Sedation with sufentanil in patients receiving pressure support ventilation has no effects on respiration: a pilot study

[La sédation avec du sufentanil chez des patients qui reçoivent une assistance ventilatoire inspiratoire n'a pas d'effet sur la respiration : une étude pilote]

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Purpose: To evaluate the effects of sedation with sufentanil on respiratory drive, respiratory pattern, and gas exchange of critically ill patients during pressure support ventilation.

Methods: In this prospective observational cohort study, we observed 12 adult patients receiving partial ventilatory support for acute respiratory failure. Each subject received a continuous infusion of sufentanil at 0.2 to 0.3 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ to obtain a modified Ramsay sedation score between 2 and 3. In basal conditions and at variable distance from the beginning of the sufentanil infusion (10', 30', 60', 120', 24 hr) we evaluated gas exchange, hemodynamic variables, respiratory rate (RR), tidal volume (TV), respiratory pattern, respiratory drive (P0.1) and inspiratory impedance of the respiratory system [P0.1/TV/inspiratory time (Ti)].

Results: The continuous *iv* administration of 0.2 to 0.3 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ of sufentanil resulted in the desired level of sedation. No significant heart rate, heart rhythm and blood pressure changes were observed. Sufentanil infusion did not affect TV, minute volume, Ti/inspiratory duty cycle, RR, P0.1, P0.1/TV/Ti and gas exchange did not change significantly over the study period.

Conclusion: A continuous infusion of sufentanil induces "awake" sedation with no detectable effects on respiratory variables in critically ill patients during partial ventilatory support.

Objectif : *Évaluer les effets de la sédation avec sufentanil sur la commande respiratoire, le rythme respiratoire et les échanges gazeux chez les grands malades pendant l'assistance ventilatoire inspiratoire.*

Méthode : *Nous avons observé 12 patients adultes sous assistance ventilatoire inspiratoire pour insuffisance respiratoire aiguë dans le cadre d'une étude prospective par observation. Chaque sujet a reçu une perfusion continue de 0,2 à 0,3 $\mu g \cdot kg^{-1} \cdot h^{-1}$ de sufentanil pour obtenir un score de sédation de Ramsay modifié entre 2 et 3. Au départ et à intervalles variables après le début de la perfusion de sufentanil (10', 30', 60', 120', 24 h), nous avons évalué les échanges gazeux, les variables hémodynamiques, la fréquence respiratoire (FR), le volume courant (VC), le rythme respiratoire, la commande respiratoire (P0,1) et l'impédance inspiratoire du système respiratoire [P0,1/TV/temps d'inspiration (Ti)].*

Résultats : *L'administration iv continue de 0,2 à 0,3 $\mu g \cdot kg^{-1} \cdot h^{-1}$ de sufentanil a produit le niveau désiré de sédation. Aucune modification significative de la fréquence cardiaque, du rythme cardiaque et de la tension artérielle n'a été observée. Le sufentanil n'a pas affecté le VC, la ventilation-minute, le Ti/cycle inspiratoire complet, le RR, la P0,1, la P0; 1/VC/Ti et les échanges gazeux n'ont pas changé de façon significative au cours de l'étude.*

Conclusion : *Une perfusion continue de sufentanil induit une sédation «vigile» sans effets détectables sur les variables respiratoires chez les grands malades pendant l'assistance ventilatoire inspiratoire.*

SEDATION and analgesia are widely used in intensive care unit (ICU) patients, particularly during mechanical ventilation.

Critically ill patients often experience stressful maneuvers such as endotracheal intubation and mechanical ventilation, suctioning or painful diagnostic and therapeutic interventions. The net effect is an increase in catecholamine secretion and oxygen demand with further systemic and coronary vasoconstriction.[1] An adequate level of analgesia and sedation (analgesia-sedation) is thus a precious tool to control

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the patient's pain and anxiety by modulating the response to stress.

Among the large variety of sedatives and analgesics commonly available,[2] opioids, especially morphine and fentanyl, are widely used because of their efficacy in pain control and psychological discomfort mitigation. However, their well known side effects such as constipation, possible dependence, difficult arousal, and, principally, respiratory depression[3] in response to the doses normally utilized have often restricted their use only to patients undergoing controlled mechanical ventilation.

The introduction into clinical use of new synthetic opioids with limited adverse effects particularly on the respiratory system has offered an option for the analgesia-sedation of critically ill patients. Sufentanil is a potent opioid with remarkable sedative properties,[4] tenfold more powerful than fentanyl. Its high liposolubility results in a faster passage through the blood-brain barrier with an easier titration, a better clearance and a shorter duration of action compared to previous opioids.[4] Experimental data in patients undergoing general anesthesia have shown that sufentanil has a lower incidence of respiratory depression and cardiovascular instability.[5]

This drug could therefore represent a good choice for critically ill patients requiring long-term analgesia-sedation, especially during partial ventilatory support techniques (i.e., ventilatory support modes preserving spontaneous breathing activity) where analgesia-sedation with minimal effects on spontaneous respiratory drive is required. Unfortunately few data are available regarding the respiratory effects of analgesia-sedation with sufentanil in patients during partial ventilatory support modes.[6]

We conducted a prospective physiologic pilot study aimed at evaluating the effects of the continuous infusion of a single sedative, sufentanil, at 0.2 to 0.3 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ on central respiratory drive, gas exchanges, respiratory pattern and inspiratory impedance of the respiratory system in a group of 12 patients during pressure support ventilation (PSV).

Patients and methods

Twelve consecutive patients, endotracheally intubated and mechanically ventilated, were enrolled from August to November 2000 in the 21-bed general ICU located in our University Hospital in Rome. The research protocol was approved by our Institutional Ethics Committee and informed consent was obtained from each patient or their next of kin.

At the time of inclusion the patients had received mechanical ventilation for an average of 7 ± 5 days. Enrollment criteria were as follows: i) ventilation with pressure support mode; and ii) presence of agitation, anxiety or restlessness requiring pharmacological sedation (a modified Ramsay Score = 1).[7] The modified Ramsay sedation score (Table I) is commonly and widely used to measure sedation on a scale ranging from 1 to 6 (where 6 = patient asleep and completely unresponsive to stimuli).

Patients with hemodynamic instability, chronic obstructive pulmonary disease, acute liver failure (serum bilirubin > 25 $mmol \cdot L^{-1}$), acute renal failure (serum creatinine > 100 $mmol \cdot L^{-1}$) and age less than 18 yr were excluded from the study.

All patients were ventilated with a Siemens 300 ventilator (Siemens Elema, Sweden) in PSV mode (mean values of pressure support: 17 ± 3 cm H_2O) and received different levels of positive end-expiratory pressure according to their clinical requirements (mean values 7 ± 2 cm H_2O, range 5–9 cm H_2O). The FIO_2 ranged between 0.4 and 0.5. The pressure trigger was set at -1 cm H_2O, checking the absence of auto-trigger effect.

For the purposes of this study, the endotracheal tube was connected directly to a differential pressure transducer for airflow (V') and airway opening pressure (Pao) recording. The V' and Pao transducers were connected to a Bicore CP 100 respiratory mechanics monitor (Bicore, CA, USA), where tidal volume (TV) is obtained by V' signal integration on time.

V', Pao and TV recording can be immediately printed on paper or digitized and stored on a personal computer via specific interface software and analyzed with a specifically designed program (Anadat™ 5.1, Bicore CP 100 edition, Montreal, QC, Canada). This system to evaluate respiratory mechanics has already been described and validated.[8,9]

Airway occlusion pressure after 100 msec (P0.1)[10] was measured by activating the expiratory pause knob of the ventilator to obtain a brief occlusion of the system (inspiratory and expiratory valves close simultaneously); as a consequence the patient's inspiratory effort occurs against a completely closed system, allowing the indirect evaluation of the central respiratory drive.[11]

Study protocol

In basal conditions, arterial blood was sampled for blood gas analysis (Stat Profile, Nova Biomedical, USA) and ten consecutive respiratory cycles were averaged to determine: respiratory rate (RR), TV, inspiratory and expiratory time (Ti, Te), inspiratory duty cycle (Ttot) and mean inspiratory flow (TV/Ti). The whole breathing cycle and its inspiratory and

TABLE I Modified Ramsay sedation score

Modified Ramsay sedation score	*Definition*
1	Anxious, agitated or restless
2	Cooperative, oriented or tranquil
3	Responds to command only
4	Brisk response to firm nail bed pressure
5	Sluggish response to firm nail bed pressure
6	No response to firm nail bed pressure or significant clinical stimulus

TABLE II Baseline characteristics of the patients

Patients	*BMI*	*Age*	*Sex*	*SAPS II*	*Diagnosis*	*Outcome*
1	23.1	53	M	28	Pneumonia/ALI	S
2	25	60	F	35	Peritonitis/ALI	S
3	28.7	57	M	23	Multiple trauma	S
4	23.18	65	M	24	Pneumonia/ALI	S
5	20.9	28	F	73	ARDS	S
6	27.1	68	M	56	CPE	S
7	21.2	72	M	45	ALI	S
8	21.3	76	F	45	ARDS	D
9	27	63	F	21	Pneumonia/ALI	S
10	21.6	21	M	31	Sepsis	S
11	23.4	79	M	39	Peritonitis/ALI	D
12	23.4	73	F	48	CPE	D

BMI = body mass index; ARDS = Acute Respiratory Distress Syndrome; ALI = acute lung injury; CPE = cardiogenic pulmonary edema; SAPS = Simplified Acute Physiology Score; S = survived; D = died.

expiratory components were expressed as Ttot, Ti and Te, respectively.

Basal P0.1 (i.e., airway occlusion pressure at 0.1 sec) was evaluated in triplicate, at 20 sec intervals. The inspiratory impedance of the respiratory system was also calculated as P0.1/ (TV/Ti).

After the basal measurements, an infusion of sufentanil was started, using a syringe pump, via a central vein at the initial dose of 0.3 $\mu g \cdot kg^{-1} \cdot hr^{-1}$; this dose was chosen following our previous clinical experience and reduced at 0.2 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ at T1 if a modified Ramsay sedation score of 2 was obtained. No medication with possible interaction with opioids was administered concomitantly.

The above-mentioned variables were again evaluated after ten minutes (T1), 30 min (T2), 60 min (T3), 120 min (T4) and 24 hr (T5). Arterial blood was sampled at T2 and T5 for blood gas analysis. At the same time intervals, the level of sedation was evaluated using the modified Ramsay sedation score; the desired modified Ramsay sedation score was between 2 and 3.

During the course of the study the electrocardiogram, invasive blood pressure and pulse oximetry were monitored continuously.

Statistical analysis

All results are expressed as mean ± standard deviation. Comparisons were performed with the one-way analysis of variance for repeated measures. Ramsay sedation score at different times was compared with Chi squared test. Significance was defined as a P value lower than 0.05.

Results

The patients' anthropometric characteristics are reported in Table II along with their admission diagnosis, severity score and outcome.

The continuous *iv* infusion of 0.2 to 0.3 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ of sufentanil allowed us to easily obtain "awake" sedation (i.e., a sedation score ranging between 2 and 3) in all patients.

No significant heart rate, heart rhythm and arterial blood pressure changes were observed during the study period (Table III). All the patients included had a mean Glasgow coma scale of 14 (range 12–15).

Our data (Figure) show that sufentanil had no significant effects on the respiratory variables evaluated. In particular, TV, minute volume, Ti/Ttot, RR, P0.1 and P 0.1/TV/Ti remained stable during the entire study, as well as gas exchange (Table III).

No other side effect, directly or indirectly related to the infusion of sufentanil was reported during the study. No patient required modifications of the infusion rate outside the prescribed range; no modification of the ventilator setting was required for clinical reasons.

Sufentanil administration was continued after the end of the study for a mean time of 5 ± 1.9 days without clinical side effects; nine out of 12 patients where discharged from the ICU, while three patients died (two of septic shock and multiple organ failure, one of cardiogenic shock).

Discussion

The results of our pilot physiologic study suggest that the continuous infusion of sufentanil may be used as a single sedative agent, allowing to mitigate patient discomfort and obtain the desired level of awake sedation with no significant effects on respiratory drive, minute volume, respiratory frequency, respiratory pattern, blood gases and hemodynamics.

Despite their clinical efficacy in terms of pain control and sedation, the use of opioids as single sedatives has been restricted in the past, especially in patients receiving partial ventilatory support,[3] by their well-

TABLE III Hemodynamic and gas exchange variables during the study

	BASAL		*T 10'*		*T 30'*		*T 60'*		*T 120'*		*T 24 hr*		***P***
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	
PaO_2	122.6	47.4	n.e.	n.e.	126	48.1	n.e.	n.e.	n.e.	n.e.	128	46	NS
$PaCO_2$	36.4	8.4	n.e.	n.e.	34.5	7.1	n.e.	n.e.	n.e.	n.e.	35	8	NS
PH	7.46	0.06	n.e.	n.e.	7.47	0.05	n.e.	n.e.	n.e.	n.e.	7.47	0.05	NS
SAP	132.5	21.4	139.7	25	137.2	26.7	128.3	24.9	126.4	14.5	126.4	14.5	NS
DAP	71.8	12.5	73.3	13.9	71.8	15.9	65.7	16.9	64.8	11.1	64.8	11.1	NS
HR	99.6	21.2	99.7	23.8	105.5	19.2	99.5	19	96.9	17.4	96.9	17.4	NS

PaO_2 and $PaCO_2$ are expressed in mmHg; SAP = systolic arterial pressure; and DAP = diastolic arterial pressure are expressed in mmHg; HR = heart rate is expressed in beats·min^{-1}; n.e. = not evaluated; NS = not significant.

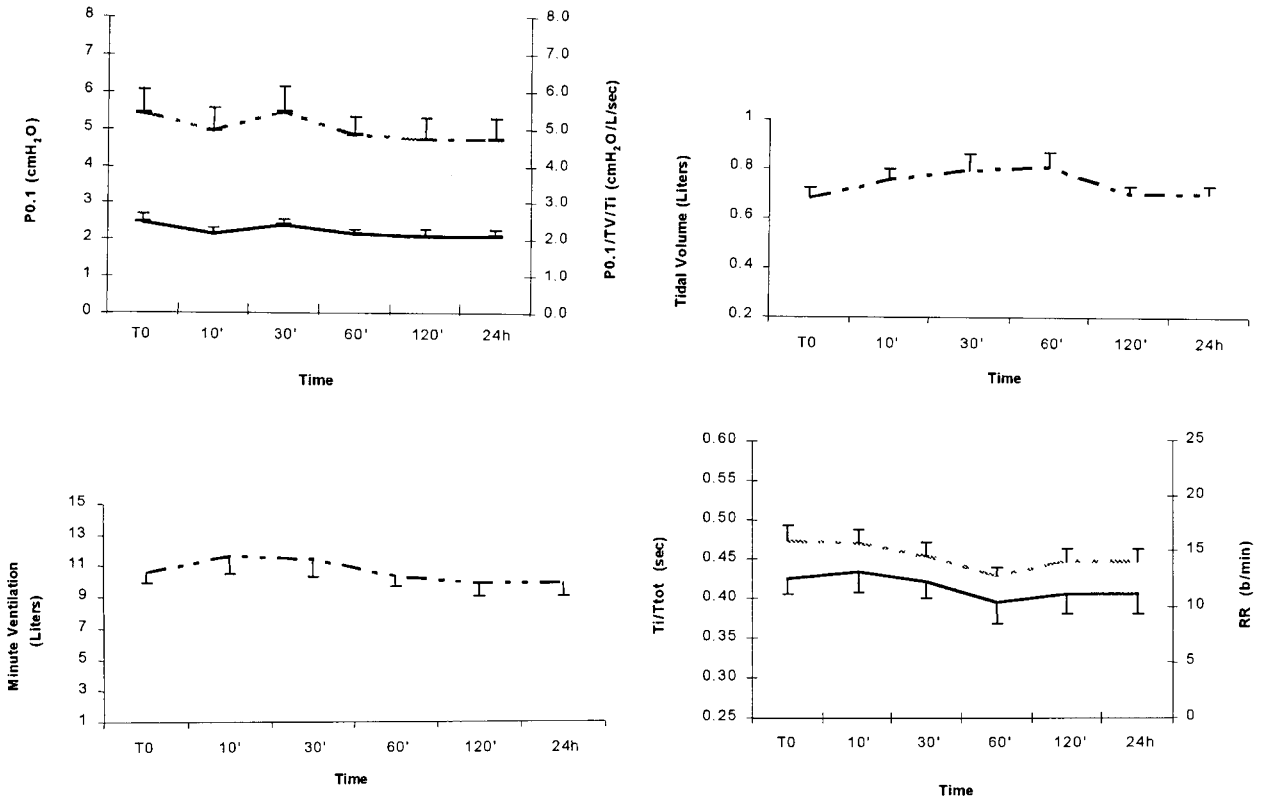

FIGURE Effects of sufentanil on respirtory variables
Top left: airway occlusion pressure (P0.1; solid line) and inspiratory impedance of the respiratory system (P0.1/TV/Ti; dashed line) *P* = NS; top right: tidal volume *P* = NS; bottom left: minute ventilation *P* = NS; respiratory rate (RR; dashed line) and breathing pattern (Ti/Ttot; solid line) *P* = NS.

known effects on respiratory drive, sometimes manifest even at low doses.

The analgesic action of opioids seems to be mainly due to an activation of μ_1-receptor with, eventually, a mild effect on μ_2 and δ-receptors, by contrast considered the receptors mostly involved in the depression of respiratory drive.[12]

Morphine and fentanyl act on all receptor subtypes, providing effective analgesia at the price of a marked respiratory drive reduction. Moreover, their accumulation effect, particularly evident after long-term continuous infusion, may exacerbate respiratory depression.

Sufentanil, a more recent synthetic opioid, possesses attractive properties for continuous infusion in ICU patients, acting almost exclusively on μ_1-receptors. Moreover, its context-sensitive half-life (i.e., the time required to obtain a 50% reduction in the plasma drug concentration after the end of the infusion) is sevenfold lower that of fentanyl with, consequently, a reduced risk of accumulation.[4,12,13]

Our data confirm and expand the finding of Prause *et al.*,[6] who retrospectively evaluated the charts of 211 critically ill patients receiving a continuous infusion of sufentanil at different doses (range 0.075–1.22 $\mu g \cdot kg^{-1} \cdot hr^{-1}$) to obtain a modified Ramsay sedation score between 2 and 4 during various partial respiratory support modes (continuous positive airway pressure, synchronized intermittent mandatory ventilation or PSV). These authors observed only a modest increase of $PaCO_2$ from 39.5 ± 7.3 mmHg (before initiating sedation) to 42.7 ± 6.8 mmHg during the continuous infusion of sufentanil. Unfortunately, in their retrospective study, the authors did not perform measurements of respiratory drive or respiratory pattern variables but major modifications were considered unlikely, in view of the stability of $PaCO_2$ values.

To our best knowledge this is the first study assessing the effects of sufentanil on respiratory drive, respiratory pattern and gas exchanges in critically ill patients receiving partial ventilatory support. At the doses used and for the short period of time considered, our data support the absence of major effects on respiratory drive, even when respiratory drive is evaluated with a precise and very sensitive variable such as P0.1, for a relatively prolonged period of time.[10,11,14]

P0.1 is an indirect parameter of central respiratory drive depending on the intensity by which respiratory centres, mechano, and chemoreceptors stimulate the inspiratory motoneurons.[10] P0.1 has been confirmed to be a reliable indicator of the activity of respiratory centres, both in spontaneously breathing subjects[10,14] and in ICU patients during assisted mechanical ventilation.[11,15,16]

Furthermore, the absence of significant modifications of the inspiratory impedance of the respiratory system [P0.1/(TV/Ti)] suggests that, at least with the doses used, other respiratory adverse effects such as chest-wall rigidity or alterations of respiratory mechanics were avoided. P0.1/(TV/Ti) measures the inspiratory mechanical transformation of the respiratory drive signal and defines the relation between central drive (P0.1) and the efficacy of V' generation for a given level of respiratory system resistances and compliance.[17]

A sufentanil infusion allowed us to maintain our patients in a condition of "awake sedation," free from pain and anxiety, well responsive to orders and, above all, breathing in partial ventilatory support mode, with all the consequent advantages related to the preservation of spontaneous breathing activity in terms of lung mechanics, hemodynamics and prevention of respiratory muscle atrophy.[18]

A major point to underline is that we always avoided the administration of an initial *iv* bolus dose of sufentanil. According to our previous clinical experience, administration of a bolus results in a high incidence of side effects (mainly consisting of transitory hypotension).

Notwithstanding our positive results, the relatively small number of patients studied and the short duration of the study may not have allowed us to detect small differences or long term adverse effects such as delirium. However, this pilot study of physiologic variables can represent the basis for larger clinical trials, assessing the safety of sufentanil as a single sedative in unselected critically ill patients.

In conclusion, the results of our pilot study suggest that, in critically ill patients breathing on a partial respiratory support mode, a continuous infusion of sufentanil at 0.2 to 0.3 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ may produce adequate "awake" analgesia-sedation, with no detectable effects on respiratory drive, respiratory pattern, and inspiratory impedance of the respiratory system and gas exchange.

References

1 *Shelly MP.* Sedation, where are we now? Intensive Care Med 1999; 25: 137–9.

2 *Fruh B.* A comparison of propofol and midazolam for long-term sedation of mechanically ventilated patients: a cross-over study (Italian). J Drug Devel 1989; 2(suppl 2): 45–7.

3 *Arunasalam K, Davenport HT, Painter S, Jones JG.* Ventilatory response to morphine in young and old subjects. Anaesthesia 1983; 38: 529–33.

4 *Monk JP, Beresford R, Ward A.* Sufentanil. A review of its pharmacological properties and therapeutic use. Drugs 1988; 36: 286–313.

5 *Bailey PL, Streisand JB, East KA, et al.* Differences in magnitude and duration of opioid-induced respiratory depression and analgesia with fentanyl and sufentanil. Anesth Analg 1990; 70: 8–15.
6 *Prause A, Wappler F, Scholz J, Bause H, Schulte am Esch J.* Respiratory depression under long-term sedation with sufentanil, midazolam and clonidine has no clinical significance. Intensive Care Med 2000; 26: 1454–61.
7 *Ramsay MA, Savage TM, Simpson BR, Goodwin R.* Controlled sedation with alphaxalone-alphadolone. BMJ 1974; 2: 656–9.
8 *Petros AJ, Lamond CT, Bennett D.* The Bicore pulmonary monitor. A device to assess the work of breathing while weaning from mechanical ventilation. Anaesthesia 1993; 48: 985–8.
9 *Kirton OC, Banner MJ, Axelrad A, Drugas G.* Detection of unsuspected imposed work of breathing: case reports. Crit Care Med 1993; 21: 790–5.
10 *Whitelaw WA, Derenne JP, Milic-Emili J.* Occlusion pressure as a measure of respiratory center output in conscious man. Respir Physiol 1975; 23: 181–99.
11 *Perrigault PF, Pouzeratte YH, Jaber S, et al.* Changes in occlusion pressure (P0.1) and breathing pattern during pressure support ventilation. Thorax 1999; 54: 119–23.
12 *Hughes MA, Glass PS, Jacobs JR.* Context-sensitive half-time in multicompartment pharmacokinetic models for intravenous anesthetic drugs. Anesthesiology 1992; 76: 334–41.
13 *Shook JE, Watkins WD, Camporesi EM.* Differential roles of opioid receptors in respiration, respiratory disease, and opiate-induced respiratory depression. Am Rev Respir Dis 1990; 142: 895–909.
14 *Rosa G, Conti G, Orsi P, et al.* Effects of low-dose propofol administration on central respiratory drive, gas exchanges and respiratory pattern. Acta Anaesthesiol Scand 1992; 36: 128–31.
15 *Conti G, De Blasi R, Pelaia P, et al.* Early prediction of successful weaning during pressure support ventilation in chronic obstructive pulmonary disease patients. Crit Care Med 1992; 20: 366–71.
16 *Conti G, Cinnella G, Barboni E, Lemaire F, Harf A, Brochard L.* Estimation of occlusion pressure during assisted ventilation in patients with intrinsic PEEP. Am J Respir Crit Care Med 1996; 154: 907–12.
17 *Hussain SN, Pardy RL, Dempsey JA.* Mechanical impedance as determinant of inspiratory neural drive during exercise in humans. J Appl Physiol 1985; 59: 365–75.
18 *Brochard S, Pluskwa F, Lemaire F.* Improved efficacy of spontaneous breathing with inspiratory pressure support. Am Rev Respir Dis 1987; 136: 411–5.