ERJ Express. Published on July 20, 2011 as doi: 10.1183/09031936.00037511

THE EFFECT OF SPONTANEOUS BREATHING ON SYSTEMIC INTERLEUKIN-6 DURING VENTILATOR WEANING

Short Title: IL-6 response during weaning

Authors:
Jacobo Sellares[1,3], MD, sellares@clinic.ub.es
Hugo Loureiro[1,3], MD, hloureirok@yahoo.com
Miquel Ferrer[1,3], MD, miferrer@clinic.ub.es
Rosanel Amaro[1], MD, ramaro@clinic.ub.es
Ramón Farré[2,3], PhD, rfarre@ub.edu
Antoni Torres[1,3], MD, atorres@ub.edu

[1]Respiratory Intensive Care Unit, Hospital Clínic-IDIBAPS, Barcelona, Catalonia, Spain; [2]Unitat Biofisica i Bioenginyeria, Facultat Medicina, Universitat Barcelona-IDIBAPS, Barcelona, Catalonia, Spain; and [3]CibeRes (CB06/06/0028), Spain.

Corresponding author:

Dr. Jacobo Sellarés, MD
Servei de Pneumologia
Hospital Clinic,
Villarroel 170
08036 Barcelona
Spain
Tel: (34) 93 2275549
Fax: (34) 93 2275549
e-mail: sellares@clinic.ub.es

Sources of support: This work was supported in part by Ministerio de Sanidad y Consumo (FIS-PI040929 and CibeRes-ISCiii-CB06/06/0028) and Ministerio de Ciencia y Tecnología (SAF2005-0110)

ABSTRACT

During the weaning process, spontaneous breathing trial (SBT) involves cardiopulmonary stress for ventilated patients. As interleukin [IL]-6 is a major modulator of the stress response, we hypothesized that systemic IL-6 increases during the SBT and that this increase is more evident in SBT failure.

Forty-nine SBTs of 30-minute duration were performed on different mechanically-ventilated patients, classified as SBT failure or success. Blood samples were drawn before and at the end of the SBT. An additional sample was drawn 24 hours later in a subset of patients (n=39). Serum IL-6 levels and other inflammatory mediators commonly associated with stress were determined.

IL-6 levels increased from mechanical ventilation to spontaneous breathing in all patients (p= 0.02) and in COPD population (p=0.05) with SBT failure compared to success, but not in non-COPD patients (p=0.12). After 24 hours of SBT stress, IL-6 levels decreased in patients with SBT failure (under MV at that point) (p= 0.02) and those with weaning success (p=0.04). No changes were observed in the remaining inflammatory mediators.

Systemic IL-6 increases during a 30-minute failed SBT, especially in COPD patients. Future studies may corroborate the different IL-6 responses among different populations who initiate weaning, together with the potential clinical implications.

Keywords:
Chronic obstructive pulmonary disease; Interleukin-6; Mechanical ventilation; Critical care; Spontaneous breathing trial; Weaning.

During the weaning process, the routine employment of daily spontaneous breathing trials (SBTs) or the use of low levels of pressure support as a weaning method decreases the duration of ventilation support and improves survival [1-4]. However, this test could result in cardiopulmonary stress for some patients. Stress is defined as "the state to which an organism is led because of external or internal forces (stressors) that threaten to alter its dynamic equilibrium (homeostasis)" [5]. This definition of stress could be applied to the weaning process after close examination of the factors that influence the pathophisology of weaning failure. The transition from mechanical ventilation (MV) to spontaneous breathing means an increase of respiratory muscle energy demands to cope respiratory load [6] (respiratory stress), with the consequent increase in oxygen demand [7,8], which in turn requires an increase in cardiac output (cardiovascular stress) [7]. Although all patients who perform a SBT must face this stress, patients who fail the SBT are subjected to higher pulmonary [6] and cardiovascular stress [7,9,10] than those who tolerate the trial. If we assumed that during a failed SBT, patients experience high cardiopulmonary stress, we could also assume that the different biological systems associated with stress response could be also activated during this process [5].

When the stress system is activated, there is a consequent increase in plasma cathecolamines due to sympathetic stimulation [11]. The secretion of cathecholamines during stress is associated with systemic interleukin [IL]-6 production [12]. Considering SBT as a "stress model", we hypothesized that after the patient has been subjected to MV, the "stress" of initiating spontaneous breathing is associated with an increase in

systemic IL-6. As IL-6 production seems to be related to the intensity of stress in other conditions (especially in acute exercise) [13,14], we also hypothesized that the increase of IL-6 during SBT is higher in patients who fail the trial because this population typically develops higher cardiopulmonary stress. Although the primary focus of our study was IL-6, we also assessed TNF-α, IL-1β, IL-8, IL-10 and C-reactive protein (CRP) to determine the inflammatory pattern associated with IL-6 changes, since these markers are usually related to IL-6 response under different stress conditions [5,14].

METHODS AND MATERIALS

Patients

This prospective study was conducted from November 2005 to June 2009 in a respiratory intensive care unit (ICU) at the Hospital Clinic of Barcelona. All intubated and mechanically ventilated patients (≥ 48 hours) were consecutively included for the study when the following criteria were fulfilled: 1) improvement or resolution of the underlying causes of acute respiratory failure; 2) no fever (≥ 38°C) or hypothermia (<36ºC); 3) hemoglobin ≥ 9 g/dl; 4) absence of vasoactive drugs; 5) normal consciousness after discontinuing sedation; and 6) PaO_2 > 60 mm Hg with fraction inspired oxygen (FIO_2) ≤ 0.4 and positive end-expiratory pressure (PEEP) ≤ 5 cm H_2O. Exclusion criteria were: 1) tracheotomy or other upper airway disorders; 2) active upper gastrointestinal bleeding; 3) lack of cooperation; and, 4) decision to limit life-sustaining treatments. The study was approved by the Ethics Committee of the institution, and informed written consent was obtained in all cases.

Protocol

A T-piece trial was performed in all eligible patients. Endotracheal suctioning was performed before the study. SBT failure was defined as the presence and persistence of one of the following criteria: 1) respiratory frequency >35 min-1; 2) arterial O2 saturation by pulse-oximetry <90% (80% in chronic respiratory failure) at FIO2 ≥ 0.4; 3) heart rate >140 or <50 min-1, or increases or decreases of more than 20% compared to mechanical ventilation; 4) systolic blood pressure >180 or <70

mmHg, or increases or decreases of more than 20% compared to mechanical ventilation; 5) decreased consciousness, agitation or diaphoresis; and 6) thoracic-abdominal paradoxical movement [15,16]. If no signs of SBT failure appeared in 30 minutes, the trial was considered successful (SBT success) and patients were extubated. Alternatively, if signs of failure appeared during this period, patients were reconnected to the ventilator (SBT failure). The decision to extubate patient or reinstitute mechanical ventilation was made solely by the primary physician.

Data collection and definitions.

All relevant data from the medical records and bedside flow charts of patients were reviewed at entry and at the end of the protocol. Maximal inspiratory (MIP) and expiratory (MEP) pressures were measured prior to the SBT, using a unidirectional valve [17].

During the first 48 hours after extubation, the patients with SBT success were followed-up and classified into: (1) weaning success, defined as extubation and the absence of ventilatory support 48 hours following the extubation [2], or (2) respiratory failure after extubation defined, in addition to reintubation criteria, as the presence and persistence, within 48 hour after extubation, of at least 2 of the following: 1) respiratory acidosis (arterial pH <7.35 with PaCO2 >45 mmHg); 2) arterial O2 saturation by pulse-oximetry <90% or PaO2 <60 mmHg at inspired O2 fraction *0.5; 3) respiratory frequency >35 min-1; 4) decreased consciousness, agitation or diaphoresis; and, 5) clinical signs suggestive of respiratory muscle fatigue and/or increased work of breathing, such as the use of respiratory accessory muscles, paradoxical motion of the abdomen, or retraction of the intercostal spaces [16]. Immediate re-intubation criteria were predefined by any of the following major clinical events: respiratory or cardiac arrest, respiratory pauses with loss of consciousness or gasping for air, psychomotor

agitation inadequately controlled by sedation, massive aspiration, persistent inability to remove respiratory secretions, heart rate below 50 min-1 with loss of alertness, and severe hemodynamic instability without response to fluids and vasoactive drugs [16].

The causes of respiratory failure after extubation were assigned using adapted published definitions: 1) upper airway obstruction; 2) aspiration or excess respiratory secretions; 3) congestive heart failure; 4) respiratory failure; and 5) encephalopathy [18]. Rescue therapy with non-invasive ventilation (NIV) was used in the case of respiratory failure after extubation if immediate reintubation was not necessary [16].

Inflammatory response

Venous blood samples were collected during MV, just before beginning the protocol and at the end of the SBT. In order to assess the recovery response of inflammatory mediators after the SBT, an additional sample was obtained 24 hours after the protocol in a subset of patients (n=39), not being able to collect the sample in the reaming patients. Serum was obtained after centrifugating the sample at 1800 rpm for 10 minutes, and it was then frozen at –80ºC until further processing. The determination of cytokine levels was performed with a commercial enzymoimmunoassay technique (Biosource, Nivelles, Belgium). The limits of detection were IL-1β and IL-6: 2pg/ml, TNFα: 3pg/ml, IL-8: 0.7 pg/ml and IL-10: 1pg/ml. CRP was measured with an immunoturbidimetric method using a commercially available test (Bayer Diagnostics, Germany) with an Advia 2400.

Statistical Analysis

Data are presented as mean ± SD, except variables not normally distributed, which are presented as median (25-75th interquartile). Absolute changes of serum inflammatory mediators levels expressed as Δ_{SBT} (change between MV and the end of the SBT) were calculated and included in the analysis. All data were tested for

normality using Kolmogorov-Smirnov test. All inflammatory mediators were not normally distributed except CRP. Levels that were undetectable were assigned a value equal to the lower limit of detection for the assay. In order to correctly assess the inflammatory response associated with SBT, we performed separately data analysis of inflammatory markers in two stages: from MV to SBT (inflammatory response over the SBT) and from SBT to 24h after the trial (recovery phase after SBT). Comparisons were carried out by unpaired or paired Student *t*-test when appropriate, if the data were normally distributed. Otherwise, Wilcoxon and Mann-Whitney non-parametric tests were used for paired and unpaired comparisons respectively.

Because chronic obstructive pulmonary disease (COPD) appears as an independent risk factor for increased duration of weaning and weaning failure,[19] we performed separate *post-hoc* analyses comparing SBT failure and success in this population and in patients without COPD.

In the absence of previous data concerning IL-6 changes during weaning, we initiated the study, analyzing IL-6 changes during weaning in 26 patients [20]. In this sample we already observed that: (1) the IL-6 increased in patients who failed the SBT, (2) when we divided the population in COPD and non-COPD patients, the increase was only present in COPD patients who failed the SBT. However, the number of patients in each subgroup was limited, so we performed a power analysis. We observed an increase of 29 pg/ml in the subgroup of COPD patients who failed the SBT. Assuming a similar result in the non-COPD patients who failed the SBT (SD = 28 pg/ml), the sample size calculation revealed a minimum of 8 patients [power analyses: 80%, α=0.05 (two-sided)].

The level of significance was set in all tests at 0.05 (all two-tailed). Statistical analysis was performed with SPSS 16 (SPSS, Chicago, IL).

RESULTS

Physiological characteristics

General clinical characteristics of the 49 patients included in this study are summarized in Table 1. From the 49 SBT assessed in this population, 33 (67%) were considered SBT success and 16 (33%) SBT failure. Within the success group, 7 patients developed respiratory failure after extubation and 26 were classified as weaning success. The causes of failure after extubation were respiratory failure (n=6), where NIV was initiated, and encephalopathy (n=1), where it was decided to limit life-support therapy.

The physiological parameters of all patients and the subgroup of the COPD population are shown in Table 2. In all trials, respiratory frequency, heart rate and mean systemic arterial pressure significantly increased at the end of SBT in failure and success group (except heart rate). There was also a significant decrease of pH and PaO2 in all trials. The MIP, MEP and f/Vt did not discriminate between patients with SBT success and failure in all patients (p=0.16, p=0.81, and p=0.11, respectively) and COPD subgroup (p=0.56, p=0.57 and p=0.22, respectively).

Inflammatory response over the SBT in the population as a whole

In the 49 patients of the study, during MV, baseline levels of IL-6 were not significantly different when patients were divided into SBT failure or success (p=0.12). Over the SBT, the increase in IL-6 was only statistically significant in patients with failure (p=0.02) (Figure 1A). ΔIL-6 in SBT failure was significantly increased compared to success group (p= 0.05) (Figure 1C). In the remaining mediators, no differences were observed in baseline values and not significant changes were obtained during the SBT (Table 3).

Inflammatory response over the SBT in COPD patients

Twenty-three weaning trials were assessed in these patients. No significant differences were observed in baseline levels of IL-6 between failure (n=8) and success (n=15) groups: 49 (22-147) pg/ml in SBT failure and 35 (11-40) pg/ml in SBT success, p=0.44. While IL-6 increased along the SBT in all patients who failed the weaning attempt (p=0.05, Figure 2A), these changes were not observed in those who tolerated the SBT (p=0.64, Figure 2B). In addition, Δ_{SBT}IL-6 in SBT failure was significantly higher (p=0.03) compared to success group (Figure 2C). By contrast, patients without COPD (Figure 3) showed no significant changes during the SBT in failed (n=8) and successful (n=18) trials. No changes were observed in the remaining mediators.

Inflammatory response 24 hours after the SBT.

From the 39 trials subgroup where an additional sample was obtained at 24 hours after SBT, 8 were classified as SBT failure, 7 as respiratory failure after extubation and 24 as weaning success. In SBT failure (under MV at 24 hours), IL-6 levels decreased after 24 hours of the trial from 82 (35-160) pg/ml to 58 (25-125) pg/ml (p=0.02). In weaning success, IL-6 significantly decreased at 24 hours after extubation from 42 (13-100) pg/ml to 29 (8-58) pg/ml (p=0.04). In the respiratory failure after extubation group, IL-6 did not significantly change in 24 hours (patients were breathing spontaneously when the sample was collected). No significant changes were observed in the remaining inflammatory markers.

DISCUSSION

The main findings of the study are that in ventilated patients who performed a 30-minute SBT: (1) IL-6 increase was higher in SBT failure compared with success; (2)

when patients were divided in COPD and non-COPD subgroups, only the subset of patients with COPD increased IL-6 during the SBT; (3) at 24 hours after SBT, IL-6 decreased in patients who remained ventilated (SBT failure) or in weaning success; and (4) the remaining inflammatory mediators assessed did not significantly change during weaning.

To the best of our knowledge, the role of inflammatory markers during the weaning process has not been studied before. In order to explain the results obtained, we have to view weaning, particularly the SBT, as a test that could represent a cause of cardiopulmonary stress for the ventilated patient. Koksal *et al.* [21] compared the endocrine stress response developed during three methods of weaning using a T-tube, CPAP and pressure support in 60 patients who were successfully weaned. The patients of the T-trial group developed a greater increase in plasma insulin, cortisol, glucose and urine valinemandelic acid, showing a higher endocrine stress response than in the other weaning modes. Along the same lines, sympathoadrenal stimulation has been described as intense and usually greater in those patients who are weaned successfully, with a consequent increase in systemic cathecolamine levels [22]. The imbalance between the capacity and loading conditions of the respiratory and cardiovascular system during the weaning process, could entail major cardiopulmonary stress, especially in patients with limited baseline conditions, developing weaning failure, triggering the somatic stress response and a potential increase in IL-6 [2,5].

In our study, the increase of serum IL-6 levels was higher in SBT failure compared to success, especially in the COPD population. These results may be attributed to the fact that COPD patients present more unfavorable reserve conditions to cope with cardiopulmonary stress during the SBT than non-COPD patients [6,10,23], which explains the high rate of weaning failure typically described in COPD [24]. From our results, only COPD patients without excessive stress (no changes in IL-6) could pass the trial. By contrast IL-6 levels were not influenced by the performance of a SBT in non-COPD patients, possibly due to the fact that they presented a better reserve to cope with the SBT stress than COPD patients. However, this hypothesis should be tested in further studies.

The post-stress response observed at 24 hours after the trial was more consonant with the initial hypothesis. The majority of the patients, except those who develop respiratory failure after extubation, showed a decrease in IL-6 at 24 hours, which was highly significant in the event of SBT failure (possibly due to the relative rest of the cardiorespiratory system after the increased stress of a failed SBT) and in weaning success (showing the relative clinical stability of patients after extubation). This IL-6 response, particularly in SBT failure, was similar to the decline observed in the post-stress period reported in the stress model of acute exercise [14].

Apart from IL-6, we did not obtain significant results from the analysis of the remaining mediators. These results suggest the absence of a marked inflammatory response during a 30-minute SBT, despite the increase in IL-6, which is similar to the "exercise" condition (stress secondary to a physical exercise) and contrasts with sepsis, where several inflammatory mediators are increased [14]. In fact, the SBT is physiologically closer to exercise than other type of stress [25]. It has even been hypothesized that IL-6 could exert inhibitory effects in TNF-α and IL-1β during acute exercise, playing an "anti-inflammatory" role [14]. Another explanation for our results could be that the remaining inflammatory markers may increase just after the SBT, because IL-6 appearance in the circulation is by far the most marked and its increase precedes the other cytokines in stress secondary to exercise [14].

From our point of view, the current study may open novel possibilities in weaning research. Physiologically, the role of IL-6 in the weaning process must be elucidated. Future research must explore the connection of IL-6 with hypothalamic-pituitary-adrenal axis and sympathetic system during the SBT and the hypothetic metabolic and hormonal implications of the rise of IL-6. As has been previously described, there is an increase in several hormonal modulators associated with stress during a SBT [21,22]. IL-6 is a major modulator of the different systems triggered during a stress response [5], so we have hypothesized that IL-6 could play a key role in the stress response associated with SBT, especially in COPD. The potential clinical consequences of an increased response of IL-6 and other stress modulators during the SBT remain unknown, but it would be of interest to determine the threshold at which an increased stress response during a SBT could have deleterious systemic effects. Actually, systemic IL-6 overproduction is associated with different actions in hematological, immunological, hepatic, neurological, cardiac and endocrine systems [12]. This hypothesis may well have important clinical implications in different prognostic outcomes. In fact, IL-6 is associated with mortality in other stress conditions such as ARDS [26]or sepsis [27].

Certain limitations of the study must be considered. Firstly, the results obtained at 24 hours must be interpreted with caution, as external factors other than weaning could have influenced the final values and this might prevent appropriate interpretation of the data. Secondly, another limitation of our study is the limited duration of SBT to 30 minutes. Patients usually fail a SBT within the first 20 minutes, so the success rate of a 30-minute SBT is very similar to a 120-minute trial [28,29]. Nevertheless, it is possible that during longer SBT the increase in IL-6 could be higher, due to the progressive increase in inspiratory effort during the trial [30]. Thirdly, the data obtained from the COPD and non-COPD population were obtained from an analysis of subgroups, so the results must be viewed with caution and stand to be confirmed in specific studies addressed to this population.

In conclusion, our results provide the first evidence that systemic IL-6 increases during the course of a 30-min failed SBT, especially in COPD patients. No significant changes were observed in the remaining inflammatory mediators studied. Future research could serve to explore the association of IL-6 levels and the mechanisms of weaning failure in COPD patients and the possible association with prognostic outcomes.

Acknowledgment: The authors wish to thank Drs. Mauricio Valencia, Xavier Filella and Silvia Blanco for their technical assistance, and Roger Marshall for his editing aid. The authors also thank the respiratory therapy and nursing staff, and the attending physicians of the intensive care unit, for cooperation in this study.

REFERENCES

1 Ely EW, Baker AM, Dunagan DP, Burke HL, Smith AC, Kelly PT, Johnson MM, Browder RW, Bowton DL, Haponik EF. Effect on the duration of mechanical ventilation of identifying patients capable of breathing spontaneously. *N Engl J Med* 1996; 335: 1864-1869.

2 Boles JM, Bion J, Connors A, Herridge M, Marsh B, Melot C, Pearl R, Silverman H, Stanchina M, Vieillard-Baron A, Welte T. Weaning from mechanical ventilation. *Eur Respir J* 2007; 29: 1033-1056.

3 Esteban A, Frutos F, Tobin MJ, Alia I, Solsona F, Vallverdú I, Fernandez R, de la Cal A, Benito S, Tomás R, Carriedo D, Macías S, Blanco J, Spanish Lung Failure Collaborative Group. A comparison of four methods of weaning patients from mechanical ventilation. *N Engl J Med* 1995; 323: 345-350.

4 Girard TD, Kress JP, Fuchs BD, Thomason JW, Schweickert WD, Pun BT, Taichman DB, Dunn JG, Pohlman AS, Kinniry PA, Jackson JC, Canonico AE, Light RW, Shintani AK, Thompson JL, Gordon SM, Hall JB, Dittus RS, Bernard GR, Ely EW. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. *Lancet* 2008; 371: 126-134.

5 Mastorakos G and Ilias I. Interleukin-6 - A cytokine and/or a major modulator of the response to somatic stress. *Ann N Y Acad Sci* 2006; 1088: 373-381.

6 Jubran A and Tobin MJ. Pathophysiologic basis of acute respiratory distress in patients who fail a trial of weaning from mechanical ventilation. *Am J Respir Crit Care Med* 1997; 155: 906-915.

7 Jubran A, Mathru M, Dries D, Tobin MJ. Continuous recordings of mixed venous oxygen saturation during weaning from mechanical ventilation and the ramifications thereof. *Am J Respir Crit Care Med* 1998; 158: 1763-1769.

8 De BD, El HP, Preiser JC, Vincent JL. Hemodynamic responses to successful weaning from mechanical ventilation after cardiovascular surgery. *Intensive Care Med* 2000; 26: 1201-1206.

9 Richard Ch, Teboul JL, Archambaud F, Hebert JL, Michaut P, Auzepy P. Left ventricular function during weaning of patients with chronic obstructive pulmonary disease. *Intensive Care Med* 1994; 20: 181-186.

10 Lemaire F, Teboul J, Cinotti L, Giotto G, Abrouk F, Steg G, Macquin-Mavier I, Zapol W. Acute left ventricular dysfunction during unsuccessful weaning from mechanical ventilation. *Anesthesiology* 1988; 69: 171-179.

11 Mastorakos G and Pavlatou M. Exercise as a stress model and the interplay between the hypothalamus-pituitary-adrenal and the hypothalamus-pituitary-thyroid axes. *Horm Metab Res* 2005; 37: 577-584

12 Papanicolaou DA, Wilder RL, Manolagas SC, Chrousos GP. The pathophysiologic roles of interleukin-6 in human disease. *Ann Intern Med* 1998; 128: 127-137.

13 Ostrowski K, Schjerling P, Pedersen BK. Physical activity and plasma interleukin-6 in humans--effect of intensity of exercise. *Eur J Appl Physiol* 2000; 83: 512-515.

14 Petersen AM and Pedersen BK. The role of IL-6 in mediating the anti-inflammatory effects of exercise. *J Physiol Pharmacol* 2006; 57 Suppl 10: 43-51.

15 Ferrer M, Esquinas A, Arancibia F, Bauer TT, Gonzalez G, Carrillo A, Rodriguez-Roisin R, Torres A. Noninvasive ventilation during persistent weaning failure. A randomized controlled trial. *Am J Respir Crit Care Med* 2003; 168: 70-76.

16 Ferrer M, Valencia M, Nicolas JM, Bernadich O, Badia JR, Torres A. Early noninvasive ventilation averts extubation failure in patients at risk: a randomized trial. *Am J Respir Crit Care Med* 2006; 173: 164-170.

17 Truwit JD and Marini JJ. Validation of A Technique to Assess Maximal Inspiratory Pressure in Poorly Cooperative Patients. *Chest* 1992; 102: 1216-1219.

18 Epstein SK and Ciubotaru RL. Independent effects of etiology of failure and time of reintubation on outcome for patients failing extubation. *Am J Respir Crit Care Med* 1998; 158: 489-493.

19 Brochard L, Rauss A, Benito S, Conti G, Mancebo J, Rekik N, Gasparetto A, Lemaire F. Comparison of three methods of gradual withdrawal from ventilatory support during weaning from mechanical ventilation. *Am J Respir Crit Care Med* 1994; 150: 896-903.

20 Sellares, J., Ferrer, M., Farré, R., Esquinas, C., Piñer, R., Filella, X., and Torres, A. Serum inflammatory biomarkers in weaning from mechanical ventilation. *Am J Respir Crit Care Med* 2008; 177, A378

21 Koksal GM, Sayilgan C, Sen O, Oz H. The effects of different weaning modes on the endocrine stress response. *Crit Care* 2004; 8: R31-R34.

22 Kennedy SK, Weintraub RM, Skillman JJ. Cardiorespiratory and sympathoadrenal responses during controlled ventilation. *Surgery* 1977; 82: 233-240.

23 Grasso S, Leone A, De Michele M, Anaclerio R, Cafarelli A, Ancona G, Stripoli T, Bruno F, Pugliese P, Dambrosio M, Dalfino L, Di Serio F, Fiore T. Use of N-terminal pro-brain natriuretic peptide to detect acute cardiac dysfunction during weaning failure in difficult-to-wean patients with chronic obstructive pulmonary disease. *Crit Care Med* 2007; 35: 96-105.

24 Vallverdú I, Calaf N, Subirana M, Net A, Benito S, Mancebo J. Clinical characteristics, respiratory functional parameters, and outcome of a two-hour T-piece trial in patients weaning from mechanical ventilation. *Am J Respir Crit Care Med* 1998; 158: 1855-1862.

25 Pinsky MR. Breathing as exercise: the cardiovascular response to weaning from mechanical ventilation. *Intensive Care Med* 2000; 26: 1164-1166.

26 Parsons PE, Eisner MD, Thompson BT, Matthay MA, Ancukiewicz M, Bernard GR, Wheeler AP. Lower tidal volume ventilation and plasma cytokine markers of inflammation in patients with acute lung injury. *Crit Care Med* 2005; 33: 1-6.

27 Song M and Kellum JA. Interleukin-6. *Crit Care Med* 2005; 33: S463-S465.

28 Esteban A, Alía I, Tobin MJ, Gil A, Gordo F, Vallverdú I, Blanch L, Bonet A, Vázquez A, de Pablo R, Torres A, de la Cal MA, Macías S, Spanish Lung Failure Collaborative Group. Effect of spontaneous breathing trial duration on outcome of attempts to discontinue mechanical ventilation. *Am J Respir Crit Care Med* 1999; 159: 512-518.

29 Perren A, Domenighetti G, Mauri S, Genini F, Vizzardi N. Protocol-directed weaning from mechanical ventilation: clinical outcome in patients randomized for

TABLE 1. BASELINE CHARACTERISTICS OF PATIENTS ON ENTRY INTO STUDY (n= 49)

Age, yr	68 ± 13
Gender, male/female	41/8

a 30-min or 120-min trial with pressure support ventilation. *Intensive Care Medicine* 2002; 28: 1058-1063.

30 Jubran A, Grant BJB, Laghi F, Parthasarathy S, Tobin MJ. Weaning prediction - Esophageal pressure monitoring complements readiness testing. *Am J Respir Crit Care Med* 2005; 171: 1252-1259.

Days of mechanical ventilation	7 ± 5
APACHE II on admission	17 ± 7
APACHE II on entry into study	10 ± 4
Underlying diseases, n (%)	
Chronic respiratory disorders*	33 (67)
COPD	23
Non-COPD	10
Chronic heart disorders†	13 (26)
Immunosuppresion‡	7 (14)
Diabetes mellitus	12 (24)
Cause for initiating mechanical ventilation, n (%)	
Exacerbation of chronic respiratory disorders	13 (27)
Congestive heart failure	6 (12)
Pneumonia	6 (12)
Sepsis	5 (10)
Postoperative respiratory failure	2 (4)
Neurologic disease	2 (4)
Other causes	15 (31)

Definition of abbreviations: APACHE II = Acute Physiology and Chronic Health Evaluation II score; COPD = Chronic obstructive pulmonary disease.

Plus-minus values represent means ± SEM.

*Chronic respiratory disorders include chronic obstructive pulmonary disease, chronic bronchitis associated with dyspnea and current or former history of smoking in the absence of pulmonary function testing, sequelae of pulmonary tuberculosis, chest wall deformity or obesity associated with a restrictive ventilatory disorder, and bronchiectasis.

†Chronic heart disorders include coronary artery disease, hypertensive or valvular heart diseases, and dilated myocardial disease of any cause.

‡Immunosuppression includes neutropenia after chemotherapy or bone marrow transplantation, drug-induced immunosuppression in solid organ transplantation or as a result of corticosteroid or cytotoxic therapy, and HIV-related disorders.

TABLE 2. PHYSIOLOGICAL PARAMETERS DURING MECHANICAL VENTILATION AND THE SPONTANEOUS BREATHING TRIAL AMONG PATIENTS WITH TRIAL FAILURE OR SUCCESS.

	All trials (n=49)			COPD trials (n=23)		
	MV	SBT	p Value*	MV	SBT	p Value*

TABLE 3. CONCENTRATIONS OF CYTOKINES (PG/ML IN SERUM) AND C-REACTIVE PROTEIN (mg/dL IN SERUM) DURING MECHANICAL VENTILATION AND THE SPONTANEOUS BREATHING TRIAL IN THE OVERALL POPULATION.

Respiratory frequency, min^{-1}						
SBT failure	17 ± 6	24 ± 11	0.009	17 ± 7	20 ± 9	0.11
SBT success	17 ± 4	20 ± 5	0.002	17 ± 4	19 ± 4	0.07
Heart rate, min^{-1}						
SBT failure	82 ± 20	95 ± 24	0.08	84 ± 23	89 ± 28	0.61
SBT success	88 ± 19	79 ± 32	0.18	89 ± 18	90 ± 32	0.71
Mean systemic arterial pressure, mm Hg						
SBT failure	84 ± 13	99 ± 16	<0.001	87 ± 15	101 ± 16	0.002
SBT success	86 ± 15	98± 17	<0.001	89 ± 12	100 ± 17	0.001
$PaCO_2$, mm Hg						
SBT failure	46 ± 11	50 ± 14	0.13	50 ± 12	56± 16	0.24
SBT success	43 ± 8	44 ± 9	0.07	47 ± 9	48 ± 11	0.44
Arterial pH						
SBT failure	7.44 ± 0.05	7.37 ± 0.08	0.006	7.43 ± 0.05	7.37 ± 0.09	0.05
SBT success	7.44 ± 0.04	7.42 ± 0.06	0.006	7.43 ± 0.04	7.39 ± 0.06	0.02
PaO_2, mmHg						
SBT failure	91 ± 19	83 ± 26	0.07	93 ± 18	76 ± 20	0.05
SBT success	101 ± 19	92 ± 26	0.01	102 ± 24	92 ± 32	0.05
f/V_t ratio						
SBT failure	-------	100 ± 70		-------	58 ± 27	
SBT success	-------	73 ± 40		-------	77 ± 35	
MIP, cm H_20						
SBT failure	-------	42 ± 18		-------	51 ± 21	
SBT success	-------	52 ± 19		-------	44 ± 13	
MEP, cm H_20						
SBT failure	-------	66 ± 29		-------	78 ± 28	
SBT success	-------	68 ± 22		-------	68 ± 25	

Definition of abbreviations: MV = Mechanical ventilation; SBT = spontaneous breathing trial; COPD = Chronic obstructive pulmonary disease; f/V_t = respiratory frequency to volume tidal ratio; MIP = maximal inspiratory pressure; MEP = maximal expiratory pressure;

Plus-minus values represent means ± SEM.

* Paired comparisons of the different parameters between ventilation (MV) and spontaneous breathing (SBT) in each group.

		MV	SBT	p Value*
IL-1β	SBT failure	2 (0-3)	2 (1-3)	0.71
	SBT success	2 (0-2)	2 (0-3)	0.59
IL-6	SBT failure	60 (28-147)	72 (35-151)	0.02
	SBT success	35 (15-86)	40 (13-105)	0.46
IL-8	SBT failure	31 (11-95)	26 (12-63)	0.71
	SBT success	38 (16-69)	33 (10-62)	0.50
IL-10†	SBT failure	1 (1-3)	1(1-4)	0.88
	SBT success	1 (1-4)	1 (1-3)	0.25
TNF-α	SBT failure	12 (6-25)	15 (5-24)	0.50
	SBT success	8 (4-17)	8 (4-15)	0.83
CRP	SBT failure	10 (8)	10 (9)	0.30
	SBT success	7 (7)	7 (6)	0.97

Definition of abbreviations: MV = Mechanical ventilation; SBT = spontaneous breathing trial; CRP = C-reactive protein

Values are expressed as mean (SD) or median (25-75th interquartile)

* Paired comparisons of the different inflammatory mediators between ventilation (MV) and spontaneous breathing (SBT) in each group

† The values of IL-10 were undetectable in the majority of patients assessed.

FIGURE LEGENDS

Figure 1. Individual values of IL-6 during mechanical ventilation (MV) and at the end of spontaneous breathing trial (SBT) in patients with SBT failure (*A*), SBT success *(B)* and the absolute change of IL-6 between MV and SBT (Δ_{SBT}IL-6) comparing SBT

failure and success in the whole population of the study (*C*). The horizontal line represents median.

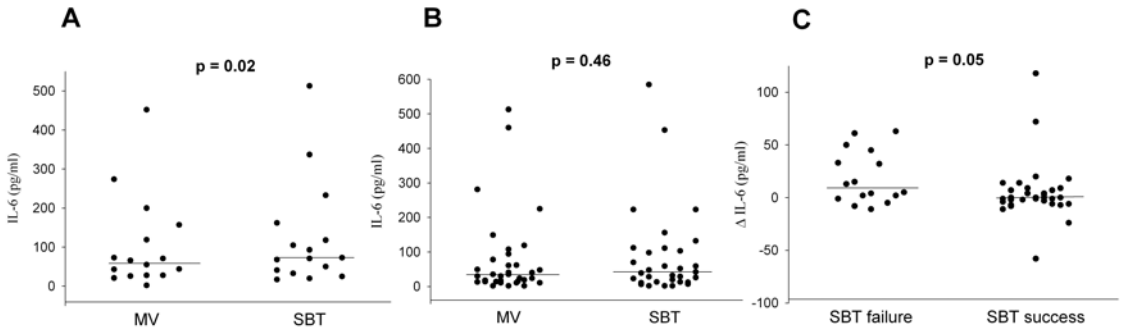

Figure 2. Individual values of IL-6 during mechanical ventilation (MV) and at the end of spontaneous breathing trial (SBT) in COPD patients with SBT failure (*A*), SBT success *(B)* and the absolute change of IL-6 between MV and SBT (Δ_{SBT}IL-6) comparing SBT failure and success (*C*). The horizontal line represents median.

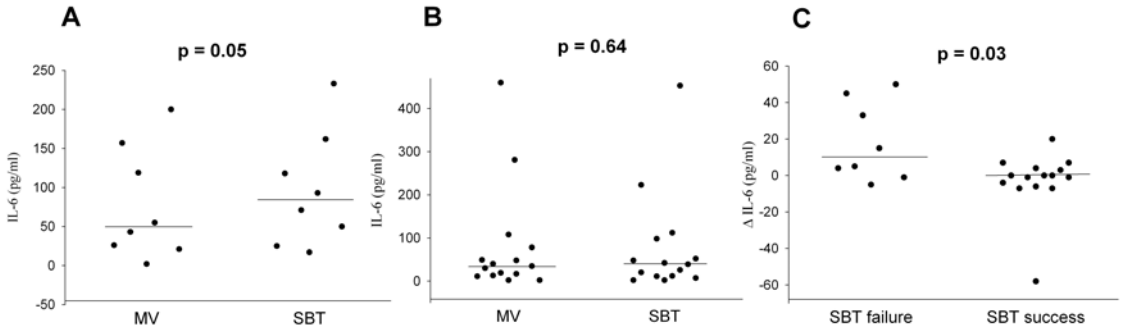

Figure 3. Individual values of IL-6 during mechanical ventilation (MV) and at the end of spontaneous breathing trial (SBT) in non-COPD patients with SBT failure (*A*), SBT success *(B)* and the absolute change of IL-6 between MV and SBT (Δ_{SBT}IL-6) comparing SBT failure and success (*C*). The horizontal line represents median.