Diaphragm dysfunction on admission to ICU: prevalence, risk factors and prognostic impact - a prospective study

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Contributors: A Demoule, S Jaber, and T Similowski designed the study. S Jaber and T Similowski coordinated the study. A Demoule, H Prodanovic, B Jung, and G Chanques were responsible for patient screening, enrolment, diaphragm assessment and follow-up. N Molinari performed statistical analysis. A Demoule, S Jaber, and T Similowski analysed the data and wrote the manuscript. All authors contributed to interpretation of the data and provided comments on the report at various stages of development.

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At a glance commentary

- **Scientific Knowledge on the Subject:** Ventilator-induced diaphragm dysfunction has become the focus of intense research in intensive care unit (ICU) patients, but diaphragm dysfunction at the onset of critical illness has not received sustained attention.

- **What This Study Adds to the Field:** Diaphragm dysfunction upon ICU admission is frequent and is related to sepsis as well as the severity of the ongoing disease. Diaphragm dysfunction is associated with a poorer prognosis but not with a longer duration of mechanical ventilation.

This article has an online data supplement, which is accessible from this issue's table of content online at [www.atsjournals.org](http://www.atsjournals.org).
ABSTRACT (247 words)

Rationale: Diaphragmatic insults occurring during intensive care unit (ICU) stays have become the focus of intense research. However, diaphragmatic abnormalities at the initial phase of critical illness remain poorly documented in humans.

Objective: To determine the incidence, risk factors, and prognostic impact of diaphragmatic impairment on ICU admission.

Methods: Prospective, six-month, observational cohort study in two ICUs. Mechanically ventilated patients were studied within 24 hours following intubation (day-1) and 48 hrs later (day-3). Seventeen anesthetized intubated control anesthesia patients were also studied. The diaphragm was assessed by twitch tracheal pressure (Ptr,stim) in response to bilateral anterior magnetic phrenic nerve stimulation.

Main Results: Eighty-five consecutive patients aged 62 [54-75] (median [interquartile range]) were evaluated (medical admission 79%; SAPS II, 54 [44-68]). On day 1, Ptr,stim was 8.2 [5.9-12.3] cmH₂O and 64% of patients had Ptr,stim <11cmH₂O. Independent predictors of low Ptr,stim were sepsis (linear regression coefficient, -3.74; standard error, 1.16; p = 0.002) and SAPS II (linear regression coefficient, -0.07; standard error, 1.69; p = 0.03). Compared to non-survivors, ICU survivors had higher Ptr,stim (9.7 [6.3-13.8] vs. 7.3 [5.5-9.7] cmH₂O, p=0.004). This was also true for hospital survivors vs. non-survivors (9.7 [6.3-13.5] vs. 7.8 [5.5-10.1] cmH₂O, p=0.004). Day 1 and day 3 Ptr,stim were similar.

Conclusions: A reduced capacity of the diaphragm to produce inspiratory pressure (diaphragm dysfunction) is frequent upon ICU admission. It is associated with sepsis and disease severity, suggesting that it may represent another form of organ failure. It is associated with a poor prognosis.
Introduction

Diaphragm dysfunction has become a subject of major concern in intensive care unit (ICU) patients, as it is associated with a higher rate of weaning failure and increased duration of mechanical ventilation (1). Diaphragm dysfunction in critically ill patients can be secondary to critical illness polyneuropathy and myopathy (2) and can also be a negative consequence of mechanical ventilation per se, due to disuse atrophy and other mechanisms (3-5). Ventilator-induced diaphragm dysfunction (VIDD) is defined as a time-dependent decrease of diaphragm strength following initiation of mechanical ventilation (6). Experimental data have shown that diaphragm strength is also sensitive to events frequently observed in the ICU, such as hypercatabolism and corticosteroid use e.g.(7). All these factors constitute insults that can alter diaphragm function more or less rapidly during the course of an ICU stay.

The diaphragm, like all striated muscles, can be involved in the shock-related generalized organ failure observed in many patients on admission to ICU. This is a well-established phenomenon for the heart (8) and also appears to be the case for limb muscles. Electromyographic and histopathological studies conducted very early during ICU stays have shown that more than fifty percent of patients with severe sepsis exhibit signs of neuromuscular damage (9). In these studies, electromyographic abnormalities and mitochondrial dysfunction were associated with higher mortality (9, 10). Findings from several groups of investigators using animals models show that the diaphragm is exquisitely sensitive to shock in general (11, 12) and to sepsis in particular (13, 14).

We therefore hypothesized that acute diaphragm abnormalities could be present in critically ill patients, as one of the expressions of organ failure. To test this hypothesis, we measured tracheal twitch pressure (Ptr,sim) following magnetic stimulation of the phrenic nerve in intubated and mechanically ventilated patient during the first 24 hours of their ICU
stay and in a control group of patients mechanically ventilated during anesthesia for elective procedures. We determined the clinical factors associated with the development of a low \( \text{Ptr,stim} \) (hereafter called “diaphragm dysfunction”) and the subsequent clinical course of patients with diaphragm dysfunction. Some of the corresponding data have been previously reported in abstract form (15, 16).
Patients and methods

(Detailed methods are provided in the online data supplement)

The study was conducted over a 6-month period (1st December 2008 to 1st July 2009) in two intensive care units: A 10-bed medical (ICU) and a 16-bed medical and surgical ICU. The study was approved by the "Comité de Protection des Personnes Sud-Méditerrannée II", Montpellier, France. All patients or their relatives provided written informed consent to participate. Data from six patients have been presented in a previously published study (4).

In addition we measured $Ptr_{stim}$ in 17 anesthetized patients intubated and mechanically ventilated for less than two hours in the context of digestive endoscopic procedures. Six of these patients have been presented in a previous study from our group (4).

Patients

Patients were eligible for inclusion in the study within the 24 hours following intubation and institution of mechanical ventilation. Exclusion criteria were an expected duration of mechanical ventilation less than 48 hours, contraindications to magnetic stimulation of the phrenic nerves (cardiac pacemaker or implanted defibrillator, cervical implants), use of neuromuscular blocking agents within the 24 hours preceding the first diaphragm assessment (with the exception of succinylcholine used during rapid-sequence induction of anesthesia for intubation), pre-existing neuromuscular disorders, cervical spine injury, factors possibly interfering with tracheal pressure measurements in response to phrenic nerve stimulation (multiple functioning chest drains, severe chronic obstructive pulmonary disease), participation in another clinical trial during the previous 30 days, age less than 18 years, known pregnancy, and a decision to withhold life-sustaining treatment.

Diaphragm assessment

Diaphragm performance was assessed in terms of the changes in endotracheal tube pressure induced by bilateral phrenic nerve stimulation during airway occlusion ($Ptr_{stim}$)
(see Figure E1 in the Online Supplement). The first $\text{Ptr,stim}$ measurement was performed within 24 hours of intubation (day 1) and, whenever possible, a second measurement was obtained 48 hours later (day 3). Phrenic nerve stimulation was performed by bilateral anterior magnetic stimulation, as described elsewhere (4, 17).

**Clinical data collection**

Demographic data, severity scores, organ dysfunction–related variables, physiological data, presence of sepsis according to the 2001 International Sepsis Definitions Conference (18), blood gas data, and medications were prospectively recorded on ICU admission, at day 1 and at day 3. The durations of mechanical ventilation, ICU stay and hospital stay were also recorded, as were decisions to perform tracheostomy, ICU mortality, and hospital mortality.

**Statistical analysis**

Statistical analysis was performed with R software (version R.2.13.2). The median and interquartile range (IQR) are reported for continuous variables (with the exception of $\text{Ptr,stim}$ values in control patients, reported as mean ± SD for normative purposes) and absolute and relative frequencies are reported for categorical variables together with the 95% confidence intervals (95% CI) when appropriate.

$\text{Ptr,stim}$ was analyzed as a continuous variable and univariate linear regression models were used to identify factors associated with higher or lower $\text{Ptr,stim}$ values. Multivariate analysis was performed using a forward logistic regression process taking into account all potential risk factors for diaphragm dysfunction.

$\text{Ptr,stim}$ was also used to identify two groups of patients based on the 11 cmH$_2$O cut-off that defines diaphragm dysfunction in other settings [see ATS/ERS statement on respiratory muscle testing (19, 20)]. Of note, the data obtained in our control subjects confirmed the relevance of this cut-off (see below, Results). Patients with a $\text{Ptr,stim}$ less than 11 cmH$_2$O
were considered to present diaphragm dysfunction. Each potential risk factor for diaphragm
dysfunction was then evaluated in a univariate model (Student's $t$ test or Mann-Whitney $U$ test
for continuous variables depending on distribution; $\chi^2$ test or Fisher's exact test for categorical
variables depending on size), and multivariate analysis was performed. For all final
comparisons, a $P$ value $\leq 0.05$ was considered statistically significant.

Finally, the impact of $P_{tr,stim}$ on ICU and hospital mortality, tracheostomy rate, duration
of mechanical ventilation and length of stay was assessed. The impact of $P_{tr,stim} < 11$
cmH$_2$O on ICU and hospital mortalities was evaluated using Kaplan-Meier survival function
estimates.
Results

Study population

During the study period, 723 patients were admitted to the two ICUs (Figure 1) and 85 patients were enrolled in the study (Table 1). Most patients were admitted to ICU for medical reasons and the two main indications for mechanical ventilation were coma and acute respiratory failure. Fifty-two percent of patients presented sepsis on the day of admission. The characteristics of the control patients are provided in Table E1 (Online Supplement).

Prevalence and risk factors for low $\text{Ptr}_{\text{stim}}$

$\text{Ptr}_{\text{stim}}$ in controls was normally distributed, with a mean value of 23.2 cmH$_2$O and a standard deviation of 6.4 cmH$_2$O, indicating that 95% of the source population had a $\text{Ptr}_{\text{stim}}$ greater than 10.7 cmH$_2$O.

Fifty-four ICU patients (64%) had a $\text{Ptr}_{\text{stim}}$ less than 11 cmH$_2$O on day 1, with a median value of 6.3 [5.1-8.1] cmH$_2$O. Median $\text{Ptr}_{\text{stim}}$ was 8.2 [5.9-12.3] cmH$_2$O in the overall population, and 13.8 [12.0-20.2] cmH$_2$O in patients with $\text{Ptr}_{\text{stim}}$ greater than 11 cmH$_2$O (Figure 2). Figure 3 depicts the individual values of $\text{Ptr}_{\text{stim}}$ in the control individuals and in patients with and without diaphragm dysfunction as defined above.

Demographic variables, body mass index, tobacco consumption, alcoholic cirrhosis and diabetes had no significant impact on $\text{Ptr}_{\text{stim}}$ (Table 1). In contrast to patient with shock as the main indication for mechanical ventilation, patients with coma had higher $\text{Ptr}_{\text{stim}}$ values. High SAPS II, SOFA scores and sepsis were significantly associated with lower $\text{Ptr}_{\text{stim}}$ values (Table 2). Heart rate, blood pressure, minute ventilation, $\text{PaO}_2$/FiO$_2$, $\text{PaCO}_2$, pH and blood lactate had no significant impact on $\text{Ptr}_{\text{stim}}$. In contrast to hypnotics, opioids and steroids, the use of vasopressors were significantly associated with a lower $\text{Ptr}_{\text{stim}}$ (Table 2).

Multivariate analysis showed that $\text{Ptr}_{\text{stim}}$ on day 1 was independently associated with sepsis (linear coefficient regression, -3.74; standard error, 1.16; $p=0.002$) and, to a lesser
extent, SAPS II (linear coefficient regression, -0.07; standard error, 1.69; p=0.03). When diaphragm dysfunction was defined as \( \text{Ptr,stim} < 11 \text{ cmH}_2\text{O} \), multivariate analysis showed similar results, with diaphragm dysfunction on day 1 independently associated with sepsis (odd ratio, 1.42; 95% confidence interval, 1.18-1.72; \( p=0.0013 \)) and, to a lesser extent, SAPS II (odd ratio, 1.01; 95% confidence interval, 1.00-1.02; \( p=0.0099 \)).

**Course of \( \text{Ptr,stim} \) between day 1 and day 3**

\( \text{Ptr,stim} \) was measured on day 3 in 52 patients. Reasons for missing second measurements of \( \text{Ptr,stim} \) were: death (n=14), extubation (n=11) and the use of neuromuscular blocking agent (n=8). On day 3, 63% of patients still presented \( \text{Ptr,stim} \) less than 11 cmH\text{2}O with a median \( \text{Ptr,stim} \) of 8.7 [6.0-13.4] cmH\text{2}O in the overall population.

In 20 (38%) patients, \( \text{Ptr,stim} \) decreased by more than 1 cmH\text{2}O between day 1 and day 3, while it increased by more than 1 cmH\text{2}O in 16 patients (31%). None of the various factors studied was significantly associated with a decrease or increase of \( \text{Ptr,stim} \) between day 1 and day 3.

**Clinical outcomes**

Lower values of \( \text{Ptr,stim} \) on day 1 were associated with a higher ICU and hospital mortality (Table 3). As compared to non-survivors, ICU survivors had higher \( \text{Ptr,stim} \) (9.7 [6.3-13.8] vs. 7.3 [5.5-9.7] cmH\text{2}O, \( p=0.004 \)). This was also true for hospital survivors vs. non-survivors (9.7 [6.3-13.5] vs. 7.8 [5.5-10.1] cmH\text{2}O, \( p=0.004 \)). The duration of mechanical ventilation, ICU and hospital stay were not associated with diaphragm dysfunction, nor was the tracheostomy rate. Patients with diaphragm dysfunction defined as \( \text{Ptr,stim} < 11 \text{ cmH}_2\text{O} \) had a poorer prognosis (Figure 4).

Changes in \( \text{Ptr,stim} \) between day 1 and day 3 were not associated with any differences in outcome.
Discussion

This study shows that diaphragm dysfunction, defined as a reduced capacity of the diaphragm to produce a negative intrathoracic pressure in response to phrenic stimulation, is frequent in recently intubated critically ill patients admitted to the ICU and is independently associated with sepsis and disease severity. It is also associated with poorer clinical outcome.

**Diaphragm dysfunction at the onset of critical illness**

Using criteria of P_{tr,stim} less than 11 cm H2O to define diaphragm dysfunction, two thirds of the patients in this study exhibited diaphragm dysfunction on day 1. This high proportion must be interpreted in the light of our case mix. For example, limiting inclusion to patients with an expected duration of mechanical ventilation of more than 48 hours probably biased the population toward greater severity. The incidence of diaphragm dysfunction in this group of critically ill patients is similar to the 40 to 60% incidence of early myocardial dysfunction in septic patients (8, 21). It is also similar to the 63% incidence of nerve conduction abnormalities demonstrated in 48 ICU patients within 72 hrs of developing severe sepsis (9). Although the biology of myocardium, diaphragm and limb muscles is very different, these data suggest that the diaphragm may also be affected by sepsis-related striated muscle dysfunction.

The median P_{tr,stim} in this patient series was 6.5 cmH_{2}O (vs. 22.4 cmH_{2}O in controls), with extreme values as low as 1.8 cmH_{2}O. While it is possible that some patients had reduced diaphragm strength before the onset of their critical illness, the very low values of P_{tr,stim} compared with normal ventilated control subjects suggest that diaphragm dysfunction may represent an example of organ dysfunction complicating critical illness.

In a population of patients with a lower rate of sepsis and less severe diaphragm dysfunction, our group reported that P_{tr,stim} worsened by the fourth day of mechanical ventilation (4). In this study, we found that diaphragm dysfunction was similar on Day 3.
While the reasons for these disparate results are not clear, we speculate that the two study populations were radically different, with a higher rate of sepsis and more severe diaphragm dysfunction in the present study population. It is also important to bear in mind that sepsis-related myocardial depression reaches a peak after 48 hours and then gradually tends to return to normal (23).

**Risk factors**

Sepsis was a major independent risk factor for diaphragm dysfunction on ICU admission in our patients. This is consistent with animal data establishing a link between sepsis and severe, early-onset diaphragm dysfunction (6, 13). Previous studies have suggested the possibility of sepsis-induced diaphragm dysfunction in humans (2, 24) based on an association between sepsis and ventilator weaning difficulties. However, in these studies, diaphragm function was not assessed directly and respiratory abnormalities were described late in the course of the critical illness.

Although histopathologic signs of ventilator induced diaphragmatic dysfunction can be detected very early after the initiation of mechanical ventilation (3), our measurement of diaphragmatic function shortly after the initiation of mechanical ventilation makes it unlikely that the changes we observed were secondary to disuse atrophy. This conclusion is further supported by our observation that patients with sepsis had more severe diaphragm dysfunction than patients with other causes of shock.

In our multivariate analysis, only sepsis and disease severity were independently associated with diaphragm dysfunction. Because severity on ICU admission is associated with the number and magnitude of organ failures (25, 26), this association suggests that diaphragm dysfunction might be another expression of critical illness multiple organ failure.

**Prognostic impact**
ICU and hospital mortalities were higher among patients with diaphragm dysfunction than in those without diaphragm dysfunction, which appears to resemble the negative prognostic value of sepsis-induced myocardial dysfunction (8, 21). This finding is also consistent with the negative prognostic value of early nerve conduction abnormalities and muscle mitochondrial dysfunction observed in septic patients (9, 10). Whether or not the link between diaphragm dysfunction and mortality is causative remains to be determined.

In contrast, early diaphragm dysfunction did not appear to be associated with a longer duration of mechanical ventilation or longer ICU and hospital stays, which may appear to be somewhat unexpected, as critical illness polyneuropathy and myopathy that occurs later during the course of the ICU stay is associated with difficult weaning (1) and prolonged mechanical ventilation (2, 27). This is especially true in the presence of respiratory muscle involvement (2). Although severity on admission is an independent risk factor for critical illness polyneuropathy and myopathy (28), as yet unknown factors may also distinguish patients developing acute diaphragm dysfunction from patients developing delayed diaphragm dysfunction. Longitudinal studies in critically ill patients should help to more clearly elucidate this issue.

**Strengths and weaknesses of the study**

To the best of our knowledge, this is the first study to provide specific information on diaphragm function in patients at an early stage of the ICU stay. It also appears to be the largest study of diaphragm function in the ICU. The study population is representative of standard ICU recruitment, with a case mix not suggesting any bias toward patients with pre-existing diaphragm abnormalities. One of the strengths of this study was that it was conducted in two centers. Diaphragm strength was tested by bilateral phrenic nerve stimulation, a gold standard method that provides a specific measurement of the capacity of the diaphragm to generate an inspiratory pressure (29). It does not require patient cooperation, which
contributes to satisfactory reproducibility even in the difficult ICU setting (22, 30, 31). It can be applied in the presence or in the absence of sedation provided that no neuromuscular blocking agent is used. These characteristics would appear to highlight the unique value of our results.

Our study has some limitations. Diaphragm function was assessed by measuring tracheal pressure (Ptr,stim) without the use of esophageal and gastric probes to measure transdiaphragmatic pressure, which would have been more precise, but also more invasive, much less practical and more difficult to control metrologically. Of note, Ptr,stim is an adequate surrogate for esophageal pressure and has been shown to provide an adequate assessment of diaphragm function in the ICU (29). If anything, Ptr,stim may slightly underestimate diaphragm dysfunction. Most importantly, Ptr,stim presents satisfactory reproducibility in the ICU setting (30). The lung volume at which phrenic stimulation was performed was not measured, which could interfere with interpretation of the results as measurements of Ptr,stim will vary as a function of lung volume (32).

This is particularly true in relation to sequential day 1 and day 3 measurements. However, all stimulations were performed at end-expiration (zero expiratory flow) with zero end-expiratory pressure and patients with severe chronic obstructive pulmonary disease with possibly labile lung volume were also excluded. Although we performed our first measurement within the 24 hrs following intubation, a contribution of mechanical ventilation to the observed diaphragm dysfunction cannot be ruled out, as ventilator-induced diaphragm dysfunction has been observed as early as 18 hrs following intubation (3). However, this hypothesis is unlikely; as we did not observe any deterioration of diaphragm function between day-1 and day-3, a timeframe in which ventilator diaphragm dysfunction is likely to occur (4). By limiting the study to patients with an expected duration of mechanical ventilation >48 hours and by including up to 61% of patients with sepsis, the population was probably biased
towards greater severity, but this does not limit the generalizability of our results. Finally, our choice to set the diaphragm dysfunction cut-off at 11 cm H$_2$O warrants discussion. While we prospectively chose this value based on reports from the literature (19, 20), we then validated its use as a cutoff value in a population of patients briefly anesthetized and mechanically ventilated for elective surgical procedures. All of these individuals had $P_{\text{tr,stim}}$ values >11 H$_2$O (median 22.4 H$_2$O).

In addition, to avoid any dependence of the associations between $P_{\text{tr,stim}}$, risk factors for diaphragm dysfunction and clinical outcomes on the selection of a given cut-off, $P_{\text{tr,stim}}$ was also analyzed as a continuous variable to identify factors associated with an increase or a decrease of $P_{\text{tr,stim}}$ and this analysis gave similar results.

**Conclusion**

Our data establish a show an inverse association between between the capacity of the diaphragm to produce inspiratory pressure and severe sepsis in mechanically ventilated patients at an early stage of their ICU stay. We therefore suggest that diaphragm dysfunction can be considered as an example of sepsis-related organ failure. Further studies are necessary to determine whether diaphragm dysfunction in this setting is only a severity marker or whether it has a causative impact on mortality. It will also be very important to determine whether or not acute diaphragm dysfunction, as described here, constitutes a risk factor for ventilator-induced diaphragm dysfunction or other ICU-related diaphragmatic insults. Identifying acute diaphragm failure on ICU admission could then have an impact on subsequent clinical management.
References


### Tables

#### Table 1. Characteristics of the study population

<table>
<thead>
<tr>
<th></th>
<th>All patients (n=85)</th>
<th>Diaphragm dysfunction (<em>Defined as P</em>tr,<em>stim</em> &lt; 11 cmH₂O)</th>
<th>Ptr,<em>stim</em> as a quantitative variable</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (n=54)</td>
<td>No (n=31)</td>
<td>p</td>
</tr>
<tr>
<td>Age, years</td>
<td>62 [54-75]</td>
<td>60 [52-71]</td>
<td>0.138</td>
</tr>
<tr>
<td>Gender (M)</td>
<td>57 (67)</td>
<td>21 (68)</td>
<td>0.738</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.5 [22.2-27.5]</td>
<td>24.3 [23.0-26.5]</td>
<td>0.803</td>
</tr>
<tr>
<td>Tobacco, n (%)</td>
<td>33 (39)</td>
<td>10 (32)</td>
<td>0.347</td>
</tr>
<tr>
<td>Alcohol, n (%)</td>
<td>25 (29)</td>
<td>10 (32)</td>
<td>0.663</td>
</tr>
<tr>
<td>Cirrhosis, n (%)</td>
<td>17 (20)</td>
<td>6 (19)</td>
<td>0.838</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>23 (27)</td>
<td>7 (23)</td>
<td>0.481</td>
</tr>
<tr>
<td>SAPS II</td>
<td>54 [44-68]</td>
<td>47 [41-56]</td>
<td>0.002</td>
</tr>
<tr>
<td>Type of admission: Medical, n (%)</td>
<td>67 (79)</td>
<td>42 (78)</td>
<td>0.345</td>
</tr>
<tr>
<td>Indication for mechanical ventilation</td>
<td></td>
<td></td>
<td>0.029</td>
</tr>
<tr>
<td>Shock, n (%)</td>
<td>14 (16)</td>
<td>3 (10)</td>
<td>0.329</td>
</tr>
<tr>
<td>Coma, n (%)</td>
<td>25 (29)</td>
<td>15 (48)</td>
<td>0.008</td>
</tr>
<tr>
<td>Acute respiratory failure, n (%)</td>
<td>45 (53)</td>
<td>13 (42)</td>
<td>0.189</td>
</tr>
</tbody>
</table>

Ptr,*stim*: tracheal pressure in response to bilateral phrenic nerve stimulation; BMI, body mass index; SAPS; Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment.

Continuous variables are expressed as median [interquartile range].
Table 2. Characteristics of the patients at first diaphragm function assessment

<table>
<thead>
<tr>
<th></th>
<th>All patients (n=85)</th>
<th>Diaphragm dysfunction (Defined as Ptr,stim &lt; 11 cmH(_2)O)</th>
<th>Ptr,stim as a quantitative variable</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Yes (n=54)</td>
<td>No (n=31)</td>
</tr>
<tr>
<td>SOFA</td>
<td>8 [5-11]</td>
<td>8 [6-11]</td>
<td>7 [3-9]</td>
</tr>
<tr>
<td>Sepsis, n (%)</td>
<td>52 (61)</td>
<td>41 (76)</td>
<td>11 (35)</td>
</tr>
<tr>
<td>Hypnotics, n (%)</td>
<td>71 (84)</td>
<td>48 (89)</td>
<td>23 (74)</td>
</tr>
<tr>
<td>Opioids, n (%)</td>
<td>60 (71)</td>
<td>38 (70)</td>
<td>22 (71)</td>
</tr>
<tr>
<td>Steroids, n (%)</td>
<td>42 (49)</td>
<td>28 (52)</td>
<td>14 (45)</td>
</tr>
<tr>
<td>Amines, n (%)</td>
<td>51 (60)</td>
<td>37 (69)</td>
<td>14 (45)</td>
</tr>
<tr>
<td>Heart rate, b/min</td>
<td>95 [78-110]</td>
<td>97 [80-113]</td>
<td>90 [75-103]</td>
</tr>
<tr>
<td>Mean ABP, mmHg</td>
<td>83 [71-93]</td>
<td>85 [71-94]</td>
<td>77 [73-88]</td>
</tr>
<tr>
<td>VE, L/min</td>
<td>9.1 [7.7-10.5]</td>
<td>9.1 [8.0-10.5]</td>
<td>9.2 [7.5-10.1]</td>
</tr>
<tr>
<td>PaO(_2)/FiO(_2), mmHg</td>
<td>227 [161-322]</td>
<td>216 [169-296]</td>
<td>272 [160-437]</td>
</tr>
<tr>
<td>PaCO(_2), mmHg</td>
<td>37 [32-42]</td>
<td>37 [33-45]</td>
<td>35 [31-40]</td>
</tr>
<tr>
<td>HCO(^3), mMol/L</td>
<td>23 [20-26]</td>
<td>23 [20-27]</td>
<td>23 [21-25]</td>
</tr>
<tr>
<td>Blood lactates, mMol/L</td>
<td>2.3 [1.6-3.6]</td>
<td>2.6 [1.8-4.6]</td>
<td>2.1 [1.6-3.0]</td>
</tr>
</tbody>
</table>

Ptr,stim: tracheal pressure in response to bilateral phrenic nerve stimulation, SOFA, Sequential Organ Failure Assessment; BP, blood pressure; VE, minute ventilation.
Continuous variables are expressed as median (interquartile range).
Table 3. Clinical outcomes

<table>
<thead>
<tr>
<th></th>
<th>All patients (n=85)</th>
<th>Diaphragm dysfunction (Defined as Ptr,stim &lt; 11 cmH₂O)</th>
<th>TwPtr as a quantitative variable</th>
<th>p</th>
<th>Linear regression coefficient</th>
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<td>Duration of MV, days</td>
<td>Tracheostomy, n (%)</td>
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<td>Hospital LOS, days</td>
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<td>19 [14-44]</td>
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| Tw,Ptr, twitch tracheal pressure in response to bilateral phrenic nerve stimulation; MV, mechanical ventilation; ICU, intensive care unit; LOS, length of stay. Continuous variables are expressed as median (interquartile range).
LEGENDS FOR FIGURES

Figure 1. Individual endotracheal tube pressure induced by bilateral phrenic nerve stimulation (Ptr,stim) in controls and in patients without and with diaphragm dysfunction.

Ptr,stim mean ± standard deviation was 23.2±6.4 cmH₂O in mechanically ventilated control patients, 10.0±5.6 cmH₂O in the whole population of intensive care unit patients, 15.8±5.0 cmH₂O in patients without diaphragm dysfunction and 6.6±2.1 cmH₂O in those with diaphragm dysfunction.

The horizontal solid line indicates mean Ptr,stim in control patients (23.2 cmH₂O). The two horizontal dashed lines indicate Ptr,stim mean ± 1.96 standard deviation (10.7 and 35.7 cmH₂O, respectively) in control patients. 95% of the control population should be between these two values.

Figure 2. Study flow chart

Technical reasons: admission on week-end, failure of phrenic nerve stimulation.

Figure 3. Endotracheal tube pressure induced by bilateral phrenic nerve stimulation (Ptr,stim) in two critically ill patients

Panel A shows a representative example of a normal Ptr,stim suggesting preserved diaphragm function. Panel B depicts a representative example of reduced Ptr,stim demonstrating diaphragm dysfunction.
Figure 4. Intensive care unit (ICU) and hospital survival probabilities

ICU and hospital survival probabilities from the day of inclusion (day 0) to day 100 (ICU survival) or day 150 (hospital survival), according to the presence or absence of diaphragm dysfunction.
Figure 1

from 1st December 2008 to 1st July 2009
two independent intensive care units

723 admissions

111 no mechanical ventilation

167 non-invasive ventilation only

119 expected duration of mechanical ventilation <48 hrs

202 ≥ 1 exclusion criteria

39 not included for technical reasons

85 included

diaphragm dysfunction

54 (64%)

no diaphragm dysfunction

31 (36%)
Figure 2

A

B

Ptr,stim (cmH₂O)

100 ms

100 ms

0

0

5

5

10

10

15

15
Figure 3

$P_{\text{tr,stim}}$ (cmH$_2$O)

Control

No Dysfunction

Diaphragmatic Dysfunction
Figure 4

ICU survival

No diaphragm dysfunction

Diaphragm dysfunction

Hospital survival

No diaphragm dysfunction

Diaphragm dysfunction

Number at risk

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Diaphragm organ dysfunction on admission to ICU: prevalence, risk factors and prognostic impact - a prospective cohort study

Alexandre Demoule, Boris Jung, Hélène Prodanovic,
Nicolas Molinari, Gerald Chanques, Catherine Coirault,
Stefan Matecki, Alexandre Duguet,
Thomas Similowski*, Samir Jaber*

*The two last authors contributed equally to this work

Online Supplement

Patients and methods

The study was conducted over a 6-month period (1st December 2008 to 1st July 2009) in two intensive care units: A 10-bed medical Intensive Care Unit (ICU) (Groupe Hospitalier Pitié-Salpêtrière, Paris) and a 16-bed medical and surgical ICU (Hôpital Saint-Eloi, Montpellier). The study was approved by the "Comité de Protection des Personnes Sud-Méditerrannée II", Montpellier, France. All patients or their relatives provided written informed consent to participate. Data from six patients have been presented in a previously published study (1). This study was registered in the US National Institutes of Health clinical trials registry (clinicaltrials.gov NCT00786526).

Patients
Patients were eligible for inclusion in the study within the 24 hours following intubation and institution of mechanical ventilation. Exclusion criteria were an expected duration of mechanical ventilation less than 48 hours, contraindications to magnetic stimulation of the phrenic nerves (cardiac pacemaker or implanted defibrillator, cervical implants), use of neuromuscular blocking agents within the 24 hours preceding the first diaphragm function assessment (with the exception of succinylcholine used during rapid-sequence induction of anaesthesia for intubation), pre-existing neuromuscular disorders, cervical spine injury, factors possibly interfering with tracheal pressure measurements in response to phrenic stimulation (multiple functioning chest drains, severe chronic obstructive pulmonary disease). In the present study, patients were considered having severe COPD if they had known values of FEV1 prior to the acute episode below 30% predicted, prior hypoxemia or hypercapnia, or received long-term oxygen therapy. When these informations were not known, patients exhibiting clinical evidence of thoracic hyperinflation and high intrinsic PEP values were also excluded. Finally, participation in another clinical trial during the previous 30 days, age less than 18 years, known pregnancy, and a decision to withhold life-sustaining treatment were also exclusion criteria.

In addition, to establish that normal values in MV patients were similar to those observed in spontaneously breathing patients, in order to validate the cut-off of 11 cmH2O to define diaphragm dysfunction in ICU patients, we measured $\text{Ptr,stim}$ in 17 anesthetized patients intubated and mechanically ventilated for less than two hours in the context of digestive endoscopic procedures. Six of these patients have been presented in the previous study from our group (1).

**Diaphragm assessment**

Diaphragm performance was assessed in terms of the changes in endotracheal tube pressure induced by bilateral phrenic nerve stimulation during airway occlusion ($\text{Ptr,stim}$)
The first $\text{Ptr}_{\text{stim}}$ measurement was performed within 24 hours of intubation (day 1) and, whenever possible, a second measurement was obtained 48 hours later (day 3).

Phrenic nerve stimulation was performed by bilateral anterior magnetic stimulation (2). Briefly, two figure-of-eight coils connected to a pair of Magstim® 200 stimulators (The Magstim Company, Dyfed, UK) were positioned immediately posterior to the sternomastoid muscles at the level of the cricoid cartilage. Stimulations were delivered at the maximum intensity allowed by the stimulator. The patients were studied in a standardized semirecumbent position, as follows: end-expiratory pressure was set to zero and the patient was allowed to exhale during an end-expiratory pause until expiratory airflow reached zero (relaxed equilibrium volume of the respiratory system). The endotracheal tube was then occluded and bilateral anterolateral magnetic stimulation was performed. The absence of active respiratory efforts in response to stimulation was determined by checking the stability of the airway pressure signal. Measurements were repeated at least three times by 2 operators to ensure reproducibility. Stimulations were always performed by the same two operators in each centre. $\text{Ptr}_{\text{stim}}$ was defined as the amplitude of the negative pressure wave following stimulation, taken from baseline to peak. It was measured at the proximal end of the endotracheal tube, using a linear differential pressure transducer (MP45 ±100 cmH$_2$O, Validyne, Northridge, Calif., USA). The pressure signal was sampled and digitized at 128 Hz (MP30, Biopac Systems, Santa Barbara, Calif., USA or Powerlab, AD Instruments, Bella Vista, Australia) for subsequent data analysis.

**Clinical data collection**

Demographic data, severity scores, organ dysfunction–related variables, physiological data, presence of sepsis according to the 2001 International Sepsis Definitions Conference (3), blood gas data, and medications were prospectively recorded on ICU admission, at day 1 and at day 3. The durations of mechanical ventilation, ICU stay and hospital stay were
also recorded, as were decisions to perform tracheotomy, ICU mortality, and hospital mortality.

**Statistical analysis**

Statistical analysis was performed with R software (version R.2.13.2). The median and interquartile range (IQR) are reported for continuous variables (with the exception of \( \text{Ptr,stim} \) values in control patients, reported as mean ± SD for normative purposes) and absolute and relative frequencies are reported for categorical variables together with the 95% confidence intervals (95% CI) when appropriate.

\( \text{Ptr,stim} \) was analyzed as a continuous variable and univariate linear regression models were used to identify factors associated with higher or lower \( \text{Ptr,stim} \) values. These potential risk factors were: Age, gender, body mass index, tobacco, alcohol, cirrhosis, diabetes, SAPS II, type of admission, SOFA, sepsis, hypnotics, opioids, steroids, amines, heart rate, mean arterial blood pressure, minute ventilation, \( \text{PaO2/FiO2} \) ratio, \( \text{PaCO2} \), pH, \( \text{HCO3}^- \), blood lactates. Multivariate analysis was performed using a forward logistic regression process taking into account all potential risk factors for diaphragm dysfunction.

\( \text{Ptr,stim} \) was also used to identify two groups of patients based on the 11 cmH\(_2\)O cut-off that defines diaphragm dysfunction in other settings [see ATS/ERS statement on respiratory muscle testing (19, 20)]. Of note, the data obtained in our control subjects confirmed the relevance of this cut-off (see below, Results). Patients with a \( \text{Ptr,stim} \) less than 11 cmH\(_2\)O were considered to present diaphragm dysfunction. Each potential risk factor for diaphragm dysfunction was then evaluated in a univariate model (Student's \( t \) test or Mann-Whitney \( U \) test for continuous variables depending on distribution; \( \chi^2 \) test or Fisher's exact test for categorical variables depending on size), and multivariate analysis was performed. For all final comparisons, a P value ≤ 0.05 was considered statistically significant.
Finally, the impact of \( \text{Ptr,stim} \) on ICU and hospital mortality, tracheostomy rate, duration of mechanical ventilation and length of stay was assessed. The impact of \( \text{Ptr,stim} < 11 \) cmH\(_2\)O on ICU and hospital mortalities was evaluated using Kaplan-Meier survival function estimates.

**References**


### Tables

**Table E1. Characteristics of the study population in the short-term mechanical ventilation group**

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<tr>
<th>Patient n.</th>
<th>Sex (M/F)</th>
<th>Age (years)</th>
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<th>History of lung disease</th>
<th>Reason for short-term mechanical ventilation</th>
<th>Ptr,stim (cmH₂O)</th>
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Ptr,stim: tracheal pressure in response to bilateral phrenic nerve stimulation; BMI, body mass index; SD: Standard deviation.

All variables are normally distributed (Kolmogorov-Smirnov and Shapiro-Wilk).
Figure Legends

Figure E1. Phrenic nerve stimulation and tracheal pressure recording

Left panel depicts bilateral anterior magnetic stimulation of the phrenic nerves that was delivered using two figure-of-eight coils positioned immediately posterior to the sternomastoid muscle at the level of the cricoid cartilage.

Right panel shows a representative example of the change in endotracheal tube pressure induced by application of bilateral phrenic nerve stimulation during airway occlusion at end-expiration (zero end-expiratory positive pressure). Ptr, tracheal pressure, as measured at the extremity of the endotracheal tube. Ptr,stim, amplitude of the negative Ptr wave following stimulation, taken from baseline to peak and used to define the presence or absence of diaphragm dysfunction.
Figure E1

![Image of a patient with medical equipment and a graph showing Ptr (cmH$_2$O) over Time (ms). The graph indicates a peak labeled Ptr,stim.](image-url)