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Sepsis Is Associated with a Preferential Diaphragmatic Atrophy

A Critically Ill Patient Study Using Tridimensional Computed Tomography

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ABSTRACT

Background: Diaphragm and psoas are affected during sepsis in animal models. Whether diaphragm or limb muscle is preferentially affected during sepsis in the critically ill remains unclear.

Methods: Retrospective secondary analysis study including 40 patients, comparing control (n = 17) and critically ill patients, with (n = 14) or without sepsis (n = 9). Diaphragm volume, psoas volume, and cross-sectional area of the skeletal muscles at the third lumbar vertebra were measured during intensive care unit (ICU) stay using tridimensional computed tomography scan volumetry. Diaphragm strength was evaluated using magnetic phrenic nerve stimulation. The primary endpoint was the comparison between diaphragm and peripheral muscle volume kinetics during the ICU stay among critically ill patients, with or without sepsis.

Results: Upon ICU admission, neither diaphragm nor psoas muscle volumes were significantly different between critically ill and control patients ($163 \pm 53 \text{ cm}^3$ vs. $197 \pm 82 \text{ cm}^3$ for the diaphragm, $P = 0.36$, and $272 \pm 116 \text{ cm}^3$ vs. $329 \pm 166 \text{ cm}^3$ for the psoas, $P = 0.31$). Twenty-five (15 to 36) days after admission, diaphragm volume decreased by $11 \pm 13\%$ in nonseptic and by $27 \pm 12\%$ in septic patients, $P = 0.01$. Psoas volume decreased by $11 \pm 10\%$ in nonseptic and by $19 \pm 13\%$ in septic patients, $P = 0.09$. Upon ICU admission, diaphragm strength was correlated with diaphragm volume and was lower in septic ($6.2 \text{ cm H}_2\text{O}$ [5.6 to 9.3]) than that in nonseptic patients ($13.2 \text{ cm H}_2\text{O}$ [12.3 to 15.6]), $P = 0.01$.

Conclusions: During the ICU stay, both diaphragm and psoas volumes decreased. In septic patients, the authors report for the first time in humans preferential diaphragm atrophy compared with peripheral muscles.

THE diaphragm is the main respiratory muscle, its dysfunction is one of the main causes of difficulties to wean from the ventilator in the intensive care unit (ICU) and sepsis affects its contractility in the critically ill.¹⁻⁵ Along with others, we have recently confirmed in humans that mechanical ventilation (MV) *per se* is associated with diaphragm dysfunction, a condition named ventilator-induced diaphragmatic dysfunction.^{4,6-8} Although ventilator-induced diaphragmatic dysfunction has recently emerged as a potentially important clinical condition, sepsis has been reported to be associated with diaphragm dysfunction in relation with both myopathy and neuropathy⁹ and is the consequence of both functional (specific force generation) and morphological (atrophy) damages.¹⁰ However, whether limb muscles or diaphragm is similarly or differentially affected during sepsis remains controversial^{2,11-13} and determining the main victim

What We Already Know about This Topic

- Septic patients lose significant muscle mass

What This Article Tells Us That Is New

- Comparisons between 14 people with sepsis and 9 similar patients without sepsis documented a significant loss of diaphragm muscle volume compared with the psoas muscle volume in the septic patients
- The loss of diaphragm muscle was associated with loss of strength

may be helpful for clinicians confronted with patients recovering from severe sepsis. Indeed, the Extended Prevalence of Infection in Intensive Care study II reported an incidence of 46 to 60% of ICU beds occupied by a “sepsis case” around the world,¹⁴ and although as many as 33% of the patients eventually died during their hospital stay, more and more

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patients do survive after sepsis. However, these survivors increasingly present profound skeletal muscle weakness and there is a need to better identify and treat sepsis-induced myopathy in the critically ill patients.¹ Our team developed a three-dimensional volumetry tool using computed tomography (CT)¹⁵⁻¹⁸ which may be of interest to compare diaphragm and peripheral muscle volume kinetics in the critically ill.

The aims of our study were therefore to compare diaphragm and psoas volumes between septic and nonseptic critically ill patients during the ICU stay and to describe the relation between diaphragm volume and diaphragm contractility in critically ill patients. We hypothesized that sepsis is associated with a preferential diaphragmatic atrophy, which is negatively correlated with diaphragm contractility.

Materials and Methods

Study Design

This study was conducted from July 2008 to August 2009 in a 16-bed medical–surgical ICU (Saint Eloi Teaching Hospital ICU, Montpellier, France) and is a retrospective secondary analysis of a trial performed with some of the patients (critically ill patients).² Given that this *post hoc* analysis did not modify current diagnostic or therapeutic strategies, the need for written consent was waived according to the French Law (Law 88–1138 relative to Biomedical Research of December 20, 1988, modified on August 9, 2004). The study design is represented in figure 1.

Study Population

A flow chart of the study is represented in figure 2. Critically ill patients were included in the *post hoc* analysis if they were

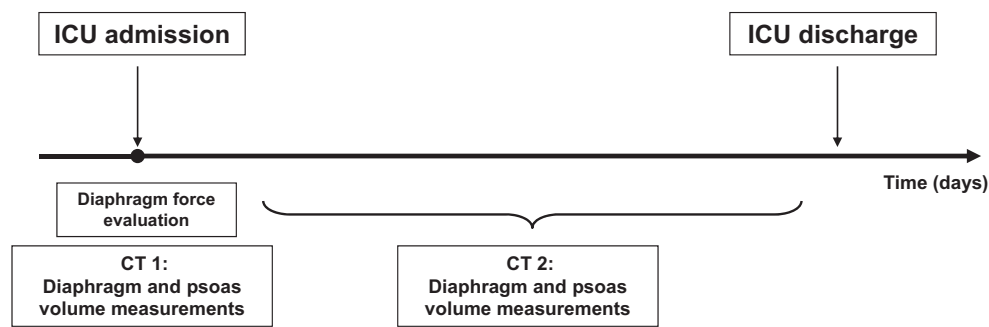


Fig. 1. Design of the study. Diaphragm force evaluation and the first computed tomography (CT) volume measurement were performed upon intensive care unit (ICU) admission. Second CT volume measurement was done during the ICU stay when a CT was indicated for diagnostic purposes.

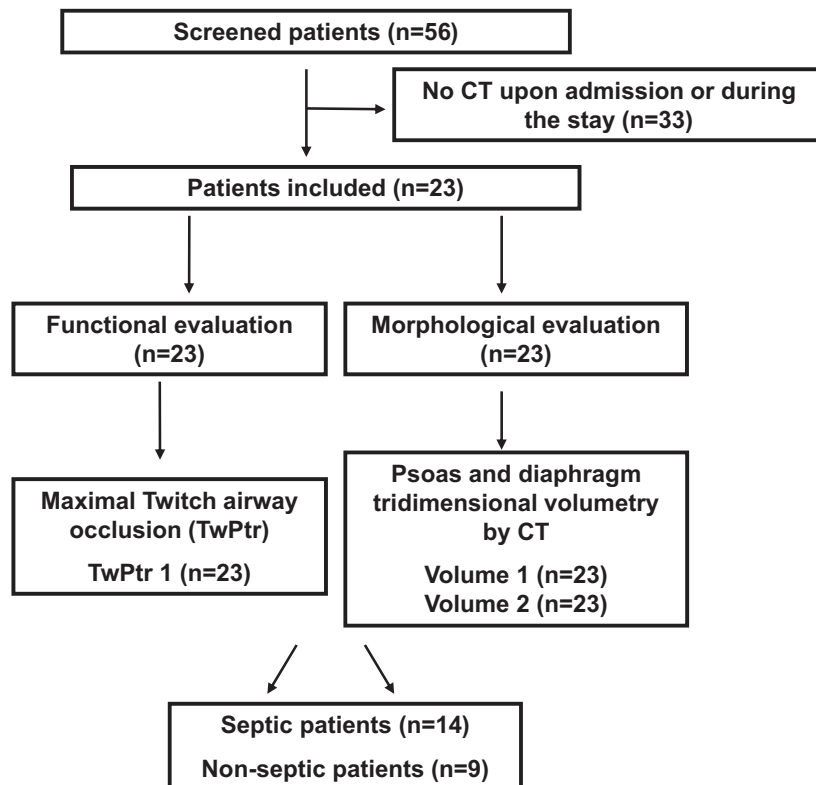


Fig. 2. Flow chart of the study. CT = computed tomography.

admitted to the ICU and had had (1) an abdominal CT scan before the ICU admission, (2) a second abdominal CT scan during the ICU stay, and (3) at least one measure of diaphragmatic contractility by measuring the change in endotracheal tube pressure induced by application of bilateral magnetic twitch stimulation of the phrenic nerves during airway occlusion (TwPtr) while being intubated.^{2,4} Patients were excluded if the CT scan did not allow measurement of the diaphragm and the psoas muscle volumes (cut diaphragm and/or psoas and artifacts) or in the case of a previously identified chronic neuromuscular disease associated with muscle atrophy. Patients in the ICU group were separated into septic and nonseptic groups according to Bone's criteria.¹⁹ Seventeen consecutive outpatients, explored with a virtual colonoscopy at our institution and who had a normal abdominal CT scan, served as controls (control group).

Measurements

We collected data for sex, age, height, weight, body mass index, Simplified Acute Physiology Score II,²⁰ Sequential Organ Failure Assessment score,¹⁴ presence of a sepsis, length of ICU stay, and ICU mortality for all patients in the ICU (table 1).

Semiautomatic measurements of the diaphragm and the limb muscle volumes by CT scan were performed using the same technique as previously described^{15,17,18} and are illustrated in figure 3. In brief, examination of the diaphragm and the psoas was performed with 64-section spiral CT (Aquilon 64; Toshiba Medical Systems, Nasu, Japan). One radiologist (S.N.), blinded of the patient's condition and of the TwPtr value, traced the diaphragm contour semiautomatically every 1 mm section after transfer to a dedicated workstation (Advantage Window 4.5 with Volume Viewer; General Electric, Milwaukee, WI). The radiologist manually traced the diaphragm borders, and then the volumetry software calculated the whole diaphragm volume using an algorithm summing up each of the cross-sectional volumes (multiply cross-sectional area by section thickness). The psoas volumes were measured with the same technique. In the critically ill, abdominal wall and paraspinal muscle cross-sectional area were measured at the level of the third lumbar vertebra as described elsewhere.²¹ Skeletal muscles were distinguished from the organs and edema by the Hounsfield unit thresholds (-29 to +150)²² and cross-sectional

Table 1. Characteristics of the 40 Studied Patients

	Controls (n = 17)	ICU Nonseptic (n = 9)	ICU Septic (n = 14)	P Value
Age (yr)	59±24	55±16	67±14	0.07
Male sex	9 (53)	6 (66)	8 (57)	0.79
Weight (kg)	80±13	79±21	73±23	0.32
Height (cm)	166±8	170±15	168±7	0.66
Body mass index (kg/m ²)	28.8 ± 4.4	27.0 ± 4.8	25.6 ± 7.0	0.36
Past medical history				
COPD	1 (6)	1 (11)	1 (7)	0.88
Cancer	0 (0)	0 (0)	2 (14)	0.15
Diabetes mellitus	2 (12)	2 (22)	4 (28)	0.50
SAPS II upon ICU admission	NA	42±14	53±22	0.18
SOFA score upon ICU admission	NA	6±3	8±4	0.20
ICU length of stay (days)	NA	24±17	34±26	0.36
Sedation	NA	9 (100)	14 (100)	>0.99
Neuromuscular-blocking agent (days)	NA	0 (0-0)	0 (0-1)	0.10
Duration of sedation (days)	NA	6 (3-19)	7 (3-11)	0.81
Duration of controlled mechanical ventilation (days)	NA	4 (3-7)	6 (5-8)	0.49
Duration of pressure support ventilation (days)	NA	11 (6-21)	12 (5-21)	0.78
Noninvasive ventilation (days)	NA	0 (0-3)	1 (1-4)	0.35
Fluid balance day 0 (ml)	NA	600 (-1,100 to 1,000)	1,700 (1,400-2,500)	0.02
Fluid balance day 1 (ml)	NA	1,100 (0-2,500)	800 (400-1,700)	0.99
Fluid balance day 2 (ml)	NA	1,100 (500-1,600)	-200 (-2,000 to 1,800)	0.27
Fluid balance day 3 (ml)	NA	600 (400-700)	200 (-1,200 to 1,300)	0.38
Fluid balance day 4 to 7 (ml)	NA	1,100 (-900 to 3,000)	0 (-1,200 to 1,200)	0.64
Parenteral nutrition (days)	NA	6 (1-9)	14 (12-25)	0.06
Enteral nutrition (days)	NA	9 (4-22)	13 (7-17)	0.54
Aminoglycosides (days)	NA	0 (0-2)	0 (0-2)	0.93
Hydrocortisone (total dose during the stay, mg)	NA	0 (0-1,400)	1,450 (1,000-1,700)	0.03
Day 28 survival	NA	8 (89)	11 (79)	0.52

Data are mean and SD or mean and quartiles or number and percentages. There was no statistically significant difference between ICU nonseptic and septic groups for the reported data. P value is between ICU nonseptic and ICU septic patients.

COPD = chronic obstructive pulmonary disease; ICU = intensive care unit; NA = not applicable; SAPS II = Simplified Acute Physiology Score; SOFA = Sequential Organ Failure Assessment score.

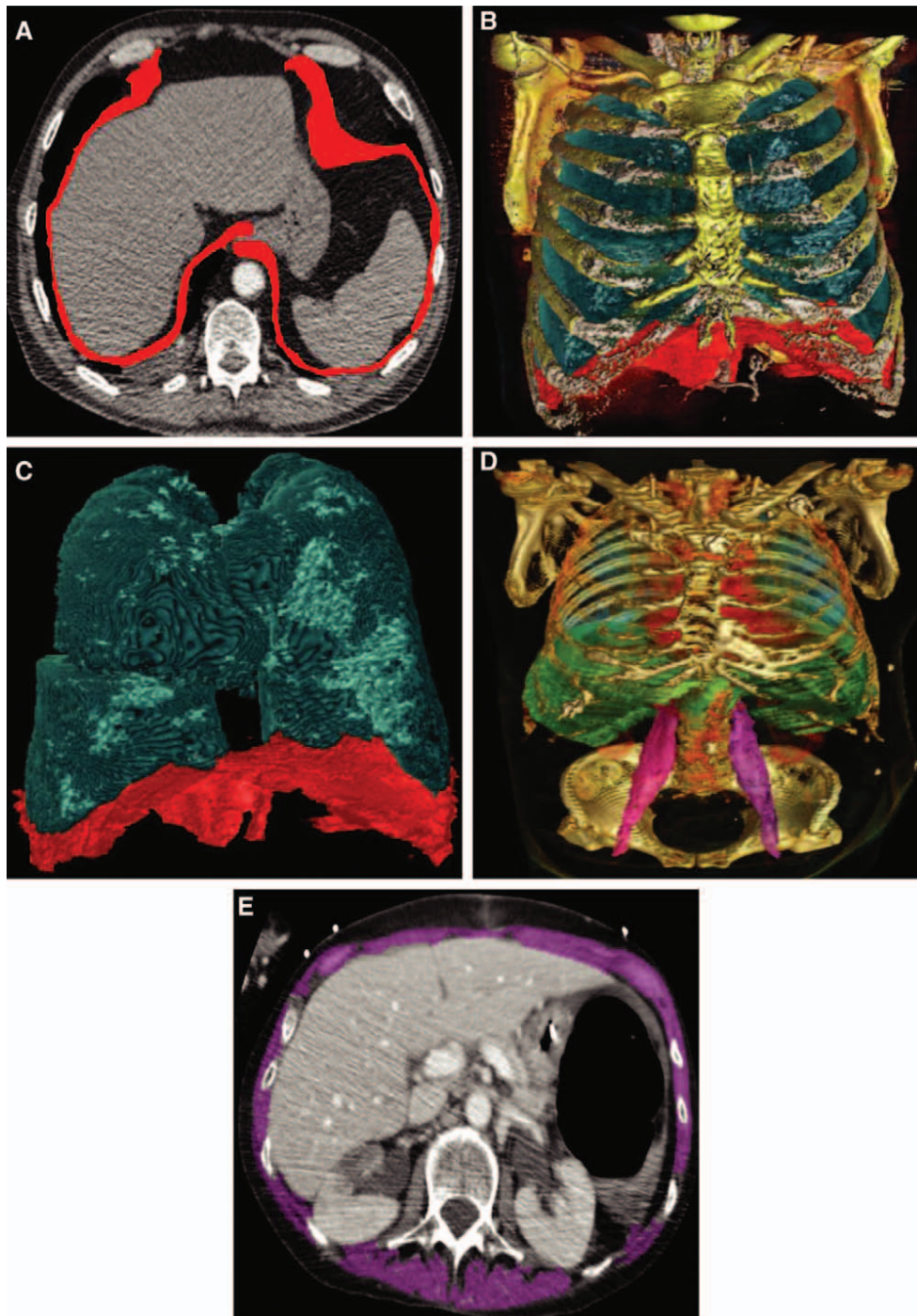


Fig. 3. Psoas and diaphragm volume measurements with three-dimensional computed tomography reconstruction and dedicated software for volumetry measurement (Advantage Window 4.5 with Volume Viewer; General Electric, Milwaukee, WI). After circling, the diaphragm and the psoas shapes on millimetric slide (A), the software automatically isolated the diaphragm from the abdomen and the chest wall (B, C), and calculated the diaphragm volume (average volume $163 \pm 53 \text{ cm}^3$). Psoas volumes were measured using the same technique (average volume $272 \pm 116 \text{ cm}^3$) (D). Cross-sectional area of the paraspinal and abdominal wall muscles was measured at the level of the third lumbar vertebra (average cross sectional area $17.1 \pm 5.4 \text{ cm}^2/\text{m}^2$) (E).

areas of all those muscles were summed and expressed as normalized to body surface.²¹ We assessed whether diaphragm and psoas volumes were correlated with weight, height, and body mass index.

Diaphragmatic contractile function was evaluated as previously described.^{2,4} In brief, we measured the change

in endotracheal tube pressure provoked by application of bilateral magnetic twitch stimulation of the phrenic nerves during airway occlusion. TwPtr was obtained upon ICU admission but not afterwards as detailed in a previous study from our group.² In the control group, no diaphragmatic contractile measure was performed.

Study Endpoints

The primary endpoint was to compare diaphragm and psoas volume changes between septic and nonseptic critically ill patients. The secondary endpoint was to describe the relation between diaphragm volume and diaphragm contractility.

Statistical Analysis

The results are expressed as mean \pm SD, median (25th to 75th percentiles), and number and percentage. Demographic characteristics, muscle volumes, and muscle surfaces were compared between controls, nonseptic, and septic patient groups using the Kruskal–Wallis, repeated-measure ANOVA, or chi-square tests according to the distribution of the variables. To compare volume kinetic in the critically ill according to the presence or the absence of sepsis, the Wilcoxon rank sum test for paired data was used. The Pearson correlation coefficient was used to assess the correlation between the muscle volume and weight, height, body mass index, and contractility. After preliminary measures conducted for the current study, we assumed a mean diaphragm volume of approximately 210 cm³ with an SD of 60 cm³ in the control patients. We then hypothesized a 30% decrease in diaphragmatic volume in critically ill during the ICU stay. Because we did not expect the possibility of muscle hypertrophy during the ICU stay, we calculated that 12

patients per group would be necessary to test our hypothesis with 80% statistical power and a one-sided α value of 0.05. Statistical analysis was performed by the Medical Statistical Department of the Montpellier University Hospital (N.M.), with R software (v2.15.2; Vienna, Austria). A *P* value of less than 0.05 was considered statistically significant.

Results

A total of 40 patients were included. Seventeen constituted the control group and 23 in the ICU group; of the ICU group, 14 of them were septic and 9 were not septic (fig. 2). Table 1 shows their main characteristics. No differences were observed among septic and nonseptic patients. Sepsis started 2 days (3 to 5) before ICU admission. Nine of the 14 septic patients presented with an intraabdominal infection, 4 presented with a pneumonia, and 1 presented with an endocarditis. Among the nine patients without sepsis, three were admitted for multiple trauma, three for scheduled esophageal surgery, one for acute on chronic respiratory failure, and two for acute liver failure.

Diaphragm and psoas volumes were both correlated with weight, height, and body mass index (fig. 4).

In the ICU group, the first diaphragm volume measurement, performed the day of admission (-3 to 0) (with extremes ranged from 33 days before admission to

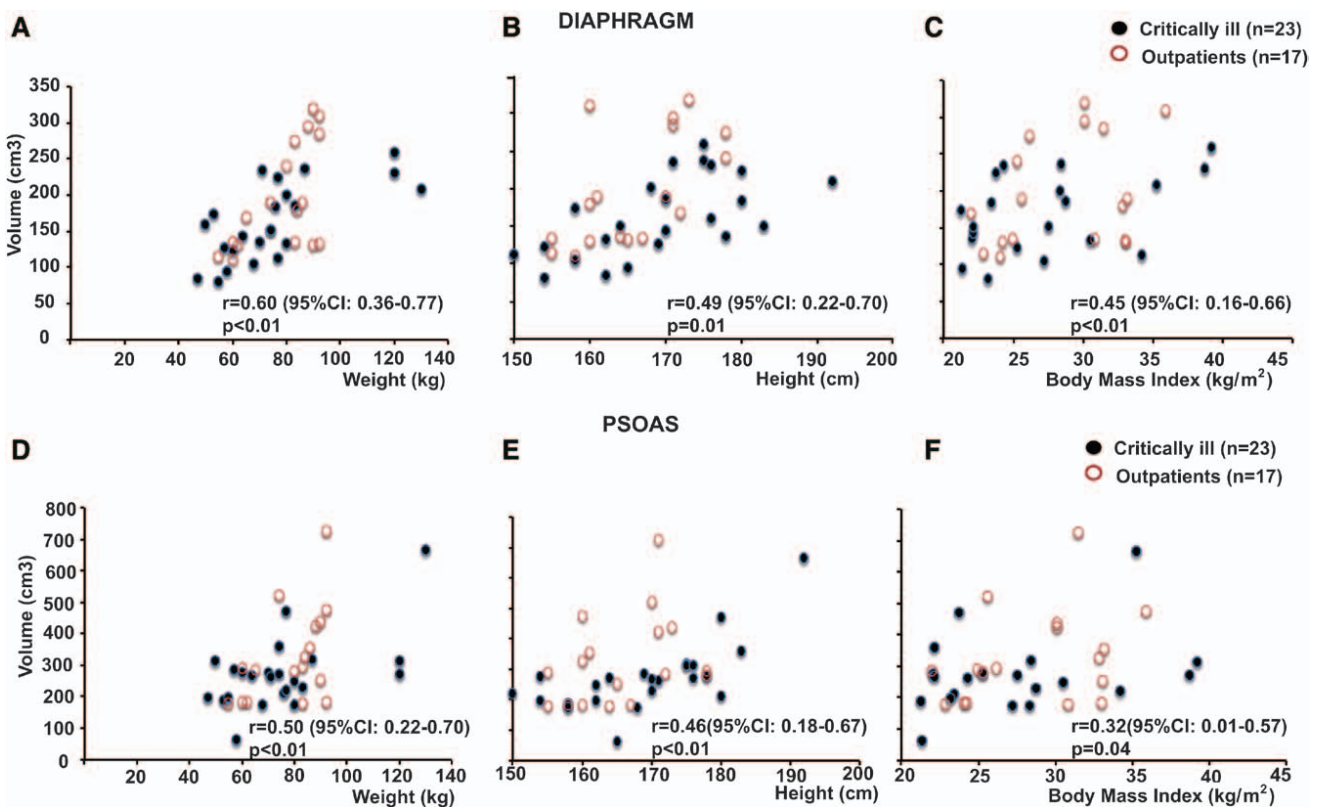


Fig. 4. Scatterplot showing the results of regression analysis of diaphragm volume and patient weight (A), (B) height, and (C) body mass index. Correlation was calculated for the entire sample (critically ill and controls). There was a linear correlation between total diaphragm volume and weight, height, and body mass index. Scatterplot showing the result of regression analysis of psoas volume and intensive care unit patient weight (D), height (E), and body mass index (F). There was a linear correlation between total psoas volume and weight, height, and body surface area.

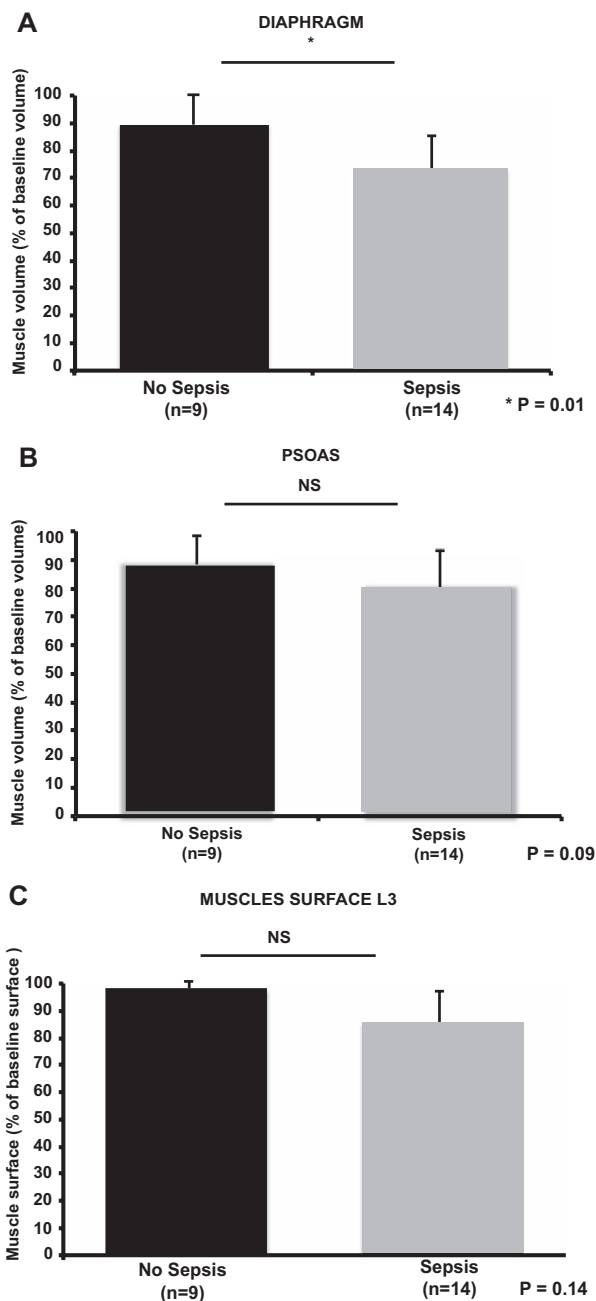


Fig. 5. (A) Diaphragm volume kinetic between the two volume measurements in nonseptic patients and septic patients. Compared with the first measurement, volume drop was larger in septic ($162 \pm 55 \text{ cm}^3$ to $120 \pm 52 \text{ cm}^3$) than that in nonseptic patients ($164 \pm 53 \text{ cm}^3$ to $145 \pm 51 \text{ cm}^3$) ($P = 0.01$). (B) Psoas volume kinetic between the two volumes measurements in nonseptic patients and septic patients. Volume drop did not differ between the two groups. (C) Skeletal total muscle surface measured at the level of the third lumbar vertebra in nonseptic patients and septic patients. Surface drop did not differ between the two groups.

1-day postadmission), was $163 \pm 53 \text{ cm}^3$ compared with $197 \pm 82 \text{ cm}^3$ in the control group ($P = 0.36$). The first psoas volume measurement was $272 \pm 116 \text{ cm}^3$ in the ICU group compared with $329 \pm 166 \text{ cm}^3$ in the control group ($P = 0.31$).

The second volume measurement was performed 25 (15 to 36) days after the first measurement. In the critically ill, diaphragm volume decreased from $163 \pm 53 \text{ cm}^3$ to $130 \pm 52 \text{ cm}^3$ ($P < 0.01$) during the ICU stay. Psoas volume decreased from $272 \pm 116 \text{ cm}^3$ to $233 \pm 108 \text{ cm}^3$ ($P < 0.01$) during the ICU stay. No correlation was found between diaphragm or psoas volume loss and time between the two CTs. Cross-sectional areas of skeletal muscles at the level of the third lumbar vertebra did not significantly decrease during the ICU stay (first measurement: $17.1 \pm 5.4 \text{ cm}^2/\text{m}^2$ and second measurement: $16.1 \pm 5.2 \text{ cm}^2/\text{m}^2$). When the volume drop between the two measures was considered, septic patients experienced a larger decrease of diaphragmatic volume compared with that by the nonseptic patients (fig. 5A). On the contrary, comparing changes in psoas volume and muscle surface on the level of the third lumbar vertebra between septic and nonseptic patients revealed no differences (fig. 5, B and C).

Contractile function of the diaphragm upon ICU admission was evaluated after magnetic stimulation of the phrenic nerves. Tracheal pressure was $9.8 \text{ cm H}_2\text{O}$ (6.0 to 13.1). Upon ICU admission, tracheal pressure was lower in the septic patients ($6.2 \text{ cm H}_2\text{O}$ [5.6 to 9.3]) compared with the nonseptic patients ($13.2 \text{ cm H}_2\text{O}$ [12.3 to 15.6]), $P = 0.01$. Diaphragm volume was correlated with tracheal pressure obtained upon ICU admission ($r = 0.43$ [0.02 to 0.72], $P = 0.04$) (fig. 6). One representative patient is presented on figure 7.

Discussion

This study, through combined functional and morphological data, shows for the first time in humans that sepsis is associated with preferential loss of diaphragm volume compared with the psoas. This loss of volume was associated with a lower diaphragm contractile force, evaluated by magnetic stimulation of the phrenic nerves.

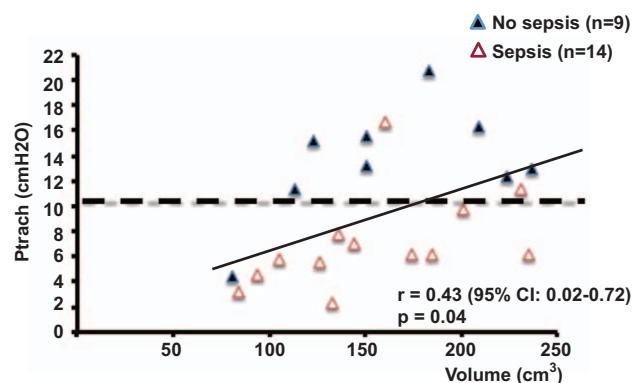


Fig. 6. Correlation between tracheal pressure measured upon intensive care unit admission and the first diaphragm volume measured upon admission (0 day [-3 to 0] before admission) in septic and nonseptic patients. There was a correlation between tracheal pressure (P_{trach}) and diaphragm volume ($r = 0.43$ [0.02–0.72], $P = 0.04$). Regardless of the diaphragm volume, all but two septic patients had a P_{trach} below $11 \text{ cm H}_2\text{O}$, which is the threshold of diaphragm dysfunction.²

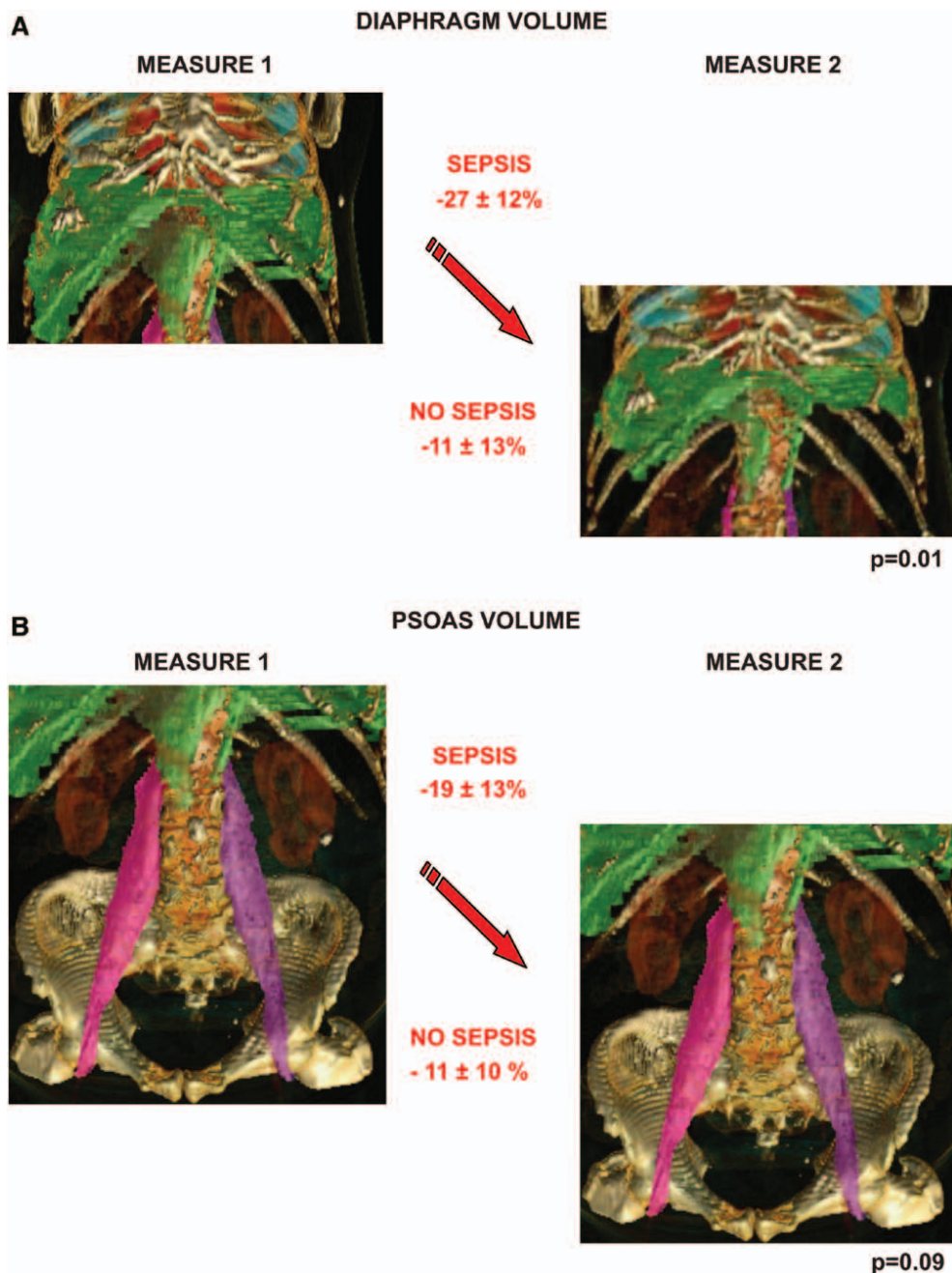


Fig. 7. Illustrative case. Mean and SD volume variation is labeled for the critically ill groups. (A) Mean diaphragm volume drop comparison between septic and nonseptic patients. Volume drop was significantly greater in the septic patients compared with that in the nonseptic patients, $P = 0.01$. (B) Mean psoas volume drop comparison between septic and nonseptic patients. Volume drop was not affected by the presence of sepsis, $P = 0.09$.

Our study has some limitations. It is a single-center study with limited patients. It highlights the atrophy that occurred during the ICU stay and provides additional data about diaphragmatic susceptibility to atrophy in the case of sepsis, but lacks mechanistic explanations, as well as data about psoas contractile force because of the study's design. However, obtaining diaphragm biopsies in humans who do not need surgery is not acceptable regarding the risk of such biopsies. Diaphragm volume was measured without data about inspiration–expiration cycling. Although

knowing lung volume is of interest when diaphragm volume is evaluated, diaphragm volume measurement was performed using the same technique for all critically ill patients, thereby diluting the impact of lung volume on diaphragm volume in the current study. Finally, we provided only two measurements of muscle volume, but repeating high-resolution CT scans would have been outside the standard of care.

In the current study, we used the same technique as we did in other situations with the aid of an experienced radiologist

(S.N.)^{15–18} and a licensed software (Advantage Window 4.5 with Volume Viewer; General Electric) that allows tridimensional reconstruction of the diaphragm. We report that diaphragm and psoas volumes are correlated with height, weight, and body mass index (fig. 4). To our knowledge, no study has evaluated the relation between diaphragm volume and body measurements and there is no definitive standard for diaphragm volume measurement.²³ At the bedside, ultrasound is an interesting noninvasive technique to evaluate diaphragm contractile properties.^{24–27} Ultrasound can also be used to measure diaphragm thickness in mechanically ventilated patients.²⁸ However, when diaphragm trophicity is questioned, ultrasound might be limited as it usually measures the right hemidiaphragm thickness at a single point on the midaxillary line.²⁸ Moreover, up to 10% of the patients cannot be evaluated by ultrasound because of a poor acoustic window.²⁶

In the current study, we report the absence of diaphragm and psoas volume differences between the 17 controls and the 23 critically ill patients upon ICU admission. The absence of previous diseases that are known to be associated with diaphragmatic atrophy (*e.g.*, chronic obstructive pulmonary disease²⁹ or cancer)³⁰ in 17 among 23 critically ill patients (75%) may have explained the absence of difference of diaphragm and psoas volumes between controls and critically ill.

In the 23 critically ill patients, we report that both psoas and diaphragm volumes decreased during the ICU stay. Prolonged stay in the ICU has been associated with skeletal muscle atrophy and neuromuscular impairment⁹ and is the consequence of several mechanisms such as inadequate energy supply, increased catabolism, proteolysis, and protein synthesis impairment which are the consequences of systemic aggression.¹

In the 14 critically ill patients with sepsis, we report that diaphragm volume loss is predominant compared with psoas, and that diaphragm volume is correlated with diaphragm force (fig. 6). Sepsis is recognized to be one of the main risk factors for development of critical illness myopathy,⁹ and as early as 1892, William Osler³¹ reported the “rapid loss of flesh” that occurs with severe sepsis. Using animal models of sepsis, it has been suggested that both limb and diaphragm muscles are affected, but to a different extent.^{10–13,32} In Human studies, our group recently demonstrated early diaphragmatic force impairment in sepsis.²

Others have shown, using invasive techniques with percutaneous stimulation and diaphragm needle electrodes, that both diaphragmatic and limb muscles were affected during the early phase of sepsis.³³ Although the current study was not designed to explore the mechanisms leading to a preferential diaphragm volume loss in sepsis, some hypotheses can be made. Early host response to pathogen and pathogen toxins induces proinflammatory cytokines release, reactive oxygen species production, sarcoplasmic reticulum calcium release channel, ryanodine receptor dysfunction,¹⁰ and sarcolemmal injuries.³⁴ In more prolonged

models of sepsis, muscle wasting results from exaggerated proteolysis and decreased protein synthesis.^{32,35,36} One explanation that might explain a preferential diaphragmatic loss of volume during sepsis is its ability to overproduce proinflammatory cytokines consecutively to a lipopolysaccharide challenge.³²

In septic patients, MV may have exacerbated the amplitude of diaphragmatic weakness caused by sepsis or might have slowed the subsequent recovery of diaphragmatic function once sepsis has resolved. Indeed, it is accepted that MV *per se* induces diaphragm dysfunction.^{4,6,8,37,38} Although one animal study reported that the diaphragm was protected by MV in the early stages of sepsis,³⁹ the interaction between sepsis and MV can also be deleterious.⁴⁰ Indeed, it has been reported that both MV⁴¹ and sepsis share activation of toll-like receptor 4 pathway.³⁵

In the current study, we combined functional and morphological analyses and reported that as soon as the patient is admitted to the ICU, diaphragm contractile force is decreased in septic compared with nonseptic patients. We also determined a statistically significant correlation coefficient between diaphragm volume and force (fig. 6).

In conclusion, in septic patients, the current study reports a preferential loss of diaphragm volume compared with psoas. Upon ICU admission, diaphragm volume was correlated with diaphragm force, evaluated using magnetic stimulation of the phrenic nerves. Muscle volume measurement using dedicated tridimensional CT scan software may be considered for global evaluation of diaphragm atrophy in the critically ill. The association between muscle volume and function remains to be explored.

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Competing Interests

Dr. Jung reports personal fees from Merck (Whitehouse Station, New Jersey) and Astellas (Tokyo, Japan) without relations with the current study; Dr. Futier reports consulting fees from General Electric Medical System (Milwaukee, Wisconsin), and lecture fees from Fresenius Kabi (Bad Homburg, Germany) without relations with the current study; Dr. Jaber reports personal fees from Maquet (Getinge, Sweden), Draeger (Lübeck, Germany), Hamilton Medical (Bonaduz, Switzerland), Fisher Paykel (Auckland, New Zealand), and Abbott (Abbott Park, Illinois) without relations with the current study. All other authors have no competing interests.

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