrenergic blocking agents were administered to 6 of 20 patients in group SP, 3 of 20 in group LP, 1 of 20 in group SV, and 0 of 20 in group LV (P = 0.02). Intervention with an iv β-adrenergic blocking agent, iv nitroglycerin, or a volatile anesthetic was required in 9 of 20 patients in group SP, 5 of 20 in group LP, 1 of 20 in group SV, and 2 of 20 in group LV (P = 0.009). Two patients, both in group SP, developed new ischemic ST-segment depression of $\geq$ 0.1 mV. Preoperative use of β-adrenergic blocking agents exerted a significant effect on hemodynamics. Mean HR was 6–7 beats · min^{-1} lower throughout the study in patients who were taking β-adrenergic blocking agents preoperatively (n = 49) compared to those who were not (n = 31) (P = 0.005). Drug interactions exert a significant and predictable effect on the hemodynamic response to induction of anesthesia with sufentanil. Careful consideration of potential drug interactions should decrease the incidence of undesirable hemodynamic responses to induction with opioids. (Key words: Anesthesia: cardiovascular. Anesthetics, intravenous: sufentanil. Drug interactions. Neuromuscular relaxants: pancuronium; vecuronium. Premedication: lorazepam; scopolamine.)

SYNTHETIC OPIOIDS are commonly used for induction of anesthesia in patients undergoing coronary artery surgery. The hemodynamic response to induction with opioids is variable and is influenced by several factors. We previously demonstrated that the chosen premedication, neuromuscular relaxant, and opioid all significantly influence the hemodynamic response to induction.[1-3] Others have shown the importance of antianginal medication and preoperative left ventricular function.[4,5] We believe that the interaction of these and other factors determines the hemodynamic response to induction of anesthesia in individual patients. This study was designed to demonstrate prospectively the range of hemodynamic responses resulting from the interaction of two of these variables: 1) type of premedication and 2) choice of neuromuscular relaxant. Because we used fentanyl in previous studies of these variables, we attempted to broaden our experience by using sufentanil in this investigation.

Materials and Methods

The Human Studies Committee of the University of Manitoba approved this protocol, and all patients gave written informed consent. We studied patients scheduled for elective coronary artery surgery whose resting ejection fraction was greater than 0.39. Patients with recent myocardial infarction and/or unstable angina were included if they had not required either continuous electrocardiographic (ECG) monitoring or intravenous (iv) infusion of antianginal medications during the 72 h prior to surgery. Other exclusion criteria were a history of substance abuse or chronic use of sedative–hypnotics. We randomly assigned patients to one of four groups, depending on the premedication–relaxant combination they were to receive:

Group SP: morphine–scopolamine + pancuronium
Group LP: lorazepam + pancuronium
Group SV: morphine–scopolamine + vecuronium
Group LV: lorazepam + vecuronium

MONITORING

Prior to induction of anesthesia, ECG leads II and CS_5 were applied and recorded continuously thereafter by a two-channel ambulatory ECG monitor (model A, Avionics). Venous, arterial, and pulmonary arterial catheters were inserted under local anesthesia. Oscilloscopic displays of ECG leads II and V5 were monitored continuously. End-tidal carbon dioxide tension was monitored continuously and ventilation adjusted to achieve normocapnia. Systemic arterial pressure, pulmonary arterial pressure, pulmonary artery wedge pressure, central venous pressure, and end-tidal carbon dioxide tension were recorded continuously by polygraph. Cardiac output was measured in triplicate by thermodilution, using 10 ml of room-temperature injectate.

ANESTHETIC TECHNIQUE

The night before surgery all patients received triazolam 6 $\mu g \cdot kg^{-1}$ orally and continued to receive their regular antianginal medications until the time of surgery. Ninety minutes before arrival in the operating room, each patient was given either lorazepam 60 $\mu g \cdot kg^{-1}$ orally or an identical placebo. Thirty minutes later they received an injection of either intramuscular morphine 0.1 mg $\cdot kg^{-1}$ plus intramuscular scopolamine 6 $\mu g \cdot kg^{-1}$, or placebo. Each patient received either lorazepam or morphine–scopolamine, but not both, in a double-blind fashion. Nasal oxygen 3 $l \cdot min^{-1}$ was begun when oral premedication or placebo was given, and was continued until induction of anesthesia. Prior to induction, the patients breathed 100% oxygen by mask, and control hemodynamics were measured after 5 min of hemodynamic stability was observed. Either pancuronium 20 $\mu g \cdot kg^{-1}$ iv or vecuronium 20 $\mu g \cdot kg^{-1}$ iv was then administered. Two minutes later, anesthesia was induced with sufentanil 10 $\mu g \cdot kg^{-1}$ iv given over 5 min. When the patients lost consciousness, an iv bolus of either pancuronium 80 $\mu g \cdot kg^{-1}$ or vecuronium 80 $\mu g \cdot kg^{-1}$ was administered, and positive pressure ventilation by mask was begun. The relaxants were comparably diluted and administered in a double-blind fashion.

After completion of the sufentanil infusion, hemodynamics were measured and endotracheal intubation accomplished. After intubation, a continuous iv infusion of either pancuronium 30 $\mu g \cdot kg^{-1} \cdot h^{-1}$ or vecuronium 100 $\mu g \cdot kg^{-1} \cdot h^{-1}$ was begun to prevent recovery of neuromuscular function and consequent defeat of the double-blind experimental design. Clinically important changes in hemodynamics were treated by administration of either vasoactive agents or volatile anesthetics. These pharmacologic interventions were made at the discretion of the attending anesthesiologist, rather than in accordance with predefined criteria. Neither additional sufentanil nor benzodiazepines were administered during the study period.

DATA COLLECTION

Upon their arrival in the operating room suite, one investigator saw all of the patients and quantified the degree of sedation and anxiety according to previously published objective criteria.[1] After the patients' transfer into the operating room, one investigator and the attending anesthesiologist independently graded the overall efficacy of the premedication as either excellent, good, fair, or poor. Hemodynamics and arterial carbon dioxide tension (Pa_{CO_2}) were measured at the following times: 1) prior to induction (control), 2) 1 min after completion of sufentanil infusion (induction), and 3) 1 min after intubation (intubation).

DATA ANALYSIS

Heart rate (HR), cardiac index (CI), and systemic vascular resistance index were calculated using standard formulae.[6] All the continuous ECG recordings were reviewed by one investigator (CLM), who was blinded with regard to the premedication–relaxant combination used for each patient. The ST-segment of the ECG was evaluated 0.06 s after the nadir of the S-wave. Myocardial ischemia was diagnosed when new ST-depression of ≥ 0.1 mV lasting for a minimum of 30 s was observed in either ECG lead II or CS_5. All potentially ischemic episodes were reviewed by a second investigator (IRT), who was also blind with respect to the treatment group. Unanimity between the two investigators was required for a diagnosis of myocardial ischemia.

STATISTICAL ANALYSES

We made intergroup comparisons of demographic data and event rates using analysis of variance (ANOVA) and X^2 analysis, respectively. Null hypotheses were rejected when P was less than 0.05. Hemodynamic variables and Pa_{CO_2} were compared by ANOVA for repeated measures. When ANOVA for repeated measures revealed significant effects ($P < 0.05$), we used the least squares means test to make appropriate multiple comparisons. We applied Bonferroni's correction and regarded corrected P values of less than 0.025 for intragroup comparisons *versus* control and 0.008 for intergroup comparisons as significant.

Results

Eighty patients, 20 in each group, participated in the study. The four groups did not differ significantly with respect to age, weight, sex, antianginal medication, preoperative HR and blood pressure, ejection fraction, left

TABLE 1. Demographics and Preoperative Hemodynamics

	Group			
	SP	LP	SV	LV
Age (yr)	62 ± 9	60 ± 7	61 ± 9	67 ± 9
Weight (kg)	79 ± 11	80 ± 12	77 ± 16	80 ± 16
Sex (M/F)	19/1	15/5	14/6	17/3
Preoperative antianginal therapy				
β-Adrenergic blocking agent (n)	10	16	12	11
Ca^{2+}-entry blocking agent (n)	19	14	17	14
Nitrate (n)	16	12	13	14
Systolic arterial pressure (mmHg)	128 ± 22	124 ± 16	122 ± 16	126 ± 15
Diastolic arterial pressure (mmHg)	76 ± 10	75 ± 9	75 ± 10	71 ± 15
Heart rate (beats · min^{-1})	64 ± 10	62 ± 13	61 ± 8	64 ± 7
Left ventricular ejection fraction	0.64 ± 0.14	0.62 ± 0.13	0.59 ± 0.14	0.67 ± 0.12
Left ventricular end-diastolic pressure (mmHg)	16 ± 9	15 ± 6	16 ± 9	17 ± 5
Coronary anastomoses (per patient)	3.5 ± 1.1	3.5 ± 1.2	3.9 ± 1.0	3.6 ± 0.6

Values are mean ± SD.

SP = morphine–scopolamine + pancuronium; LP = lorazepam + pancuronium; SV = morphine–scopolamine + vecuronium; LV = lorazepam + vecuronium.

ventricular end-diastolic pressure, or the number of distal coronary artery grafts (table 1).

SEDATION AND ANXIETY

The type of preanesthetic medication (morphine–scopolamine *versus* lorazepam) did not influence the degree of anxiety or sedation objectively assessed on arrival in the operating room. The overall efficacy of the two premedications, graded subjectively by either the investigator or the attending anesthesiologist, was similar. We do not present these data in detail because they are essentially identical to our previous results.[1] However, in contrast to our previous findings, control Pa_{CO_2} was significantly higher in patients premedicated with morphine–scopolamine compared to those given lorazepam (44 ± 4 *vs.* 41 ± 5 mmHg).

HEMODYNAMICS

The hemodynamic data at control, induction, and intubation are summarized below and in table 2. Figures 1–3 demonstrate the changes in HR, mean arterial pressure (MAP), and CI occurring at induction and intubation.

Heart Rate: HR increased significantly in groups SP and LP, but no change was noted in either group SV or LV. The greatest increase was seen in group SP, where HR after induction was significantly higher than in the other three groups. The HR after induction was higher in group LP compared to groups SV and LV. There was considerable interpatient variability in the HR response to induction and intubation. Figure 4 shows the change in HR between control and intubation for each patient in the study.

Mean Arterial Pressure: In group SP, MAP was unchanged after induction. Significant and quantitatively similar decreases in MAP were noted in groups LP, SV, and LV. After induction, MAP was significantly higher in group SP compared to the other three groups.

Cardiac Index: Premedication with lorazepam was associated with significant decreases in CI on induction. CI decreased significantly in groups LP and LV but was unchanged in groups SP and SV. After induction, CI was significantly higher in group SP, compared to the other three groups.

Systemic Vascular Resistance: Significant decreases in systemic vascular resistance index followed induction in all groups except group LV. There were no significant intergroup differences in systemic vascular resistance index.

Pulmonary Artery Wedge Pressure: Significant decreases in pulmonary artery wedge pressure followed induction in all groups. In group LP, the pulmonary artery wedge pressure was significantly lower at control compared to groups SP and SV.

Central Venous Pressure: In group LP, the central venous pressure was significantly lower at control, compared to the other three groups. Very small, but statistically significant, changes in central venous pressure were noted in groups SP and LP.

INTERVENTIONS

Table 3 indicates the frequency with which the attending anesthesiologist administered either vasoactive drugs or volatile anesthetics between the start of induction and the commencement of surgery. The need for β-adrenergic blocking agents was significantly influenced by treatment group: it was greatest in group SP (6 of 20) and least in

TABLE 2. Hemodynamics

	Group	Control	Induction	Intubation
Heart rate (beats · min⁻¹)	SP	56 ± 11	69 ± 13*	69 ± 12*
	LP	56 ± 8	62 ± 14*†	61 ± 12*†
	SV	53 ± 9	54 ± 7†‡	52 ± 7†‡
	LV	55 ± 7	52 ± 8†‡	51 ± 8†‡
Mean arterial pressure (mmHg)	SP	96 ± 14	91 ± 16	90 ± 17
	LP	95 ± 12	80 ± 15*†	83 ± 13*
	SV	91 ± 16	79 ± 10*†	79 ± 12*†
	LV	93 ± 8	81 ± 13*†	81 ± 12*†
Central venous pressure (mmHg)	SP	9 ± 3	9 ± 2	8 ± 2*
	LP	7 ± 3	8 ± 2*	7 ± 2
	SV	9 ± 3‡	9 ± 2	8 ± 2
	LV	9 ± 3†	10 ± 2	9 ± 2‡
Pulmonary artery wedge pressure (mmHg)	SP	16 ± 5	14 ± 4*	12 ± 4*
	LP	12 ± 4†	11 ± 3	10 ± 3*
	SV	15 ± 5‡	12 ± 3*	11 ± 3*
	LV	15 ± 4	13 ± 3	12 ± 3*
Cardiac index (l · min⁻¹ · m⁻²)	SP	2.48 ± 0.38	2.50 ± 0.58	2.64 ± 0.44
	LP	2.45 ± 0.39	2.24 ± 0.37*†	2.27 ± 0.49†
	SV	2.34 ± 0.52	2.22 ± 0.39†	2.21 ± 0.34†
	LV	2.33 ± 0.40	2.08 ± 2.13*†	2.13 ± 0.40*†
Systemic vascular resistance index (dyn · s · cm⁻⁵ · m²)	SP	2870 ± 660	2700 ± 540	2520 ± 500*
	LP	2960 ± 580	2620 ± 600*	2750 ± 590
	SV	2890 ± 670	2610 ± 550*	2600 ± 540*
	LP	2980 ± 590	2830 ± 700	2770 ± 610

Values are mean ± SD.

SP = morphine–scopolamine + pancuronium; LP = lorazepam + pancuronium; SV = morphine–scopolamine + vecuronium; LV = lorazepam + vecuronium.

* $P < 0.025$ versus control.
† $P < 0.008$ versus SP.
‡ $P < 0.008$ versus LP.

group LV (0 of 20). In group SP, 9 of 20 patients required a β-adrenergic blocking agent, nitroglycerin, or a volatile anesthetic during the study period, compared to 5 of 20 in group LP, 1 of 20 in group SV, and 2 of 20 in group LV ($P = 0.009$). The frequency with which either atropine or phenylephrine was administered did not differ significantly between groups.

ISCHEMIA

Two patients in group SP developed new ECG changes indicative of myocardial ischemia during induction and intubation. In both patients, onset of ischemia was associated with increased HR, from 51 beats · min⁻¹ at control to 71 beats · min⁻¹ after intubation in one patient and
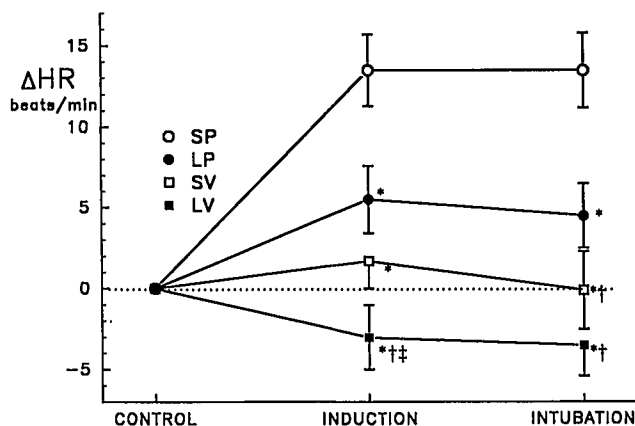

FIG. 1. Change in heart rate (ΔHR) in the four treatment groups (mean ± SEM). *$P < 0.008$ versus group SP. †$P < 0.008$ versus group LP. ‡$P < 0.008$ versus group SV. SP = morphine–scopolamine + pancuronium; LP = lorazepam + pancuronium; SV = morphine–scopolamine + vecuronium; LV = lorazepam + vecuronium.
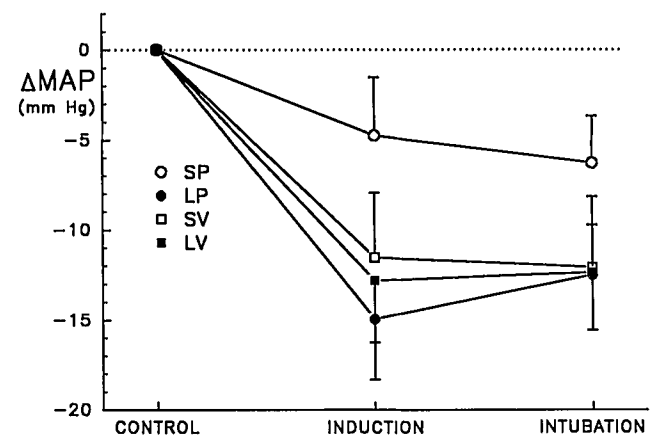

FIG. 2. Change in mean arterial pressure (ΔMAP) in the four treatment groups (mean ± SEM). ANOVA revealed no significant intergroup differences. SP = morphine–scopolamine + pancuronium; LP = lorazepam + pancuronium; SV = morphine–scopolamine + vecuronium; LV = lorazepam + vecuronium.
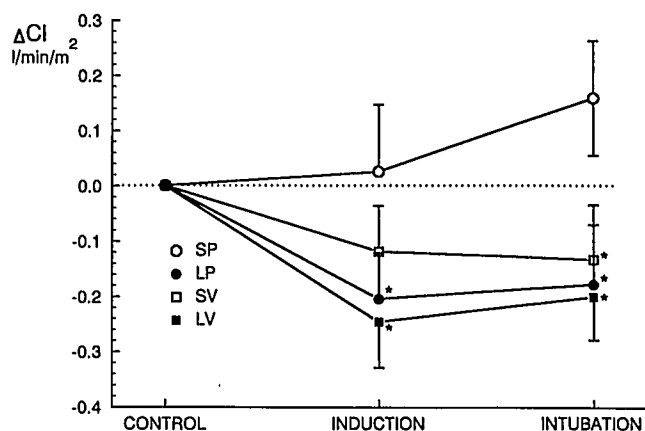
FIG. 3. Change in cardiac index (ΔCI) in the four treatment groups (mean ± SEM). *$P < 0.008$ versus group SP. SP = morphine–scopolamine + pancuronium; LP = lorazepam + pancuronium; SV = morphine–scopolamine + vecuronium; LV = lorazepam + vecuronium.

TABLE 3. Pharmacologic Interventions

	Group				
	SP	LP	SV	LV	P*
β-adrenergic blocker	6	3	1	0	0.022
Nitroglycerin	4	4	1	2	NS
Volatile anesthetic	2	0	0	1	NS
Either 1, 2, or 3	9	5	1	2	0.009
Phenylephrine	2	6	6	6	NS
Atropine	0	1	3	0	NS
Either 5, or 6	2	6	6	6	NS

SP = morphine–scopolamine + pancuronium; LP = lorazepam + pancuronium; SV = morphine–scopolamine + vecuronium; LV = lorazepam + vecuronium; NS = no significant difference.

* The probability that the null hypothesis is correct by X^2 analysis of a 4 × 2 contingency table.

from 49 to 77 beats·min^{-1} in the other. New ischemia was not observed in any other patients. The incidence of new myocardial ischemia did not differ significantly between groups.

PREOPERATIVE β-ADRENERGIC BLOCKADE

Retrospective analysis revealed that preoperative β-adrenergic blockade had a highly significant effect on HR ($P = 0.005$) throughout the study. Mean HR was 6–7 beats·min^{-1} lower, at all time periods, in patients who were taking β-adrenergic blocking agents preoperatively (n = 49), compared to those who were not (n = 31). We then examined how this effect might extend the range of hemodynamic responses produced by premedication–relaxant interactions. In figure 5, the HR response to induction and intubation in group SP patients who were not receiving preoperative β-adrenergic blocking agents is compared to that of group LV patients who were taking β-adrenergic blocking agents. Mean HR in the two groups

differed by 6 beats·min^{-1} at control and 25 beats·min^{-1} after induction.

Preoperative therapy with β-adrenergic blocking agents tended to influence the rate of pharmacologic intervention during the study, although not significantly. For example, 7 of 10 patients who required iv β-adrenergic blocking agents during induction were not taking β-adrenergic blocking agents preoperatively (5 of 6 in group SP, 2 of 3 in group LP, and 0 of 1 in group SV) ($P = 0.07$). Similarly, 10 of the 17 patients who required an iv β-adrenergic blocker, iv nitroglycerin, or a volatile agent were not taking β-blockers preoperatively (6 of 9 in group SP, 2 of 5 in group LP, 0 of 1 in group SV, and 2 of 2 in group LV) ($P = 0.10$). In contrast, 16 of 20 patients who required phenylephrine during the study were taking β-adrenergic blocking agents preoperatively ($P = 0.08$).

Discussion

When using synthetic opioids for induction of anesthesia in patients undergoing coronary artery surgery, the anesthesiologist also selects premedication and a muscle relaxant. This study indicates how these drugs interact
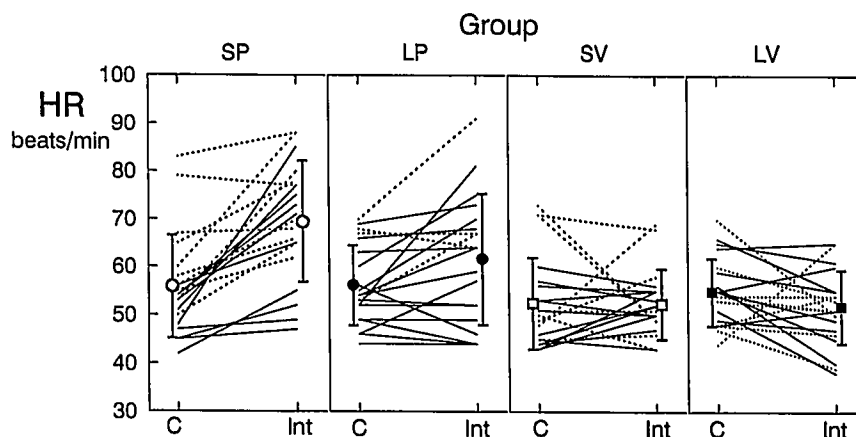

FIG. 4. Heart rate changes between control and intubation for all 80 patients, by treatment group. Solid lines indicate patients who were, and dashed lines those who were not, receiving β-adrenergic blocking agents preoperatively. Mean ± SD for each group is also indicated. C = control; Int = intubation. SP = morphine–scopolamine + pancuronium; LP = lorazepam + pancuronium; SV = morphine–scopolamine + vecuronium; LV = lorazepam + vecuronium.
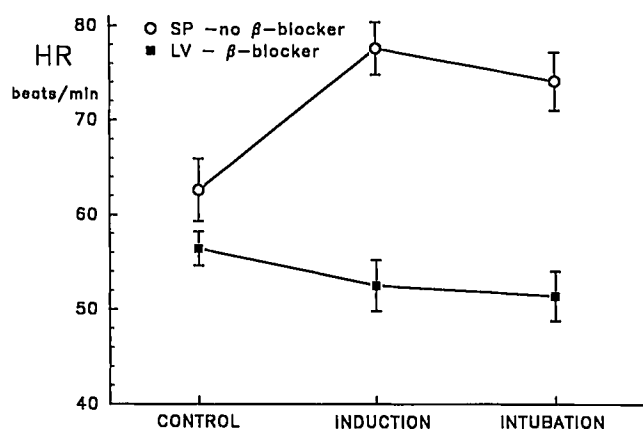
FIG. 5. Heart rates in group SP patients who were not receiving β-adrenergic blocking agents preoperatively and in group LV patients who were receiving β-adrenergic blocking agents preoperatively (mean $\pm$ SEM). A statistical analysis was not performed. SP = morphine-scopolamine + pancuronium; LV = lorazepam + vecuronium.

to influence the hemodynamic response to induction of anesthesia with sufentanil. Three important circulatory variables, HR, MAP, and CI, were significantly affected by premedication–relaxant interactions. Four distinct patterns of cardiovascular response were observed. In group SP, mean HR increased by 13.6 $\pm$ 10.4 beats $\cdot$ min^{-1} while MAP and CI were stable. In group LP, HR increased only 4.5 $\pm$ 9.0 beats $\cdot$ min^{-1}, and significant decreases in MAP and CI were observed. In group SV, HR and CI were stable, but MAP decreased significantly. Finally, in group LV, HR was unchanged while MAP and CI decreased significantly.

A major finding of this study is that the combination of scopolamine premedication with the muscle relaxant pancuronium (group SP) produces a hyperdynamic circulatory response during induction of anesthesia with sufentanil. After induction and intubation, HR, MAP, and CI were significantly higher in group SP than in any of the other three groups. This hyperdynamic response would have been greater had the attending anesthesiologists not intervened and treated 9 of 20 group SP patients with a combination of β-blockers, nitroglycerin, or volatile anesthetics (table 3). New myocardial ischemia was noted exclusively in group SP, although this finding was not statistically significant ($P = 0.06$). These findings are consistent with a previous study in which we noted that the combination of scopolamine and pancuronium was associated with tachycardia and myocardial ischemia during induction of anesthesia with fentanyl.[2] Other investigators have observed similar hyperdynamic responses to scopolamine–pancuronium.[7–9] A specific drug interaction involving scopolamine and pancuronium is clearly operative. The opioid may also participate in the interaction.[10]

The mechanism of the resulting sympathomimetic response is unclear but presumably involves muscarinic blockade at multiple sites in the autonomic nervous system.[11] The combination of scopolamine and pancuronium should be avoided during induction of anesthesia with opioids in patients for whom an increase in HR is undesirable.

The combination of lorazepam premedication with pancuronium was also associated with a unique cardiovascular response to induction with sufentanil. Although HR increased significantly in group LP in response to induction and intubation, the average change of six beats $\cdot$ min^{-1} was relatively small. The resultant HR in group LP was significantly lower than that in group SP and significantly higher than that in groups SV and LV. The MAP declined significantly after induction in group LP and was significantly lower than in group SP but not different from groups SV and LV. Other investigators have noted similar responses with this premedication–relaxant combination.[12–14] Presumably, the sympatholytic interaction of benzodiazepines and opioids[15] attenuates the sympathomimetic effects of pancuronium.

The results from groups SP and LP help resolve a longstanding controversy regarding the use of pancuronium during opioid anesthesia in patients undergoing coronary artery surgery. This study prospectively demonstrates that the hemodynamic response to administration of an opioid and pancuronium depends upon the choice of premedication. The hyperdynamic circulatory response to pancuronium is greater in patients who have been premedicated with scopolamine. Pharmacologic intervention is frequently required to attenuate this hyperdynamic response, especially in patients who are not taking β-adrenergic blocking agents preoperatively. In patients who have been premedicated with lorazepam, the circulatory response to pancuronium is less acute. Although prospective documentation is lacking, the hyperdynamic response to scopolamine–pancuronium appears to be somewhat attenuated if a benzodiazepine is added to the premedication regimen.[16,17] Similarly, intravenous administration of sedative–hypnotic agents during induction substantially blunts the hyperdynamic response to scopolamine–pancuronium.[18,19]

The hemodynamic responses to induction in groups SV and LV were remarkably similar. Both combinations were associated with stable HR and significant decreases in MAP. Although CI decreased in group LV and not in group SV, the intergroup differences were not significant. The similarity between groups SV and LV is surprising, because it indicates that premedication exerts a minimal effect on the hemodynamic response to induction with sufentanil–vecuronium. In this and other studies, premedication has been shown to significantly alter the he-

modynamic response to induction with sufentanil–pancuronium, fentanyl–atracurium, and sufentanil–succinylcholine.[1,20] We hypothesize that premedication exerts its hemodynamic effects by interacting with other drugs that affect the autonomic nervous system, such as opioids, succinylcholine, or pancuronium. Accordingly, in groups SP and LP, premedication might have interacted with both sufentanil and pancuronium, thus exerting a substantial effect. However, since vecuronium has no autonomic side effects,[21] the influence of premedication in groups SV and LV was less. In fact, premedication probably did exert a small but significant effect on postinduction hemodynamics in groups SV and LV. Figure 1 shows the mean change in HR at induction and intubation in the four treatment groups, rather than the absolute values. A decrease in mean HR on induction occurred only in group LV, and this change was significantly different from that observed in group SV.

Our study design allowed us to quantify prospectively the range of hemodynamic responses produced by controlling two variables that influence the hemodynamic response to induction with opioids. However, by including a retrospective analysis of the effect of preoperative β-adrenergic blockade, we were able to examine the combined effect of three variables. Although the effect of each variable is relatively small, their cumulative effect is substantial. As illustrated in figure 5, the combined effects of premedication, relaxant, and β-adrenergic blockade alter postinduction HR by an average of 25 beats · min^{-1}. Ideally, the additional effect of β-adrenergic blockade should have been assessed prospectively. However, the compatibility of the observed effect with the pharmacology of β-adrenergic blocking agents supports the validity of our retrospective analysis.

The incidence of preoperative β-adrenergic blockade did not differ significantly between groups. However, 80% of patients in group LP were taking β-adrenergic blocking agents preoperatively compared to 50% of those in group SP ($P = 0.10$). We wondered if this trend might explain the differing hemodynamic responses in groups SP and LP. Therefore, we compared the hemodynamic response to induction in patients from groups SP and LP who were receiving β-adrenergic blocking agents preoperatively. These groups differed significantly with respect to both HR and CI ($P = 0.004$ and $P = 0.02$ respectively). In group SP patients who were receiving β-adrenergic blocking agents (n = 10), the average HR increase at intubation was 15.6 ± 10.9 beats · min^{-1} compared to 4.7 ± 9.5 beats · min^{-1} in patients receiving these agents in group LP (n = 16). Similarly, CI increased 0.31 ± 0.35 l · min^{-1} in group SP β-blocker recipients and decreased 0.12 ± 0.44 l · min^{-1} in those in group LP. These changes in these β-blocked patients are virtually identical to those

observed in the groups as a whole. Therefore, it is extremely unlikely that intergroup differences in the incidence of preoperative β-adrenergic blockade significantly biased our hemodynamic results.

Some potential limitations of our study require discussion. First, we studied only a single dose of each premedication and relaxant, in combination with a single dose of sufentanil. However, we used moderate doses that reflect current clinical practice. If significant dose-related responses occur with the various agents used, then even larger effects might have been demonstrated at extremes of dosage. Second, almost 50% of our patients required acute pharmacologic intervention to treat hemodynamic disturbances during the study. Hemodynamic data from these patients have been included in our analyses. However, these pharmacologic interventions undoubtedly minimized the observed intergroup differences in hemodynamics. Therefore, our results underestimate the real magnitude of premedication–relaxant drug interactions.

Opioids are often used for induction of anesthesia in patients with cardiovascular pathology, with the expectation that their administration will be associated with hemodynamic stability. However, as our study demonstrates, the hemodynamic response to opioid administration is highly dependent on other variables. The combined effect of three variables, (premedication, relaxant, and β-adrenergic blockade) is analyzed above. Other variables, such as baseline left ventricular function,[5] premedication with α_2 adrenergic agonists,[22] concomitant administration of iv sedative–hypnotics,[15,18,19] and the specific opioid chosen[3] are also important. The dose, timing, and rate of administration of these various drugs are probably influential though their effects remain ill-defined.

We believe that the majority of adverse responses to opioids result from the cumulative effect of several variables on the hemodynamic response to induction. The hyperdynamic response to scopolamine–pancuronium is described above. Our data and experience suggest that severe tachycardia and myocardial ischemia with scopolamine–pancuronium are most likely when fentanyl is administered to patients with good left ventricular function who are not receiving β-adrenergic blocking agents.[2,10] Conversely, severe bradyarrhythmias and asystole have been reported to follow induction of anesthesia with opioids. Most frequently, this complication follows the combined iv administration of a benzodiazepine, sufentanil, and vecuronium to patients who are taking β-adrenergic blocking agents preoperatively.[23,24] Severe bradyarrhythmias after sufentanil–vecuronium are relatively infrequent when iv benzodiazepines are avoided. In our study, only 3 of 40 patients given sufentanil–vecuronium required atropine. Consideration of the poten-

tial interactions delineated in this study and those described by other investigators would make most adverse reactions to opioid administration predictable and therefore avoidable.

Our results indicate that the other components of an opioid-based anesthetic, specifically premedication and neuromuscular blockers, should not be selected in isolation. Instead, they must be chosen with regard to their interactions with each other and with other important variables, such as the presence or absence of preoperative β-adrenergic blockade. No single opioid-based anesthetic regimen will be suitable for all clinical scenarios. On the contrary, anesthetic management should be individualized. When planning an opioid anesthetic, we begin by evaluating preoperative drug therapy, baseline ventricular function, and resting hemodynamics. We then set hemodynamic goals that are appropriate for the patient's cardiovascular pathology. Finally, we choose a premedication–opioid–relaxant combination that is likely to achieve our hemodynamic goals in that patient.

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