

Ventilatory Compliance after Three Sufentanil-Pancuronium Induction Sequences

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Poor ventilatory compliance, a predictable side effect of high-dose opioid induction techniques, is purportedly blunted by pretreatment with nondepolarizing muscle relaxant. This study used both total compliance and a subjective compliance score to compare three different sequences of opioid induction using a 2-min infusion of sufentanil $3 \mu\text{g} \cdot \text{kg}^{-1}$. Nineteen patients in each of three groups received a total of $100 \mu\text{g} \cdot \text{kg}^{-1}$ of pancuronium, in the following randomized double-blinded fashion: control, all pancuronium 1 min after sufentanil; pretreated, 1 mg pancuronium 1 min before sufentanil and the balance of pancuronium 1 min after sufentanil; and mixed, all pancuronium mixed with sufentanil. Topical lidocaine prior to induction permitted early oral airway insertion midway through the sufentanil infusion. Immediately at the conclusion of sufentanil infusion, a tightly fitted mask, anterior jaw thrust, and mechanical ventilator permitted measurement of plateau airway pressure and exhaled volume in five replicates. Pressure and volume measurements were repeated 5 min later. Total compliance was calculated as the median plateau airway pressure divided into its associated exhaled volume. Groups did not differ in demographics. In one control patient and two pretreated patients hemoglobin oxygen saturation as measured by pulse oximetry decreased below 90%. Immediately after sufentanil infusion, the total compliance for control patients of $4.1 \text{ ml} \cdot \text{cmH}_2\text{O}^{-1}$ (mean [2.6-6.5, 95% confidence interval]) did not differ from that of the pretreated group ($6.3 [3.5-11.4] \text{ ml} \cdot \text{cmH}_2\text{O}^{-1}$), but the mixed group exhibited higher compliance ($40.3 [33.8-47.9] \text{ ml} \cdot \text{cmH}_2\text{O}^{-1}$) than the other groups ($P < 10^{-5}$). All groups achieved similar total compliances several minutes after a total of $100 \mu\text{g} \cdot \text{kg}^{-1}$ pancuronium had been administered. Subjective compliance scores (0, 1, 2, or 3) agreed with objective data in all comparisons. Pretreatment with pancuronium did not effectively prevent the difficulty in ventilation associated with anesthesia induction using moderate-dose sufentanil. However, concomitant infusion of sufentanil and pancuronium substantially improved compliance, measured both subjectively and objectively, without causing early paralysis in suitably premedicated patients. (Key words: Analgesics, opioid: sufentanil. Complications: airway obstruction; chest rigidity. Lungs: compliance. Neuromuscular relaxants: pancuronium. Ventilation: airway pressure.)

DIFFICULTY WITH VENTILATION often accompanies induction of anesthesia with high-dose opioids ($\geq 50 \mu\text{g} \cdot \text{kg}^{-1}$ fentanyl or equivalent).^{1,2} This difficulty has been ascribed to chest wall rigidity¹⁻³ or opioid-induced supra-

glottic airway obstruction.^{4,5} Regardless of mechanism, high-dose opioid induction produces impaired ventilatory compliance⁶ or even total inability to ventilate the lungs.^{1,4,7} Studies to date have documented ventilatory compliance subjectively without^{1,4,6-8} or with^{9,10} a scoring system.

Pretreatment with various substances, including benzodiazepines,¹¹ dopamine agonists,¹² serotonin antagonists,¹³ α_2 -adrenergic agonists,^{14,15} and nondepolarizing muscle relaxants^{3,8,16,17} may alleviate this problem. One popular scheme uses a small dose of nondepolarizing muscle relaxant.^{16,18} In a manner analogous to the use of defasciculating or priming doses of nondepolarizing muscle relaxants, this pretreatment dose may reduce the muscle activity that causes difficult ventilation without causing early paralysis.

Moderate-dose opioid anesthesia ($\approx 20 \mu\text{g} \cdot \text{kg}^{-1}$ fentanyl or equivalent)^{19,20} has become more popular, perhaps because of the perceived advantages of early extubation and economy. Difficult ventilation occurs with moderate-dose opioid anesthesia as well as with the high-dose technique. Does pretreatment with relaxant or a combination of relaxant with opioid ablate the ventilatory problem without engendering early paralysis? Does a subjective measure of difficult ventilation agree generally with an objective one? The authors sought answers to these questions concerning ventilatory difficulty accompanying moderate-dose sufentanil induction.

Materials and Methods

With institutional review board approval, 61 adult patients for cardiac surgery gave written, informed consent for induction of anesthesia with one of three schemes. Patients successfully enrolled in the study did not suffer from neuromuscular disease, chest wall deformity, morbid obesity, symptomatic pulmonary disease, chronic renal failure, or any other major systemic noncardiovascular disease. Prior thoracic surgery, the appearance or history of a difficult-to-manage airway, or age greater than 80 yr also served to exclude patients from participation.

All patients received intramuscular morphine $100 \mu\text{g} \cdot \text{kg}^{-1}$ and scopolamine $6 \mu\text{g} \cdot \text{kg}^{-1}$ at least 60 min prior to induction. Administration of concurrent oral medications continued through the morning of surgery. After application of finger pulse oximetry (Nellcor N-100, Hay-

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ward, CA) and an automatic noninvasive blood pressure cuff, but prior to placement of oximetry pulmonary arterial catheters, patients who displayed evidence of insufficient sedation received intravenous midazolam to supplement the preanesthetic medication. No benzodiazepine administration occurred within 15 min of induction of anesthesia. After establishment of hemodynamic monitors, an oropharyngeal spray of 10% lidocaine and a tongue blade coated with 5% lidocaine ointment (total topical dose ≈ 150 mg) provided anesthesia of the tongue and pharynx.

Inhalation with 100% oxygen *via* clear face mask occurred for 2 min prior to induction of anesthesia with one of three sequences (fig. 1), chosen randomly. The control group received 1 ml intravenous saline at the beginning of the induction sequence ($t = 0$), a 2-min infusion of $3 \mu\text{g} \cdot \text{kg}^{-1}$ sufentanil from $t = 1$ to $t = 3$ min, and $100 \mu\text{g} \cdot \text{kg}^{-1}$ pancuronium at $t = 4$ min. The pretreatment group received 1 mg intravenous pancuronium at $t = 0$, a 2-min infusion of $3 \mu\text{g} \cdot \text{kg}^{-1}$ sufentanil from $t = 1$ to $t = 3$ min, and the balance of pancuronium ($100 \mu\text{g} \cdot \text{kg}^{-1}$ less 1 mg) at $t = 4$ min. The protocol used a fixed pretreatment dose of pancuronium, 1 mg, rather than one based on body weight in the attempt to reproduce realistically the clinical application of this principle. The mixed group received saline at $t = 0$, a 2-min infusion of $3 \mu\text{g} \cdot \text{kg}^{-1}$ sufentanil mixed with pancuronium $100 \mu\text{g} \cdot \text{kg}^{-1}$ from $t = 1$ to $t = 3$ min, and 10 ml saline at $t = 4$. Addition of saline to coded syringes provided blinding of all clinical personnel as to the patient's assigned group: only the pharmacist, who randomized the groups and prepared the coded syringes, knew and recorded in sealed envelopes the group assignments. For each patient, the injection volumes were 1 ml for pretreatment, 20 ml for opioid \pm relaxant, and 10 ml for final relaxant or saline.

Between $t = 1$ and $t = 3$ (during sufentanil infusion), all patients received an oropharyngeal airway to ensure absence of tongue-induced airway obstruction. At $t = 3$, an anesthesiologist (J.T.A. or D.L.L.), manually ventilating the lungs *via* a semi-closed circle system, subjectively scored ventilatory compliance as one of the following: 0, cannot empty any air from breathing bag; 1, able to ventilate with more than ordinary effort; 2, able to ventilate

with usual effort; 3, near-effortless ventilation. Mechanical ventilation (Narcomed 2A, North American Dräger) *via* mask followed immediately, using a delivered tidal volume setting of $10 \text{ ml} \cdot \text{kg}^{-1}$ and rate of 10 breaths per min. Simultaneous measurement of airway pressure, *via* the inline gauge (North American Dräger) zeroed to atmosphere, and actual exhaled tidal volume, *via* a recently factory-calibrated Wright[®] respirometer placed at the mask, permitted calculation of ventilatory compliance.

The 30 s from $t = 3$ to $t = 3.5$ min afforded collection of five paired values for plateau airway pressure and exhaled volume. During this time, the anesthesiologist managing the airway provided an airtight mask seal and anterior jaw thrust. Each circuit was tested for leakage prior to patient arrival. Any mask leak was detected by the anesthesiologist managing the airway and by the investigator, who stood next to the patient's right ear. All recorded pressure measurements sustained a plateau for a full 1 s without decrement. Calculation of total compliance²¹ used the median of five values for airway pressure and its associated volume or, in the event of duplicate median pressures, the average of their associated volumes. Although the vast majority of paired measurements for volume and pressure were identical, use of the median minimized the effect of a rare outlying value.

Also at $t = 3$ min, the start of the compliance measurement, the assisting anesthesiologist (J.C.H. or D.F.V.R.) assessed the patient's level of consciousness as "responsive" or not, based on eyelash reflex and response to a command to open the eyes. Specific criteria sought evidence of early paralysis, systemic hypotension, and bradycardia. Uncoordinated patient movements, rocking chest and abdominal movements, and autonomic criteria (two or more of the following: tachycardia, hypertension, lacrimation, and diaphoresis) defined early paralysis. Systolic arterial blood pressure < 80 mmHg or mean arterial pressure < 50 mmHg defined hypotension, and heart rate < 40 beats per min was considered bradycardia. A Marquette series 7000RA monitor with direct digital writer provided real-time recording of hemodynamic data from $t = 0$ to $t = 9$. During continuous pulse oximetry monitoring, any hemoglobin oxygen saturation $< 90\%$ was noted.

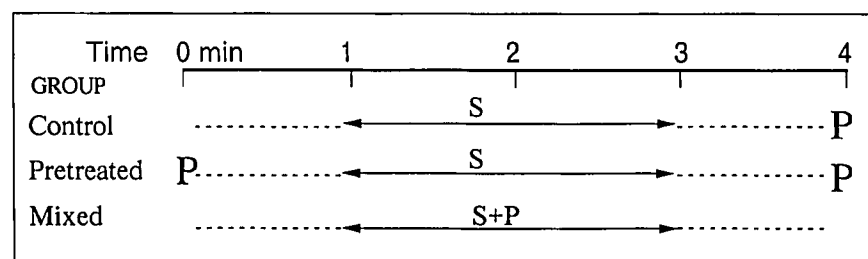


FIG. 1. Design of the experiment. The administration of sufentanil (S) and various doses of pancuronium (P) for the control, pretreated, and mixed groups appear for the first 4 min of the experiment. Subjective and objective measurement of compliance occurred at 3 min and at 8 min.

After measurement of total compliance at $t = 3$ min and administration of relaxant or placebo at $t = 4$ min, manual ventilation resumed until $t = 8$ min, at which time subjective compliance scoring and measurement of total compliance (exactly as at $t = 3$ min) were repeated. Data collection ended with tracheal intubation at $t = 9$ min. An assistant manually recorded the data in real time. A postoperative interview elicited each patient's recall of induction events.

DATA ANALYSIS

Analysis of variance provided comparisons of continuous variables, and likelihood ratio χ^2 statistics analyzed frequency data among the three groups. Compliance measures underwent logarithmic transformation prior to analysis to provide normal distribution.²² Raw data lack a normal distribution because of the impossibility of negative values for compliance. Logarithmic transformation restores sufficient symmetry for a normal distribution, thus permitting valid application of the more common and more powerful statistical tests. Since the subjective compliance scores and groups comprise sets of ordered alternatives, Kendall's τ rank-order correlation coefficient assessed concordance for these frequency data.²³ When analysis of variance indicated a significant effect, Tukey's HSD test or Sheffé's F test further analyzed pairwise differences between groups. Data are reported as mean \pm standard error of the mean for normal distributions, as back-calculated mean and 95% confidence interval for lognormal distributions, or as number of patients. All tests are two-tailed with $P < 0.05$ determining significance.

Results

Fifty-seven patients completed the study, with 19 in each group. No patient received clonidine or chronic opioids. Patients in the three groups did not differ with respect to age (overall 64 ± 10 years), body weight (79 ± 12 kg), type of procedure (51, aortocoronary bypass grafts; 3, valve replacements; and 3, combined valve replacement and coronary grafts), or the need for additional sedation upon arrival in the operating room (28 of 57 overall). Table 1 displays the premedication supplementation data along with the frequency of noted undesirable occurrences during induction: responsiveness after sufentanil, early paralysis, hypotension, bradycardia, and hemoglobin oxygen saturation $< 90\%$. After surgery, every patient denied memory of events surrounding induction of anesthesia.

Four patients did not complete the study. In three patients, objective static compliance measurement at $t = 3$ min did not occur because of the necessity for immediate effective ventilation: one patient displayed severe periph-

TABLE 1. Incidence of Additional Sedation and of Untoward Events during Induction

Group	Control (n = 19)	Primed (n = 19)	Mixed (n = 19)
Responsiveness	4	2	1
Early paralysis	1	0	0
Hypotension	0	1	0
Bradycardia	0	0	0
SpO ₂ $< 90\%$	1	2	0
Additional sedation*	10	9	9

Entries are number of patients. See Materials and Methods section of text for definitions of untoward events.

* $\chi^2 = 0.14$, P not significant for difference among groups in frequency of additional sedation. For other event frequencies, entries were too small for statistical comparison. The compliance measured in patients receiving additional sedation did not differ from that of patients without additional sedation ($P = 0.19$ by two-way analysis of variance).

eral and pulmonary arterial hemoglobin oxygen desaturation; a second regurgitated at $t = 3$ min; and the third appeared awake and rigid at $t = 3$ min. All of these patients had been assigned to the control group. The fourth patient did not complete the study when the investigators determined that his large tongue caused airway obstruction despite placement of the largest size oropharyngeal airway.

Figure 2 displays the ventilatory compliance data at $t = 3$ and $t = 8$ min. Analysis of variance disclosed a strong effect of induction sequence group on calculated ventilatory compliance at $t = 3$ min ($P < 10^{-8}$). Total mean compliance in the pretreated group, $6.3 \text{ ml} \cdot \text{cmH}_2\text{O}^{-1}$ (95% confidence interval 3.5–11), did not differ from that of the control group, $4.1 \text{ ml} \cdot \text{cmH}_2\text{O}^{-1}$ (2.6–6.5). However, each was significantly less ($P < 0.0001$) than that of the mixed group, 40 (33–47) $\text{ml} \cdot \text{cmH}_2\text{O}^{-1}$. At $t = 8$ min, groups did not differ in objective lung compliance (overall $46 \text{ ml} \cdot \text{cmH}_2\text{O}^{-1}$ [43–50]). Compliance increased significantly in the pretreated group (by $39 \text{ ml} \cdot \text{cmH}_2\text{O}^{-1}$, $P = 0.00013$) and the control group (by $41 \text{ ml} \cdot \text{cmH}_2\text{O}^{-1}$, $P = 0.00013$); a smaller increase in the mixed group ($7.7 \text{ ml} \cdot \text{cmH}_2\text{O}^{-1}$) also achieved statistical significance ($P = 0.014$). The 28 patients who received supplemental preanesthetic medication did not display a compliance at $t = 3$ min different from the 29 patients who received no such supplement (13 [7.6–21] vs. 8.3 [4.9–14] $\text{ml} \cdot \text{cmH}_2\text{O}^{-1}$; $P = 0.19$ by two-way analysis of variance).

Table 2 displays data describing the subjective impression of compliance, which corroborate the objective data. Group strongly influenced the subjective impression of compliance at the end of sufentanil infusion ($t = 3$ min): the lungs of many patients in the control (12 of 19) and pretreated (10 of 19) groups could not be ventilated at all (score 0), in contrast to the single patient in the mixed group ($P = 0.0025$). At $t = 8$ min, at least 4 min after

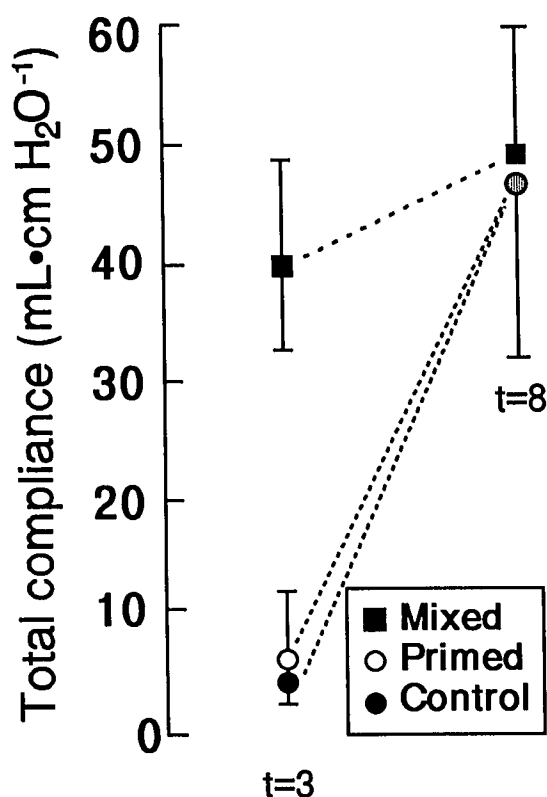


FIG. 2. Objective compliance at $t = 3$ and at $t = 8$ for each of the three study groups ($n = 19$ for each). Open circles = control group; closed circles = primed group; shaded circle = confluence of open and closed circles; closed squares, mixed group. Error bars are 95% confidence intervals. Dashed lines connecting each group at $t = 3$ and $t = 8$ are for visual ease. See text for analysis of results.

relaxant administration for all patients, 56 of the 57 patients demonstrated good or excellent subjective compliance ($P =$ not significant for difference among groups), the sole exception being a patient in the control group. The objective and subjective measures demonstrated excellent agreement in regard to extent of compliance. Analysis of variance demonstrated that the patients with

low subjective scores demonstrated lower objective compliance at both $t = 3$ ($P = 0.0001$) and $t = 8$ ($P = 0.0003$). Table 3 presents the aggregate data. Subjective data also correctly reflected the small increase in objective compliance in the mixed group from $t = 3$ to $t = 8$ (likelihood ratio χ^2 test, $P = 0.007$).

Discussion

These data substantiate that difficult ventilation, despite the absence of tongue obstruction, occurs commonly during anesthesia induction with moderate-dose sufentanil. At $t = 3$, all patients in the control and pretreated groups displayed poor compliance. Hill *et al.*, using subjective criteria for ventilatory compromise in 20 patients, compared simultaneous administration of pancuronium and high-dose fentanyl to induction with fentanyl alone. Simultaneous infusion avoided chest wall rigidity.⁸ Many clinicians, however, choose a pretreatment scheme over a simultaneous infusion of relaxant and opioid for fear that in the latter technique paralysis may precede loss of consciousness. The present study corroborates Hill *et al.*'s⁸ findings of hemodynamic stability and the absence of early paralysis during simultaneous administration of opioid and relaxant. Furthermore, it extends the findings of Hill *et al.*⁸ to a moderate-dose sufentanil induction model. These data show the ineffectiveness of a pretreatment scheme to avert difficulty in ventilation as well as the efficacy of mixing induction drugs. In addition, the study documents agreement of the objective measurement of total compliance with a subjective scoring system. The adverse respiratory events forcing three patients in the control group not to complete the study underscores the poor ventilatory compliance of that group.

A different pretreatment protocol, using larger pancuronium doses or longer intervals, might be more effective than the pretreatment protocol investigated here. However, the studied scheme is similar to those in clinical practice and reported in the literature. Of greater interest, this report identifies a superior alternative to pretreatment, namely, mixing sufentanil and pancuronium.

TABLE 2. Subjective Compliance Scores

	Group	Control	Primed	Mixed
$t = 3 \text{ min}^*$	Score 0	12	10	1
	Score 1	4	4	3
	Score 2	2	2	8
	Score 3	1	3	7
$t = 8 \text{ min}^\dagger$	Score 0	0	0	0
	Score 1	1	0	0
	Score 2	6	8	4
	Score 3	12	11	15

Entries are number of patients.

* $\chi^2 = 20.2$, $P = 0.0025$; Kendall's $\tau = 0.46 \pm 0.086$ (SE), $P < 0.01$.

† $\chi^2 = 4.02$, P not significant; Kendall's $\tau = -0.029 \pm 0.132$ (SE), P not significant.

TABLE 3. Objective Compliance Grouped by Subjective Compliance Scores

Score	Compliance at $t = 3$			Compliance at $t = 8$		
	Mean*	95% CI	n	Mean†	95% CI	n
0	3.3	2.3–4.7	23			0
1	7.6	3.5–17	11	32		1
2	33	24–45	12	38	33–43	18
3	40	29–55	11	51	47–55	38

Compliance = milliliters per cmH₂O. CI = confidence interval.

* (Score 0 = Score 1) < (Score 2 = Score 3) by Scheffé's F test.

† Score 2 < Score 3 by Scheffé's F test.

This study used an objective measure of total compliance in addition to the usual subjective measure. Since blinding of all personnel to patient group assignment should eliminate biased subjective scoring, why should an additional objective method be desirable? First, the superior precision provided by an objective measure provides greater confidence in conclusions drawn from the data. Second, the objective data represent a continuous variable, thus facilitating statistical comparisons. Finally, some have questioned the legitimacy of previous studies using subjective data alone; comparison of simultaneously acquired objective and subjective data provides perspective on the validity of those subjective data.

Measurements of exhaled tidal volume and plateau airway pressure can be affected by experimental error and anatomic factors. Several methods employed in this study sought to minimize or eliminate these confounding influences. First, no morbidly obese patients participated. Second, early oropharyngeal airway placement precluded tongue obstruction in all but one patient, who was then not permitted to continue in the study. Third, anterior jaw thrust during compliance measurement further minimized the possibility of upper airway obstruction. Fourth, the tight mask seal prevented gas leaks from influencing the pressure and volume measurements. Finally, a mechanical ventilator standardized delivery of tidal volume. Despite these measures, inconsistent pressure readings appeared on occasion associated with transient adjustments of operator grip from muscle fatigue. For that reason, the mean of the five repeated pressure measurements for each patient does not represent well the underlying population value. The median value minimizes the effects of rare outlying values.

This study did not use electromyography for several reasons. First, controversy surrounds the contribution of chest wall muscular rigidity to impairment of ventilation during opioid administration.^{4,5,7} Poor correlation often occurs between subjective assessments of rigidity and electromyography.¹¹ Findings of increased electromyographic activity have been questioned as being merely associated with but not related to ventilatory compromise.⁴ Second, determination of the location of the mechanism of ventilatory impairment would not answer the scientific questions posed by this clinical investigation. Those issues have received suitable attention elsewhere.^{13,15} The outcome variable of clinical interest to this investigation is the ability to ventilate the lungs, not the activity of any muscle group.

The data describing the subjective impression of compliance agree with their objective counterparts. Indeed, subjective measurements demonstrated sufficient sensitivity to track properly the small increase in objective compliance measured in the mixed group between $t = 3$ and $t = 8$. One might even argue that the subjective mea-

sure reflects clinical considerations better than does the objective compliance measurement. Without validation by an objective measure, subjective measures remain open to justifiable skepticism. Although these data provide evidence that subjective criteria reflect objectively quantified changes in a physiologic variable in this study, they do not validate subjective data collected in previous investigations.⁸⁻¹⁰

One should resist the temptation to interpret the $t = 3$ values of compliance in the pretreated group ($6.3 \text{ ml} \cdot \text{cmH}_2\text{O}^{-1}$) and the control group ($4.1 \text{ ml} \cdot \text{cmH}_2\text{O}^{-1}$) as evidence of a beneficial effect of pretreatment. Statistical analysis demonstrates no significant difference with 19 patients in each group. Although this negative result carries only 18% power and would require 105 patients in each group to attain 80% power,²⁴ the improvement is of little clinical relevance considering that at $6.3 \text{ ml} \cdot \text{cmH}_2\text{O}^{-1}$, mean plateau pressures $> 100 \text{ cmH}_2\text{O}$ would be needed for tidal volumes of 700 ml. The accompanying subjective data provide further justification to reject a true difference in these compliances ($\chi^2 = 1.2$, $P = 0.76$).

Hemoglobin oxygen saturation remained acceptable despite difficulty with ventilation. This likely stems from inhalation of 100% oxygen for 3 min prior to opioid infusion. Had oxygen breathing prior to drug administration not occurred, more patients in the control and pretreated groups might have suffered arterial oxygen desaturation.

Midazolam in particular is recommended to prevent opioid-induced chest wall rigidity.²⁵ For several reasons we believe that supplementation of inadequate preoperative sedation with midazolam did not affect the frequency or severity of impaired ventilatory compliance. First, Neidhart *et al.* have demonstrated that midazolam, 5 mg intravenously, administered 3 min prior to moderate-dose fentanyl infusion ($20 \mu\text{g} \cdot \text{kg}^{-1}$) does not prevent chest wall rigidity.¹⁰ Likewise, prevention of rigidity with 2.5 mg midazolam requires administration within 1 min of induction.²² In the current study, injection of small doses of midazolam occurred at least 15 min prior to the beginning of induction. Second, supplementation occurred with similar frequency in all groups. Third, patients who received supplemental premedication upon arrival in the operating room did not display a total compliance difference from that of unsupplemented patients.

These data indicate that decreased ventilatory compliance occurs with moderate-dose sufentanil induction and that pretreatment with pancuronium does not prevent it. Furthermore, mixing pancuronium and sufentanil together successfully averts the difficulty in ventilation and maintains hemodynamic stability without causing early paralysis or awareness during induction in suitably premedicated patients. Elucidation of the mechanism of

opioid-induced rigidity continues.^{13,15} Specific inhibitors such as ketanserin or dexmedetomidine appear promising. While awaiting more definitive options for the management of rapid opioid administration, one can recommend simultaneous administration of sufentanil and pancuronium to induce anesthesia in suitably prepared patients.

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