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Physiology of Alfentanil-induced Rigidity

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The authors investigated the hemodynamic, metabolic, electroencephalographic (EEG), and electromyographic (EMG) characteristics of narcotic-induced rigidity during induction of anesthesia with alfentanil (175 μg/kg) in 10 patients. Thiopental (4 mg/kg) was administered to a ten-patient control group. Rigidity was quantified in eight muscle groups (sternocleidomastoid, deltoid, biceps, forearm flexors, intercostal, rectus abdominus, vastus medialis/lateralis, and gastrocnemius). Marked rigidity was observed in all muscle groups in all patients receiving alfentanil and in none receiving thiopental. Central venous pressure increased with onset of rigidity, while mean arterial pressure and cardiac index remained unchanged. Manual ventilation was extremely difficult during alfentanil-induced rigidity. Arterial oxygen tension decreased more rapidly during rigidity than during the same time interval in the control group, while patients experiencing rigidity were more acidotic, as reflected by greater increases in base deficit. The EEG demonstrated an anesthetic state without seizure activity. The immediate increase in central venous pressure with the onset of rigidity, along with occasional simultaneous parallel variations in central venous pressure and the EMG, strongly suggest a mechanical mechanism for the change in central venous pressure. The metabolic changes during rigidity may be partly related to the absence of the normal cardiovascular reflexes that are reported to occur during voluntary isometric muscle contractions. A neurochemical mechanism of narcotic-induced rigidity is briefly reviewed. (Key words: Analgesics: alfentanil. Anesthetics, intravenous: alfentanil. Brain: electroencephalography. Muscle: electromyography; rigidity.)

THE ANESTHETIC MANAGEMENT of high-risk patients with large doses of potent narcotics is firmly established. While the high-dose narcotic technique generally fulfills the objective of minimal change in cardiopulmonary function, it is often associated with extreme muscle rigidity. Such rigidity commonly interferes with positive pressure ventilation prior to intubation. Increased central venous and pulmonary artery pressures are often noted during rigidity, although the mechanisms are unclear.[1] Although of high incidence, the physiology of narcotic-induced rigidity is poorly understood, and the neurochemical mechanisms of this phenomenon, which have been described in the neurochemical literature, have not been appreciated by anesthesiologists.

Considering the paucity of information surrounding this phenomenon, we designed a study to answer the following questions: 1) What are the hemodynamic changes that accompany muscle rigidity? 2) What blood gas changes accompany rigidity? 3) What is the anatomic distribution of rigidity among muscle groups? 4) Are there electroencephalographic (EEG) correlates? For example, do seizures occur?

Methods

The experimental protocol was approved by both the University of California, San Diego, and the Veterans Administration Human Subjects Committee approval, and written informed consent was obtained from each patient. Twenty patients scheduled for elective surgery were randomly assigned either alfentanil (ten patients) or thiopental sodium (ten patients) as induction agents. A prerequisite for patient participation was the absence of clinical cardiopulmonary dysfunction or central nervous system disease.

Cardiovascular monitoring consisted of an ECG lead CMV_5, intraarterial and central venous catheters, and a continual beat-to-beat pulse contour cardiac output computer,** which was calibrated with triplicate green-dye cardiac output determinations. Electrophysiologic measurements included bilateral EEG recordings (frontal–mastoid configuration), FP1-01, FP2-02 with on-line aperiodic analysis (Neurometrics, Inc., San Diego, CA 92121-1723), and recordings of eight widely distributed surface electromyograms (EMG). Following Omniprep® skin preparation, triplets of EMG electrodes, placed 8 cm apart, were arranged over each of the following muscle groups: sternocleidomastoid, deltoid, biceps, forearm flexors, intercostal (7, 8 or 9th interspace), rectus abdominus, vastus medialis/lateralis, and gastrocnemius. Both EEG and EMG electrodes were connected *via* shielded cables to Hewlett-Packard® 8811A Bioelectric Amplifiers, with band-pass filtering from 0.5–1,000 Hz (EEG) and 1.0–1,500 Hz (EMG). Recorded on each channel was a

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10-Hz calibration signal equivalent to 100 μV of the EEG or EMG signal.

Patient oxygenation was monitored continuously *via* pulse oximetry (Nellcor®) and transcutaneous P_{O_2} (Tc_{O_2}) (Novametrix®) recordings. In addition to polygraphic recordings, all analog data were recorded on magnetic tape using Crown Vetter® A-1 eight-channel and Ampex® fourteen-channel FM recorders. The results of the EEG aperiodic analysis were stored in digital form on floppy disks generated by the Neurometrics®.

A pneumatic tourniquet on one upper arm was inflated to 300 mmHg before induction and maintained until after the initiation of inhalation agents following intubation. With access of both alfentanil and relaxants blocked to this extremity, a distally placed EMG was used to assess the possibility of direct effects of alfentanil on muscle and persistence of rigidity after the administration of relaxants.

All patients received lorazepam 1–3 mg and cimetidine 300 mg orally the evening before the study, and cimetidine 300 mg orally, with intramuscular morphine 0.1–0.15 mg/kg 90 min before induction.

Before induction each patient was given lactated Ringer's solution 7 ml/kg iv over 5 min, followed by 100% oxygen (5 l/min) by mask for 5 min. Induction of anesthesia was accomplished with either alfentanil (175 μg/kg) or thiopental (4 mg/kg) infused over 1 min. The alfentanil group was then observed for clinical and EMG manifestations of rigidity without assisted ventilation for a variable period up to a maximum of 5 min. Then the rigidity was terminated with muscle relaxants (pancuronium 50 μg/kg and metocurine 100 μg/kg), and controlled ventilation with 100% O_2 was initiated. The patients receiving thiopental sodium (4 mg/kg) were given the same amount of muscle relaxants 1 min after induction to maintain apneic times comparable with the alfentanil group.

In both groups of patients an independent anesthesiologist continuously evaluated patient status. Intermittent positive pressure ventilation by mask was instituted for any of the following circumstances: 1) a decrease in blood oxygenation approaching 90% saturation of hemoglobin; 2) a rapid rate of decrease in transcutaneous P_{O_2} (>75 mmHg/min); or 3) adverse hemodynamic changes (hypertension > 120 mmHg mean, tachycardia > 110 beats/min, or dysrhythmia). With any of these changes, neuromuscular blocking agents were administered, and ventilation with 100% O_2 was commenced. In both groups, if a patient developed hypertension, tachycardia, or light anesthesia as assessed by the reappearance of higher EEG frequencies (10–30 Hz) using the on-line Neurometrics®, supplemental thiopental was administered before laryngoscopy and intubation. After intubation, isoflurane and nitrous oxide were administered as required.

Arterial blood gases were sampled when the subject was breathing room air, following preoxygenation, and after apnea before ventilation resumed. The values were corrected for temperature. Because the absolute apneic time interval varied with each patient, the absolute change in a variable from the preoxygenation to the postapneic measurement was normalized for time. For each group the normalized blood gas values were then averaged, and mean ± SEM values for each blood gas variable were compared *via* unpaired Student's *t* tests.

The EMGs were rectified and integrated to yield root mean square (RMS) values. RMS values before induction and peak values during rigidity were compared using Student's *t* test. Hemodynamic variables for the two groups were compared by unpaired Student's *t* test, using Microstat® software on a Z-2 Cromemco® Computer. In addition, changes in hemodynamic values were assessed against baseline values established just before the administration of alfentanil using paired Student's *t* test. All values are given as mean ± SEM.

Results

There were no statistical differences between the two groups of patients with respect to age, weight, body surface area, or a history of smoking or ethanol consumption. In both the thiopental and alfentanil groups, positive-pressure ventilation by mask was initiated prior to the maximum period of 5 min, although the average respective apneic times for the two groups were not significantly different (table 1).

Clinical rigidity and EMG. In each patient receiving alfentanil, increased EMG activity was observed at every electrode location (see table 1), along with clinically recognizable rigidity. The increased EMG activity was first noted in the upper part of the body (sternocleidomastoid, deltoid, biceps, forearm), followed by the remainder of the body, with otherwise no regular sequence of activation. The mean onset time of upper-extremity activity was 47 s from the beginning of alfentanil administration. Clinical observation in correlation with simultaneous EEG and EMG recordings demonstrated that the onset of rigidity corresponded with unresponsiveness and loss of consciousness. Rigidity and EMG activity were often provoked or increased by stimulation of the patient, for example, by passive movement of an extremity, manipulation of the mask, or loud auditory stimulus.

Clinically, rigidity was often explosive in onset, with the subjects assuming postures typified as follows: flexion of the upper extremity at the fingers, wrists, and elbows; extension at the toes, ankles, knees, and hips; rigid immobility of the head with atlanto–occipital flexion of the chin onto the chest; and severe rigidity of the abdominal and chest wall musculature. In two patients receiving al-

TABLE 1. Integrated EMG, Preinduction, and Maximum Response during Rigidity in μV with Statistical Significance for the Change—The Time to Onset of Rigidity from the Beginning of Alfentanil Administration

	Preinduction (μV)		Rigidity (max) (μV)		Time to Onset of Rigidity (s)	
	Mean	±SEM	Mean	±SEM	Mean	±SEM
Sternocleidomastoid n = 9	15.4	3.6	55.8*	15.0	65	8
Deltoid n = 5	8.2	2.9	53.1†	8.6	47	15
Biceps n = 6	4.2	2.1	95.1†	24.4	63	3
Forearm n = 7	1.6	0.67	71.2†	16.3	59	7
Intercostal n = 8	26.3	9.1	74.6*	11.1	83	20
Rectus abdominus n = 10	9.9	3.9	53.7†	12.8	71	10
Quadriceps n = 10	1.6	1.0	33.8†	7.4	71	4
Gastrocnemius n = 10	3.8	2.0	59.1†	8.8	82	20

* $P < 0.05$. † $P < 0.02$.

fentanil, ineffective inspiratory efforts were observed after 2–3 min of apnea when rigidity was still present. Following apnea in the alfentanil group, but before the onset of paralysis and relaxation, extension of the neck and insertion of an oral airway were impossible. At this time, two individuals were required to ventilate the patient; one to maintain a mask fit and another to apply positive pressure. Relaxants completely eliminated all clinical as well as EMG evidence of rigidity, and no difficulties in ventilation or intubation were subsequently encountered.

In all patients receiving alfentanil, rigidity was observed in the extremity isolated from both narcotic and relaxant by tourniquet. This rigidity persisted when rigidity in the rest of the body was abolished by the neuromuscular blocking agents.

None of the patients receiving thiopental had any clinical or EMG evidence of increased muscle tone throughout the apneic period. Following the apneic interval, ventilation and endotracheal intubation were easily accomplished in these patients.

No postoperative anesthetic morbidity occurred in either group, including complaints of muscle soreness in the alfentanil group. There was no incidence of postoperative recall with either induction agent.

Hemodynamics. There were no statistical differences in any of the baseline hemodynamic variables when the alfentanil and thiopental groups were compared.

Alfentanil. While the apneic interval varied, complete observations were collected in all patients for at least 3 min of rigidity (fig. 1). With the onset of unconsciousness and rigidity, statistically significant decreases in systolic (−17 ± 4 mmHg ± SEM), diastolic (−6 ± 3 mmHg) and mean (−10 ± 3 mmHg) arterial pressures occurred ($P < 0.05$). These variables spontaneously returned toward baseline within 30 s for the duration of rigidity. In contrast, central venous pressure (CVP) increased 1.8 ± 0.6 mmHg at induction with the onset of rigidity ($P < 0.02$) with maximal changes (5.3 ± 1.3 mmHg, $P < 0.02$) seen at 3 min. In one patient EMG activity fluctuated, and simultaneous parallel changes in CVP were observed (fig. 2). Following injection of the neuromuscular blocking agents, the CVP rapidly returned to the baseline value. Heart rate (HR) gradually increased, the change from control becoming statistically significant after 1½ min of rigidity ($P < 0.05$). Systemic vascular resistance index (SVRI) did not significantly change during rigidity but decreased significantly following relaxants and before intubation.

Thiopental. Immediately following thiopental, the decreases in systolic, diastolic, and mean arterial pressures and cardiac index were not significantly different from those observed in the alfentanil group (table 2). The CVP at induction decreased (−1.4 ± 0.7 mmHg), a change significantly different from the change following alfentanil ($P < 0.01$). Because relaxants were administered 1 min after induction to establish the thiopental patients as controls for metabolic and EMG variables, the subsequent hemodynamics are not directly comparable with the alfentanil group. With thiopental, hypertension and tachycardia were the most common reasons for the initiation of artificial ventilation before the end of the 5-min period, and additional thiopental was given to five patients before intubation.

Blood gas results. There were no statistical differences in preinduction *p*H, Pa_{CO_2}, Pa_{O_2}, or base deficit values between groups. The difference between mean apneic

times of the two groups did not achieve statistical significance (table 3). The patients receiving alfentanil became more acidotic than did those in the thiopental group ($P < 0.002$). While there was no statistical difference in the normalized change in Pa_{CO_2} between groups, the rate of change in base deficit was significantly greater in rigid patients ($P < 0.01$). Arterial oxygen tension decreased at a greater rate in the alfentanil group ($P < 0.02$), when compared with the control group. The possibility of hypoxia necessitated the administration of neuromuscular blocking agents and early ventilation prior to 5 min in five of ten patients in this group of patients. There was no correlation between Pa_{O_2} and corresponding base deficits at the end of the apneic interval.

EEG results. There was no evidence of seizure activity in either the raw or processed EEG with any of the cortical surface EEGs nor with a nasopharyngeal EEG lead in the one patient (alfentanil) undergoing this measurement, nor was there any evidence of postictal activity. High-amplitude *delta* waves were the predominant characteristic of the EEG in patients receiving alfentanil. Thiopental initially produced high-amplitude waves of all frequencies followed by a rapid loss of *delta* waves and a persistence of a high-frequency pattern. Thiopental often had only transient EEG effects over a 2- to 3-min period, and a second dose of drug was considered necessary before laryngoscopy in five of the ten patients.

Discussion

In summary, all patients receiving alfentanil 175 μg/kg became rigid, with markedly increased EMG activity present in all muscle groups investigated. The patients assumed a characteristic posture during rigidity. Following the apneic period, ventilation was extremely difficult until neuromuscular blocking agents were given. The principle hemodynamic change occurred in CVP, which increased immediately with the onset of rigidity. In one patient, the CVP and the intercostal and abdominal EMGs fluctuated simultaneously. In 77 subsequent studies with alfentanil, we have observed two additional patients whose CVP and EMGs fluctuated *pari passu.* Cardiac index and arterial pressure were not significantly changed during rigidity, and although heart rate gradually increased, the change was not clinically important. The rigid patients were more acidotic than those in the group receiving thiopental, due to greater base deficits, while the rate of increase in Pa_{CO_2} was not statistically different from the thiopental group. Arterial oxygen tension declined significantly during rigidity, while there was little change in oxygenation in apneic patients receiving thiopental. There was no EEG evidence of seizure activity before, during, or following rigidity.

Interpretation. Incomplete alveolar preoxygenation and increased O_2 consumption, lack of oxygen transfer due to airway obstruction, and a decrease in functional residual capacity (FRC) during rigidity, the last as reported by Kallos,[2] may all be contributing factors that predispose to decreased Pa_{O_2} during rigidity. In addition to the decreased FRC described during rigidity,†† Scamman[3] reported that pulmonary compliance in patients with tracheostomies was decreased 16% with fentanyl and O_2 alone

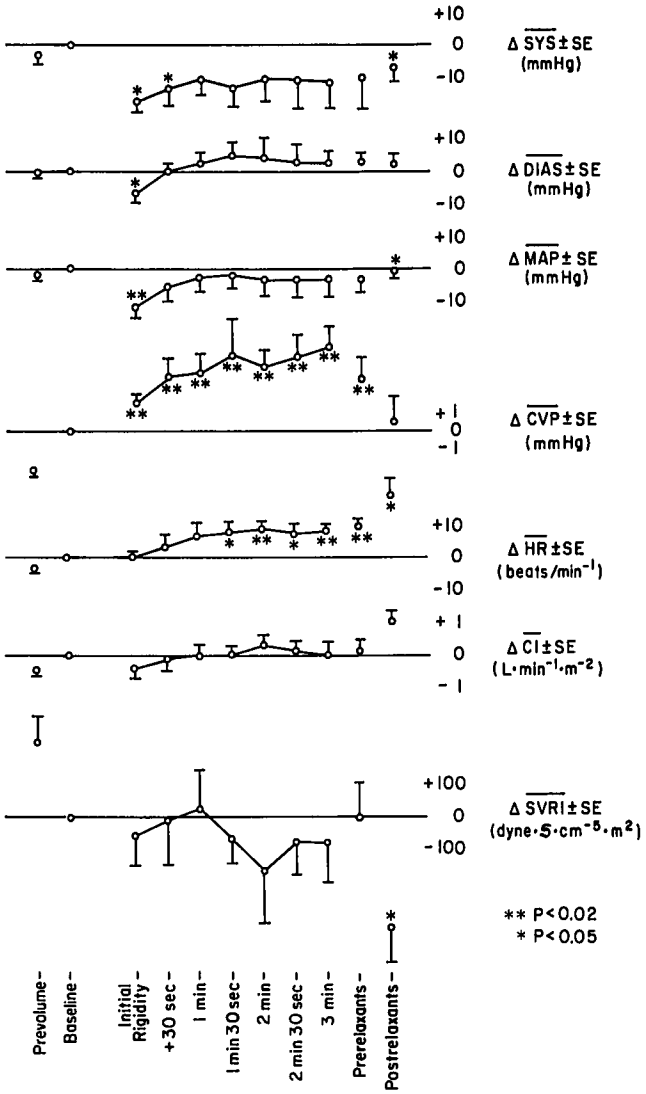

FIG. 1. Hemodynamic changes during alfentanil-induced rigidity. The changes are given as the mean ± SE of the mean in relation to the baseline values taken just before administration of alfentanil. The changes are displayed before and after the infusion of lactated Ringer's (baseline) and for 3 min of rigidity including the changes that occurred when rigidity was eliminated using muscle relaxants.

†† Smith NT, Wesseling KH, Weber JAP, deWit B: Preliminary evaluation of a pulse contour cardiac output computer in man. Feasibility of brachial or radial arterial pressures. Proceedings of the San Diego Biomedical Symposium 13:113–119, 1974.

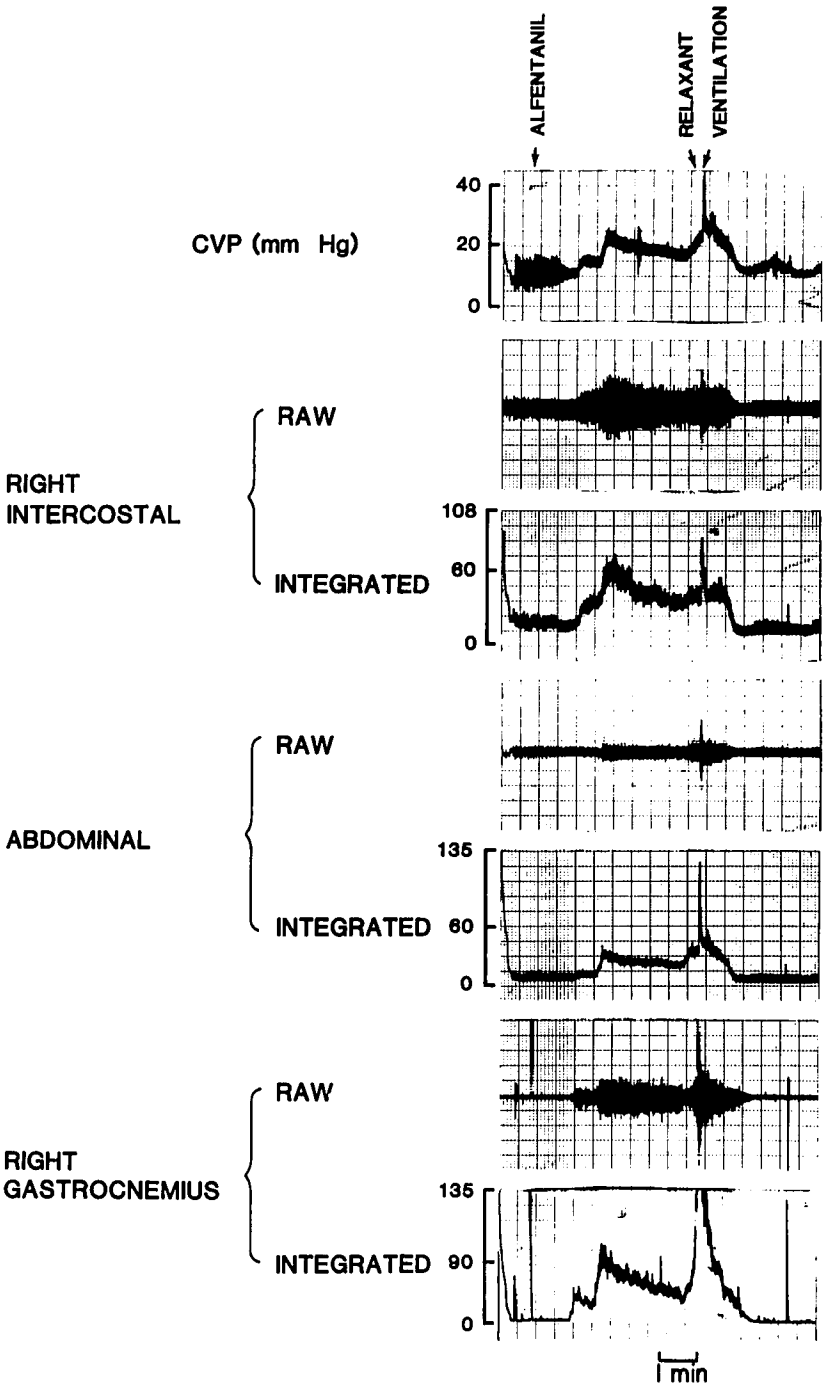

FIG. 2. The relationship between CVP and EMG during rigidity. This figure demonstrates simultaneous fluctuations in EMG and CVP in one patient, suggesting a mechanical etiology for the CVP increase. Also shown are the parallel changes in the widely distributed EMGs and the intensification of rigidity due to stimulation, in this instance, of the airway. These observations suggest a CNS source for rigidity. EMG values are given in μv.

and 38% with nitrous oxide–oxygen and fentanyl, although neither was enough to account for the failure of bag and mask ventilation. From this study he postulated a glottic mechanism of airway obstruction. In our study, the inability to extend the mandible, accompanied by rigid immobility of the neck, suggests that a supraglottic site of obstruction is also possible. Neuromuscular mechanisms for maintaining airway patency during spontaneous ventilation have been described.[4,5] Although we did not measure EMG activity in these muscles, the whole-body distribution of rigidity suggests that airway obstruction through a supraglottic mechanism could be important. (More recently, we have learned that an open glottis has been observed *via* fiberoptic endoscopy in patients.‡‡)

While none of the patients studied were allowed to

‡‡ Orsak, Kathleen. Unpublished results.

become hypoxic, a relatively rapid decrease in oxygenation occurred in five of the ten subjects who were rigid, necessitating early manual ventilation. There was no correlation between the rate or absolute change in Pa_{O_2} and smoking history or severity of rigidity, but pulmonary function was not examined in detail in these patients. We did note a correlation between the rate of increase of Tc_{O_2} during preoxygenation and the absolute Tc_{O_2} just prior to ventilation (correlation coefficient 0.679, $P < 0.05$). Whether the former can be taken as an indication of alveolar gas exchange is currently not known. Although not measured, increased O_2 consumption due to muscle metabolism during rigidity may have contributed to the observed decline in Pa_{O_2}.

Rigidity has been associated with hypercapnia and elevated CVPs during the induction of anesthesia.[1-6] Hill *et al.*[6] investigated the efficacy of simultaneous fentanyl and pancuronium infusions to attenuate rigidity in cardiac patients undergoing fentanyl–oxygen inductions. In patients receiving fentanyl alone, mean pulmonary artery pressures (MPAP) increased. These authors proposed that the hypercapnia associated with rigidity results in pulmonary vasoconstriction. Our observations suggest that changes in CVP occur immediately and vary directly with changes in muscle tension as reflected by the EMG. These findings support an hypothesis that mechanical compression of the chest by the thoracic and abdominal musculature in the presence of an obstructed airway results in increased central venous and, presumably, pulmonary arterial pressures. Although not investigated, rigidity of the extremities might be expected to increase venous return and contribute to the increased central pressures, at least initially. Because MPAP was not measured in our study, pulmonary vasoconstriction in response to progressive acidosis cannot be excluded.

The cardiovascular response during narcotic-induced muscle rigidity is different from the hemodynamic changes following a voluntary increase in muscle tone. Increased intramuscular pressure will compress and obstruct arterial blood flow at muscle tensions less than those achieved during maximal voluntary contraction.[7,8] Mitchell *et al.* demonstrated that a normal response to increased isometric muscle tension and EMG activity is an immediate and simultaneous increase in heart rate and arterial pressure mediated by both central and peripheral mechanisms.[9] These responses maintain blood flow and offset mechanical compression of vascular flow and thereby maintain O_2 delivery. However during alfentanil-induced rigidity, increases in cardiac index, heart rate, and systemic pressures are either absent or attenuated by alfentanil. Although not measured in our study, muscle blood flow during rigidity may be compromised in the absence of normal cardiovascular reflexes. Inadequate O_2 delivery combined with elevated muscle metabolism would explain the base deficits seen in these patients.

Sokoll *et al.*[10] and Freund *et al.*[11] used electromyographic techniques to study abdominal muscle rigidity induced by morphine and nitrous oxide. These authors concluded that rigidity originated at a supraspinal level.

TABLE 2. Comparisons in Hemodynamic Changes between Thiopental Control Group at the Onset of Sleep and Alfentanil Group at the Onset of Sleep/Rigidity

	Thiopental Mean ± SEM	Alfentanil Mean ± SEM	Significance
Systolic BP mmHg	−29.7 ± 6.4	−22.0 ± 4.7	NS
Diastolic BP mmHg	−6.9 ± 3.1	−6.5 ± 3.1	NS
Mean BP mmHg	−11.7 ± 3.4	−14.9 ± 3.3	NS
CI $l \cdot min^{-1} \cdot m^{-2}$	−0.3 ± 0.2	−0.3 ± 0.3	ND
HR beats/min	5.6 ± 3.0	−0.2 ± 2.4	NS
CVP mmHg	−1.4 ± 0.7	1.8 ± 0.6	$P < 0.005$
SVRI $dyn \cdot s \cdot cm^{-5} \cdot m^{-2}$	−151.0 ± 64.4	−17.6 ± 107	NS

BP = blood pressure; CI = cardiac index; HR = heart rate; CVP = central venous pressure; SVRI = systemic vascular resistance index; NS = not significant.

TABLE 3. Comparative Preinduction Arterial Blood Gas Values and Postinduction Changes in Normalized Blood Gases

	Alfentanil	Thiopental	Significance
Apnea time (min) preinduction:	4.3 ± 0.2	3.8 ± 0.2	NS
Pa_{O_2} mmHg	401 ± 19	425 ± 19	NS
*p*H	7.37 ± 0.005	7.37 ± 0.01	NS
Pa_{CO_2} mmHg	40.7 ± 1.26	41.8 ± 0.84	NS
BE mEq/l	−1.98 ± 0.47	−1.63 ± 0.46	NS
Change in:			
Pa_{O_2} mmHg/min	−51 ± 12	−12 ± 6	$P < 0.02$
*p*H μ/min	−0.035 ± −0.002	−0.026 ± 0.002	$P < 0.002$
CO_2 mmHg/min	4.5 ± 0.36	4.4 ± 0.40	NS
BE $mEq/\cdot l^{-1} \cdot min^{-1}$	−0.72 ± 0.17	−0.14 ± 0.11	$P < 0.01$

All values mean ± SEM.

In our study, we demonstrated a nonperipheral mechanism of rigidity by the observation of rigidity and EMG activity in an extremity isolated by a pneumatic tourniquet before the administration of alfentanil. In addition, phasic changes in rigidity were clinically and electromyographically synchronous (fig. 2). The observation that tactile and auditory stimulation often markedly accentuated rigidity suggests that, unlike the myoclonic activity seen with etomidate, this phenomenon originates at a level above the spinal cord.[12] While high-dose narcotics can produce seizures in animals,[13] we observed no such activity, probably because the doses demonstrated by de Castro *et al.* to produce seizures were 100–1,000 times those producing deep surgical anesthesia.[13] We could not relate rigidity with detectable EEG events, except for the anticipated artifact associated with muscle activity. This observation is important because the rigidity occasionally resembled a tonic seizure in the suddenness of onset and in the posture and general appearance of the patient and could on occasion be misinterpreted as a seizure.

A neurochemical explanation of rigidity has been proposed. In 1903, Mavrojannis§§ first described morphine-induced catalepsy in rats. Wand *et al.*[14] developed a simple model of narcotic-induced rigidity by administering morphine in increments up to 17.5 mg/kg intraperitoneally to rats and demonstrating dose-dependent EMG activity in the gastrocnemius–soleus muscle during rigidity. Using this model, subsequent extensive studies of basal ganglia neurophysiology suggest that rigidity is produced by *mu* receptors located on interneurons (most probably GABA-ergic) in the caudate nucleus.[15] Strionigral GABA pathways are also important to this mechanism, and GABA agonists/antagonists applied to the substantia nigra can be shown to modulate critically a narcotic-induced rigidity.[16,17] The behavioral complex of catalepsy and rigidity has been reviewed.¶¶ Although of completely different etiologies, the final common pathway of narcotic rigidity may be shared by some of the motor abnormalties seen in Parkinson's disease and extrapyramidal drug reactions. With an understanding of the underlying neurochemistry and neuroanatomy, logical pharmacologic interventions to prevent rigidity may be devised.

In conclusion, while narcotic-induced rigidity is frequently described as involving the chest wall, alfentanil-induced rigidity actually involves all muscle groups studied. An elevation of CVP occurs, and a mechanical mechanism involving the thoracoabdominal musculature is hypothesized. The metabolic acidosis in rigid patients may be related to the absence of the normal cardiovascular reflexes that are reported to occur during a voluntary isometric muscle contraction. There was no EEG evidence of seizure activity. A hypothetical neurochemical mechanism of narcotic-induced rigidity is briefly reviewed.

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