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Noninvasive Evaluation of Breathing Pattern and Thoraco–Abdominal Motion Following the Infusion of Ketamine or Droperidol in Humans

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The authors compared the respiratory effects of an intravenous infusion of ketamine (1 mg · kg^{-1}) with droperidol (0.1 mg · kg^{-1}), or placebo on three different occasions in a double-blind, randomized fashion in eight healthy volunteers. Breathing pattern, thoraco–abdominal motion, end-expiratory positions of the rib cage and abdomen, arterial hemoglobin oxygen saturation (Sa_{O_2}), and end-tidal carbon dioxide concentration (FE_{CO_2}) were continuously measured with noninvasive techniques. During the 1-h monitoring period following drug injection, droperidol produced occasionally significant but clinically unimportant differences in respiratory variables when compared with placebo. In contrast, ketamine induced a significant ($P < 0.001$) and persistent increase in minute ventilation (+75%) from 5 to 20 min after start of infusion by increasing both the driving (*i.e.*, tidal volume/inspiratory time [V_T/T_I]) and the timing (*i.e.*, inspiratory time/total respiratory cycle time [T_I/T_{tot}]) components of ventilation (Milic-Emili J, Grunstein MM: Chest 70 (Suppl): 131–133, 1976). This was obtained without any significant change in end-expiratory positions or change in relative rib cage contribution to tidal volume. Despite multiple apneic episodes observed with ketamine, the subjects maintained a stable Sa_{O_2} and FE_{CO_2}, indicating no resting respiratory depression. This study, performed with a noninvasive respiratory monitoring technique, confirms that droperidol infused over 5 min at a clinically used dosage does not cause respiratory depression in healthy subjects, whereas ketamine produces an important ventilatory stimulation. (Key words: Anesthetics, intravenous: droperidol; ketamine. Measurement techniques: noninvasive. Ventilation: breathing pattern.)

SINCE THE INTRODUCTION OF ketamine as a clinical anesthetic agent, most studies have dealt with its hemodynamic or psychoactive effects. There are few controlled investigations concerning its effects on respiration, despite the fact that ketamine is administered mainly to spontaneously breathing patients. Furthermore, conflicting results have been reported in animal as well as human studies.[1–6] Whereas most studies in humans indicate no significant respiratory depression with the use of intravenous ketamine in anesthetic doses,[1–4] Domino *et al.*[5] reported transient decreases both in respiratory frequency (f) and in tidal volume (V_T), associated with arterial O_2 desaturation. More recently, Zsigmond *et al.*[6] demonstrated dramatic arterial hypoxemia (in some patients Pa_{O_2} decreased below 40 mmHg) with a concomitant increase in arterial CO_2 after a 2 mg · kg^{-1} bolus injection of ketamine.

Because respiration is influenced by the investigational environment[7] as well as by the measuring apparatus itself (mouthpiece, face mask),[8] we used a noninvasive respiratory monitoring technique to evaluate the effects of an intravenous infusion of ketamine on breathing patterns in healthy volunteers in a quiet, controlled experimental environment. This noninvasive method allows quantification of V_T ventilation as the sum of the separate excursion of rib cage (RC) and abdomen (ABD) and their respective contributions to V_T. In addition, a continuous assessment of respiratory end-expiratory positions of the RC and ABD is possible, which may indicate a change in functional residual capacity (FRC). The respiratory effects of ketamine were compared in a double-blind, randomized fashion with those produced by an infusion of either a placebo, or droperidol, which is known to have opposite and antagonistic hemodynamic and central nervous properties to those of ketamine.[9,10]

Methods

SUBJECTS

Eight healthy male volunteers (mean age 30 ± 4 (SD) yr; mean weight 75 ± 8 kg) accustomed to an investigational environment were studied. None had a previous notable medical history, took regular medication, or had ingested alcohol. Informed consent was obtained, and the Committee for Ethics in Human Research of our institution approved the study.

RECORDING PROCEDURES

Respiratory variables were continuously measured with a noninvasive respiratory monitoring system, which has previously been described.[11] Briefly, it consists of two air-filled rubber-bellows pneumographs (model 108 pneumograph, Hewlett-Packard) attached circumferentially around the RC at nipple level and the ABD at umbilical

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level. The bellows were connected to differential pressure transducers (Hewlett-Packard 267BC), and the electrical signals of pressure changes within the bellows were amplified and recorded on a eight-channel polygraph (Hewlett-Packard 7798A) and simultaneously stored and analyzed by a microcomputer (Apple® II, 48K). Recording from two bellows pneumographs allows the study of a two-compartment contribution to changes in lung volume. Circumferential variations in RC or ABD excursions produce linear pressure changes within the bellows, at least for approximately 80% of a vital capacity.[11] The frequency response of this device, including the 120-cm manometer tubing, a single three-way stopcock, and the pressure transducer, is stable up to 6 Hz.

The bellows pneumographs were calibrated before each experiment using the computer-aided least squares method described by Abraham *et al.*[12] We determined the calibration factors of the RC and ABD bellows in the supine position by asking the volunteers to breathe with variable V_T and contribution of RC to tidal breathing.[11] Validation of correct calibration was obtained from the analysis of 20 successive different breaths with simultaneous collection of the analog signals from the RC and ABD as well as the analog output from the integrated electrical flow signal of a calibrated pneumotachograph (Godart, type 17212). These signals were sampled by the microcomputer, which then calculated mean ± SD of the percentage difference between the noninvasive and the pneumotachograph volumes, the latter taken as reference (% difference = $100 \times [V_{T\,\text{pneumograph}} - V_{T\,\text{pneumotachograph}}]/V_{T\,\text{pneumotachograph}}$). Calibration was judged satisfactory when this percentage difference was less than ±10% during various breathing patterns over a range of breathing volumes of 200–1,500 ml. In addition to V_T measured from the sum of RC and ABD excursions, the following variables were derived by the computer: f, minute ventilation ($\dot{V}_E$), inspiratory time (T_i), expiratory time (T_e), mean inspiratory flow (V_T/T_i), respiratory duty cycle (T_i/T_{tot}), and the RC/V_T ratio. Changes in end-expiratory level, which can be defined as end-expiratory volume (EEV) once the noninvasive device is properly calibrated, were derived from separate changes in end-expiratory positions of RC and ABD excursions.

In addition, arterial hemoglobin oxygen saturation (Sa_{O_2}) was continuously measured with a Hewlett-Packard 47201A® ear oximeter, and end-tidal carbon dioxide concentration (FE_{CO_2}) was measured with an infrared CO_2 analyzer (Godart, model KK), the expired air being continuously sampled from a small catheter introduced through the nostrils into the pharynx after topical anesthesia. Arterial blood pressure and heart rate were recorded each min during the first 10 min, then every 5 min, with an automatic blood pressure device (Dinamap®, Applied Medical Research Corporation, Tampa, FL).

Experimental Protocol

Each subject was studied three times at intervals of at least 1 week, once after administration of ketamine, once after droperidol, and once after a placebo, the sequence being performed in a double-blind, randomized fashion. Each drug was administered at a constant rate over a 5-min period in a running intravenous 5% dextrose infusion. Total dose of ketamine was 1 $mg \cdot kg^{-1}$, and of droperidol 0.1 $mg \cdot kg^{-1}$. The subjects were studied in the afternoon, at least 6 h after the last meal. They were investigated in a quiet, dark room, lying supine in a standard hospital bed, having the arms at the sides.

During the calibration procedure, the volunteers wore a nose clip and breathed through a mouthpiece and a heated Fleisch® #2 pneumotachograph. After proper calibration, the subjects were disconnected from the pneumotachograph. They were comfortably installed with ear phones, listening to music, and with the eyes covered with a cloth, so that they were not aware of what was going on around them. After a 30-min rest period, data recording was begun. Observations were made during the 15 min before and for 60 min after administration of each "drug." The calibration procedure was repeated at the end of the experiment to test the reliability of our results.

Data Analysis

The microcomputer printed out respiratory variables for each single breath and additionally calculated mean ± SD values and their variation coefficient ($SD/\bar{x}$) of data for periods of 1 min. This breath-by-breath computer analysis in conjunction with the visual examination of the chart recorder tracings enabled us to disregard artifacts due to gross body movement. Mean FE_{CO_2} and Sa_{O_2} data for each min were read from the chart recorder by taking mean values of five consecutive breaths. Because of a large variability in the timing of the responses, respiratory data were cumulated and averaged for periods of 5 consecutive min for statistical analysis and presentation in figures. The number and duration of apneic episodes, defined as an expiratory pause lasting longer than 10 s, were measured throughout the study.

A one-way analysis of variance was used to detect a statistical effect over time as well as to compare the three different treatment groups. A modified two-tailed unpaired *t* test (Bonferroni method) served to detect significance among groups, with a probability value of $P < 0.05$ considered to be significant.

Results

After calibration of the noninvasive respiratory monitoring device, comparison between volumes measured

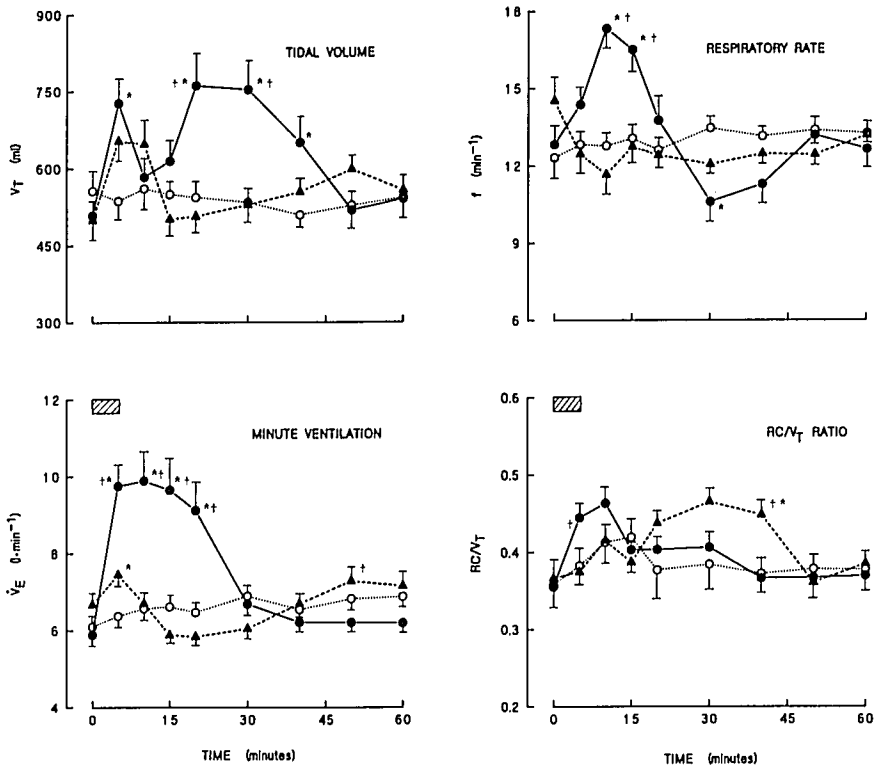

FIG. 1. Effect of placebo (O), droperidol (▲; 0.1 mg·kg^{-1}), or ketamine (●; 1 mg·kg^{-1}) on tidal volume (V_T), respiratory rate (f), minute ventilation ($\dot{V}_E$), and rib cage/tidal volume ratio (RC/V_T). Drugs were administered at a constant rate over a 5-min period (*hatched bar*). Each point represents mean values ± SE of data recorded between 2 min before and 2 min after the data point in eight subjects. * indicates that the data point is significantly different ($P < 0.05$) from the time-matched placebo data point; † indicates a significant difference ($P < 0.05$) between droperidol and ketamine data points.

simultaneously by the pneumographs and the pneumotachograph showed that the former differed from the latter by a mean difference of +0.7 ± 3.3% ($\bar{x}$ ± SD), which means that the 95% confidence limits for an individual V_T measurement with the pneumographs was approximately ±7% (2 SD) of the V_T measured with the pneumotachograph. At the end of the experiment, the difference in volume estimation was −0.2 ± 5.8%, which was not statistically different from data obtained at the beginning of the study.

The effects of the three treatment regimens on respiratory variables are illustrated in figures 1 and 2. No significant change in any variable was detected after administration of placebo (one-way analysis of variance). Droperidol produced only minimal and inconsistent effects on breathing patterns. In contrast, ketamine induced a significant ($P < 0.001$) and persistent increase in $\dot{V}_E$ from 5 to 20 min after the start of the drug infusion. This was the result of a successive contribution of an increase in V_T and f. V_T changed in a biphasic pattern. A first peak increase occurred at 5 min, followed by a second peak between 20 and 30 min. Superimposed on this V_T contribution, a delayed increase in f, peaking between 10 and 15 min, was responsible for a sustained elevated $\dot{V}_E$ for 20 min. At 30 min, still significantly increased V_T values were associated with a relatively reduced f, resulting in baseline $\dot{V}_E$ values.

Partitioning of $\dot{V}_E$ into respiratory driving (V_T/T_i) and timing (T_i/T_{tot}) component demonstrates that respiration was stimulated with ketamine by both components for the first 15 min (fig. 2). Thereafter, only V_T/T_i was significantly increased, and its stimulatory effects was partially neutralized by a significant decrease in T_i/T_{tot}. Ketamine produced most of its effects on f by changing T_e, since T_i was only minimally affected. Despite the important increases in V_T and f with ketamine, the RC contribution to V_T (RC/V_T ratio) was not significantly different from values obtained during placebo administration in which no change in respiratory pattern occurred. All respiratory variables returned to baseline values at 50 min.

A representative recording of the effect of ketamine on separate excursions of RC and ABD contributions to V_T (V_T = RC + ABD) is illustrated in figure 3. Two minutes after the start of ketamine infusion, V_T increased consistently without change in f. At 7 min, V_T had returned to preinjection values, but with an increased f. Finally, the right panel of fig. 3 shows the breathing pattern between 25 and 30 min after the start of the ketamine infusion. This is characterized by large V_T interrupted by periods of expiratory pauses, some lasting more than 10 s. Note the slight increase in the end-expiratory position of the RC (~130 ml), which is matched with a correspondent decrease of the end-expiratory positions of the ABD, so that overall EEV is not significantly affected.

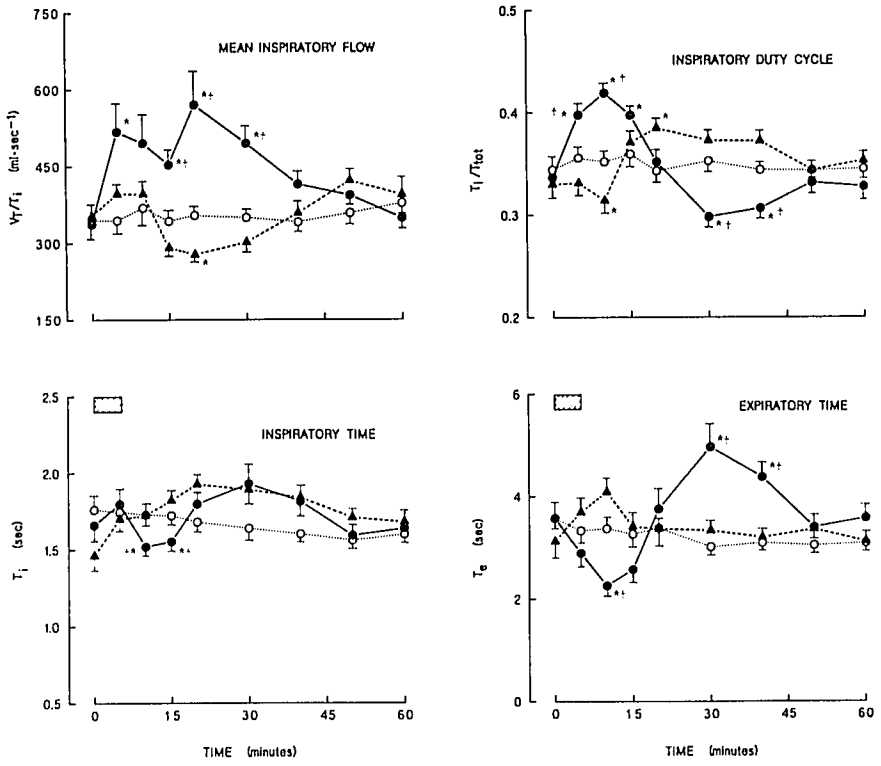

FIG. 2. Effect of placebo (O), droperidol (▲; 0.1 mg·kg^{-1}), or ketamine (●; 1 mg·kg^{-1}) on mean inspiratory flow (V_T/T_i), inspiratory duty cycle (T_i/T_{tot}), inspiratory time (T_i), and expiratory time (T_e). Drugs were administered at a constant rate over a 5-min period (*hatched bar*). Each point represents mean values ± SE of data recorded between 2 min before and 2 min after the data point in eight subjects. * indicates that the data point is significantly different ($P < 0.05$) from the time-matched placebo data point; † indicates a significant difference ($P < 0.05$) between droperidol and ketamine data points.

EEVs relative to preinjection values were not significantly changed with placebo. Droperidol produced a slight, although significant, decrease in EEV of about 60 ml between 10 and 30 min. In contrast, EEV was initially increased with ketamine and thus significantly different from droperidol for 10 min.

Analysis of variation coefficients (SD/$\bar{x}$) for each respiratory variable cumulated over the entire study period indicated that breathing pattern with ketamine was more variable, *i.e.*, resulting in a significantly higher mean SD/$\bar{x}$ for each variable (except for RC/V_T), than with the administration of droperidol or placebo (table 1). This was due to an increased variability in individual respiratory responses to ketamine combined with a nonhomogeneity of its effects at identical time intervals.

Sa_{O_2} values during the whole study period were never significantly different between treatment groups, although different individual baseline values were recorded. During

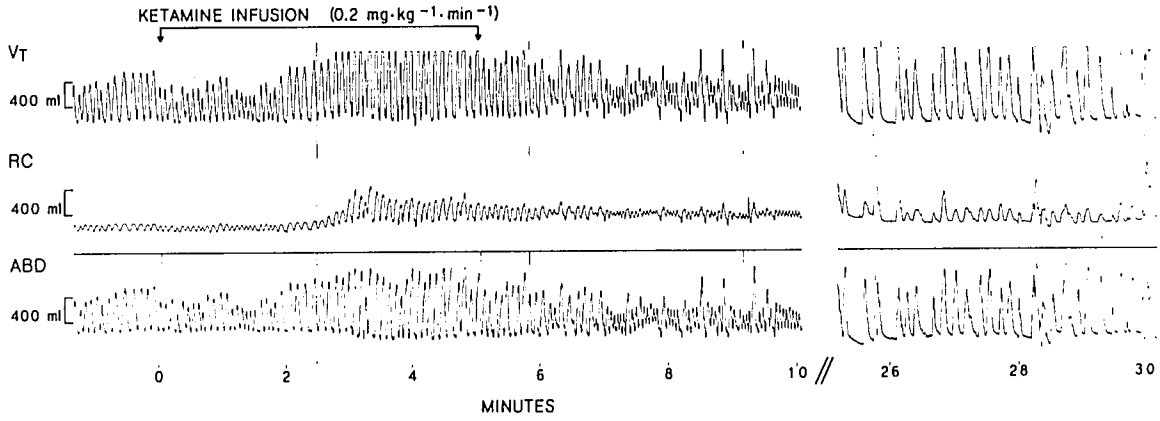

FIG. 3. Pneumograph recording of breathing pattern during and after infusion of ketamine in a representative subject. *Upper panel* represents tidal volume (V_T) as the electrical sum of rib cage (RC, *middle panel*) and abdominal (ABD, *lower panel*) tracings expressed in milliliters after calibration. Note three distinct phases induced by ketamine: 1) increased V_T; 2) increased f; 3) large V_T with low f and occasional apneas. End-expiratory position of V_T and the RC/V_T ratio (range, 0.17–0.24) remained stable.

TABLE 1. Mean ± SD Variation Coefficients of Respiratory Variables Cumulated over the 60-min Study Period Following Drug Administration

Variable (%)	Placebo	Droperidol	Ketamine	F ratio
V_T	37 ± 27	33 ± 26	47 ± 37*	20.4
f	22 ± 14	23 ± 21	34 ± 25*	46.5
V_T/T_i	34 ± 27	35 ± 29	46 ± 82*	8.2
T_i/T_{tot}	22 ± 13	22 ± 16	29 ± 18*	26.9
RC/V_T	27 ± 52	23 ± 22	24 ± 19	NS
EEV	1.5 ± 1.8	2.4 ± 4.7*	2.4 ± 3.9*	7.7

Variation coefficient: (1 SD/mean) × 100.
Data represent the mean ± SD of the 60 variation coefficients obtained for every min after the start of drug infusion from each of the eight subjects; n = 60 × 8 = 480.
See text for abbreviation of respiratory variables.
* $P < 0.05$ significantly different from placebo; NS = not significant.

the 60-min study period, there was an overall inverse relationship between FE_{CO_2} and correspondent $\dot{V}_E$ values. However, during the important ventilatory stimulation observed with ketamine between 5 and 20 min, FE_{CO_2} data were not lower than those measured later when $\dot{V}_E$ values were back to baseline.

The mean number and cumulative duration of apneic episodes noted during the 60-min period following drug administration are presented in table 2. Apneic episodes occurred in seven of eight subjects following ketamine, but important individual differences were noted both in number as well as in cumulative duration. Ketamine produced significantly ($P < 0.01$) more periods of apnea than droperidol or placebo. With droperidol, apneic episodes occurred mainly between the 6th and 10th min after administration. With ketamine, the first episodes were observed between the 6th and 8th min, and thereafter recurred between the 25th and 40th min. The absence of paradoxic movement of RC and ABD excursions during these episodes of flat V_T tracings suggests that the apneic episodes were of central origin and not due to upper airway obstruction. This is further supported by the stable end-expiratory CO_2 level recorded during the apneic episodes.

TABLE 2. Incidence, Mean ± SD Number, and Cumulative Duration of Apneic Episodes during the 60-min Period Following Drug Administration

	Placebo (n = 8)	Droperidol (n = 8)	Ketamine (n = 8)
Number of subjects with apneic episodes	3	5	7
Mean number of apneic episodes	3 ± 5	4 ± 8	18 ± 17*
Range	0–11	0–24	0–55
Mean cumulative duration of apneic episodes (s)	40 ± 59	72 ± 129	254 ± 245*
Range	0–132	0–365	0–770

Apneic episodes: expiratory pause > 10 s.
* $P < 0.01$ significantly different from placebo.

Administration of droperidol produced a moderate, although statistically significant, decrease in systolic and diastolic blood pressure between 20 and 40 min after injection, without significant change in heart rate. Ketamine induced a major, clinically important cardiovascular stimulation during the first min of administration, with systolic blood pressure and heart rate remaining significantly different from placebo for 15 and 25 min, respectively.

Although the study was not designed to evaluate psychoactive or other side effects, every volunteer receiving ketamine reported hallucinatory dreams, mainly floating sensations and sensory dissociation. Six out of eight subjects described these experiences as pleasant. Droperidol did not produce sleep or amnesia, but the subjects experienced different degrees of inner restlessness, dysphoria, and tiredness, which lasted several hours after drug infusion. Despite the restlessness, all subjects remained in the same supine position during the 1-h monitoring period.

Discussion

This study demonstrates that in healthy volunteers, ketamine infused over 5 min at a dose of 1 $mg \cdot kg^{-1}$ produces no respiratory depression as documented by a continuous noninvasive assessment of $\dot{V}_E$, FE_{CO_2}, and Sa_{O_2}. The multiple apneic episodes recorded during and after ketamine infusion seem to occur as compensation for the hyperventilation induced by ketamine, and not due to a primarily respiratory depressant effect, because FE_{CO_2} values were never above 6 volume per cent and Sa_{O_2} values did not decrease below 92%. This is in direct contrast to the observations made by Zsigmond *et al.*,[6] who reported major arterial hypoxemia after bolus administration of 2 $mg \cdot kg^{-1}$ ketamine in adult gynecology patients. This difference may be explained by an effect of dose or injection rate. However, Virtue *et al.*[2] and, more recently, Rust *et al.*[3] administered ketamine as a rapid bolus injection in subjects breathing room air at the same dosage as Zsigmond and did not show any significant change in Pa_{O_2}, Pa_{CO_2}, or arterial–venous blood oxygen content difference $[C(a-v)_{O_2}]$. Furthermore, the rate of ketamine administration seems not to influence its effects to any great extent, since Wilson *et al.*[1] reported respiratory effects with a bolus injection that were similar in intensity, onset, and duration to those observed with our 5-min infusion. In addition, the cardiovascular and psychoactive effects we measured were comparable with those reported by others administering ketamine by bolus injection.[1,2,5] The patients in the study by Zsigmond *et al.* had been premedi-

cated with intramuscular diazepam (0.15 $mg \cdot kg^{-1}$) and meperidine (1.5 $mg \cdot kg^{-1}$) or morphine (0.15 $mg \cdot kg^{-1}$). This fact alone may have enhanced, if not induced, the occurrence of the long-lasting apneic episodes with concomitant arterial hypoxemia they observed.

The experimental design of the present study differed greatly from previous reports investigating the effects of drugs on respiration in humans. First, the double-blind administration of a placebo allowed a statistical comparison that took into account the spontaneous variability of breathing pattern observed over time. (Note particularly the number of apneic episodes recorded with placebo, shown in table 2). Second, we standardized the subject population to minimize the possible influence of age, gender, health status, and chronic drug intake, or the concomitant use of premedicant drugs that have been administered in some of the previous human investigations.[2,3,6] Finally, the use of a "noninvasive" respiratory measuring method avoided the disturbing influence of face mask or mouthpiece, which not only adds dead space and resistance to breathing, but also stimulates the central nervous system by oro–nasal afferent stimuli, hence significantly affecting respiration pattern.[8]

Whereas every subject presented a characteristic cardiovascular stimulation and consistent psychoactive effects with ketamine, respiration was more variably affected among individuals, both in terms of intensity and duration of its effects. Nevertheless, a statistically and clinically significant ventilatory stimulation was produced, with both components of respiratory control,[13] *i.e.*, neuromuscular inspiratory drive (V_T/T_I), and central cyclic timing mechanism (T_I/T_{TOT}), being stimulated. These results are in accordance with an early study in burned children, where an intravenous bolus administration of 1 $mg \cdot kg^{-1}$ ketamine produced a 250% increase in $\dot{V}_E$ and a 100% increase in V_T, with a peak effect occuring between 2 and 5 min after injection.[1] The increase in $\dot{V}_E$ induced by ketamine is specific to this anesthetic agent, because other intravenous anesthetics investigated so far depress ventilation either by decreasing T_I/T_{TOT} (althesin, gamma-hydroxybutyric acid),[14] or V_T/T_I (diazepam, midazolam),[15,16] or both (thiopentone).[17]

The underlying mechanism by which ketamine stimulates ventilation in humans is not known. A central and/or peripheral stimulatory mechanism may be involved. Based on studies evaluating its effects on the cardiovascular system, the sympathomimetic actions of ketamine are thought to be primarily the result of a direct stimulation of central brain stem structures.[18] Because respiratory and cardiovascular neurones are anatomically intimately intertwined, it is possible that they are similarily affected. Ketamine also produces activation of the pituitary–adrenal axis with adrenal release of catecholamines,[19] which may secondarily increase respiration. Indeed, in human subjects, intravenous infusion of norepinephrine and isoproterenol has been shown to increase $\dot{V}_E$ and reduce FE_{CO_2} by peripheral stimulation of arterial chemoreceptors.[20] However, the absence of a major decrease in FE_{CO_2} despite the important increase in $\dot{V}_E$ observed in the present study suggests that, besides its probable direct effect on medullary respiratory neurones, the ventilatory stimulation of ketamine might also be due to a concomitant increase in CO_2 production, balanced by an appropriate increase in $\dot{V}_E$, with the physiologic dead space (V_D/V_T) remaining constant. An increase in V_D/V_T due to the bronchodilating properties of ketamine in the absence of increased CO_2 production is an alternative explanation.

Our data indicate that the respiratory stimulation produced by ketamine is not confined to a preferential breathing compartment, because the RC/V_T ratio was unchanged. These findings are similar to those reported by Gilbert *et al.*[21] in subjects investigated during inhalation of CO_2, in whom the fraction of RC to total ventilation was found to be independent of the actual value of $\dot{V}_E$ in seven of ten subjects, and slightly increased in the other three. This suggests that, unlike other anesthetics that depress either the RC (halothane,[22,23] and morphine[24]) or the ABD (midazolam[16]) contribution to ventilation, ketamine stimulates both the spinal motor control system serving peripheral intercostal neurones and also the medullary respiratory center controlling phrenic motor neurones.

Neither during its maximal respiratory stimulation, nor during subsequent breathing, did ketamine significantly affect the EEV measured from separate end-tidal positions of RC and ABD. The absence of a decrease in EEV suggests that respiratory muscle tone at end-expiration was conserved, and that there was no significant change in lung volume remaining in the chest during tidal breathing. One cannot rule out the occurrence of some microatelectasis reducing FRC measured by a gas dilution method, which would be matched by a parallel shift of peripheral blood into the chest maintaining similar external chest-wall dimensions.[25] However, this seems unlikely, since a recent study in young children documented no significant changes in FRC determined by a closed-circuit helium dilution method.[26]

Although droperidol has opposite and antagonistic actions to those of ketamine on both the circulation and central nervous system,[9,10] the present study shows that it has no consistent and clinically important effects on breathing pattern and thoraco–abdominal motion in human volunteers. This confirms a recent investigation by Prokocimer *et al.*[27] demonstrating no significant effect of an intravenous dose (0.3 $mg \cdot kg^{-1}$) on ventilatory and mouth occlusion pressure responses to CO_2 rebreathing in healthy subjects, although important individual variations in response were noted. Cottrell *et al.*[28] reported a

moderate decrease in FRC measured by the dilution method following 0.07 $mg \cdot kg^{-1}$ intramuscular droperidol. This is similar to the significant, although clinically unimportant, decrease in EEV measured in the present study.

The clinical implications of this study are that ketamine administered by intravenous infusion (0.2 $mg \cdot kg^{-1} \cdot min^{-1}$) is devoid of respiratory depressant effects in healthy subjects. Although a large number of apneic episodes may occur, their potential effect on gas exchange is counterbalanced by a centrally and/or peripherally mediated important ventilatory stimulation of both driving and the timing of the respiratory control mechanism. Droperidol, except for a moderate decrease in EEV, has no respiratory effect when administered alone. Further studies are required to evaluate if the effects of droperidol that reduce or abolish the hemodynamic and psychoactive actions of ketamine are also effective in opposing the respiratory stimulation produced by this drug.

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