Prevalence and Impact on Weaning of Pleural Effusion at the Time of Liberation from Mechanical Ventilation

A Multicenter Prospective Observational Study

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ABSTRACT

Background: Pleural effusion is frequent in intensive care unit patients, but its impact on the outcome of weaning remains unknown.

Methods: In a prospective study performed in three intensive care units, pleural ultrasound was performed at the first spontaneous breathing trial to detect and quantify pleural effusion (small, moderate, and large). Weaning failure was defined by a failed spontaneous breathing trial and/or extubation requiring any form of ventilatory support within 48 h. The primary endpoint was the prevalence of pleural effusion according to weaning outcome.

Results: Pleural effusion was detected in 51 of 136 (37%) patients and was quantified as moderate to large in 18 (13%) patients. As compared to patients with no or small pleural effusion, their counterparts were more likely to have chronic renal failure (39 *vs.* 7%; $P = 0.01$), shock as the primary reason for admission (44 *vs.* 19%; $P = 0.02$), and a greater weight gain (+4 [0 to 7] kg *vs.* 0 [−1 to 5] kg; $P = 0.02$). The prevalence of pleural effusion was similar in weaning success and weaning failure patients (odds ratio, 1.23; 95% CI, 0.61 to 2.49; $P = 0.56$), as was the prevalence of moderate to large pleural effusion (odds ratio, 0.89; 95% CI, 0.33 to 2.41; $P = 1.00$). Duration of mechanical ventilation and intensive care unit length of stay were similar between patients with no or small pleural effusion and those with moderate to large pleural effusion.

Conclusions: Significant pleural effusion was observed in 13% of patients at the time of liberation from mechanical ventilation and was not associated with an alteration of weaning outcome. **(Anesthesiology 2017; 126:1107–15)**

FAILURE to wean from mechanical ventilation occurs in a minority of patients but is associated with high morbidity.[1] Preventing weaning failure is therefore of major importance and must be based on a better understanding of its mechanisms.[2,3] Weaning failure results from a load-capacity imbalance,[4] which occurs when the mechanical or chemical loading of the respiratory system increases to the point where it exceeds the capacity of the respiratory muscles. Weaning failure also results from gas-exchange impairment.[5]

Pleural effusion is one of several factors that increase loading of the respiratory system and compromise gas exchange. Experimental studies and clinical series of mechanically ventilated patients have reported that pleural effusion is associated with impairment of respiratory system mechanics mostly secondary to decreased compliance.[6] In addition, pleural effusion is associated with hypoxemia caused by alterations in intrapulmonary shunt.[7,8] The causal role of pleural effusion in these alterations is supported by reports of improvement in lung mechanics and oxygenation after drainage of pleural fluid in humans.[9,10] Altogether, these

What We Already Know about This Topic

- Pleural effusion is common in mechanically ventilated patients and can adversely impact pulmonary mechanics, but its impact on weaning or on duration of ventilation is unknown.

What This Article Tells Us That Is New

- Pleural effusion was detected in 37% of patients and was significant in 13%. However, the presence of significant effusion was not associated with an increase in duration of—or weaning from—mechanical ventilation or with length of intensive care unit stay.

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data suggest that pleural effusion may contribute to weaning failure.

Importantly, to our knowledge, no published study has reported the prevalence, characteristics, and prognostic impact of pleural effusion at the time of weaning from mechanical ventilation. The few studies that have investigated the prevalence and risk factors of pleural effusion in intensive care unit (ICU) patients considered the entire ICU stay and did not specifically focus on weaning.[11–13] The potential impact of pleural effusion on weaning therefore remains unknown.

We therefore conducted this multicenter prospective observational study to investigate the prevalence and risk factors of pleural effusion in ICU patients at the time of liberation from mechanical ventilation and to determine its potential impact on the outcome of a spontaneous breathing trial (SBT) and subsequent extubation. Preliminary results of the current study have been presented in abstract form.[14]

Materials and Methods

The study was conducted in three ICUs (one medical and two medical and surgical ICUs) of the greater Paris area between May and October 2015. The protocol was approved by the Comité de Protection des Personnes (Ile de France 6, Paris, France) independent ethics committee (approval no. 2014-A010745-42). The investigators informed patients or their relatives about the study. They were informed that they could decline to participate at any time.

Patient Selection

All patients mechanically ventilated *via* an endotracheal tube for at least 24 h and deemed ready to perform their first SBT were eligible for the study. Readiness to wean was defined *a priori* when all of the following criteria were met[15]: arterial oxygen partial pressure to inspired oxygen fraction ratio (Pa_{O_2}/$F_{I_{O_2}}$) of more than 150, $F_{I_{O_2}}$ of less than 40%, positive end-expiratory pressure of at most 8 cm H_2O, respiratory rate of at most 35/min, absence of hemodynamic instability or vasopressor support, and a cooperative cognitive state. Patients with chest tube suctioning and those with a decision to withdraw or withhold life support were not considered for inclusion.

Weaning Process

Each morning, the same investigator of each center screened the patients. A 30-min SBT was performed as soon as the patients met the readiness-to-wean criteria. The SBT was performed with either pressure-supported ventilation set at 7 cm H_2O with zero positive end-expiratory pressure or a T-piece according to each center's usual practices.[15,16]

Definitions

The SBT was considered a failure when one or several of the following events occurred[15]: (1) pulse oximetry saturation (Sp_{O_2}) of less than 90% with $F_{I_{O_2}}$ of at least 50%; (2) acute respiratory distress (respiratory rate of at least 35 min^{-1} or increased by at least 50%, agitation, cyanosis); (3) systolic arterial blood pressure of at least 180 mmHg; (4) cardiac arrhythmias; and (5) respiratory acidosis defined as a pH of less than 7.32 with Pa_{CO_2} of at least 50 mmHg.

SBT was considered to have failed in the presence of criteria of clinical intolerance (see above). Otherwise, the SBT was considered to be successful, and patients were subsequently extubated according to the attending physician's decision. Successful weaning was defined as a successful SBT followed by extubation without any form of ventilatory support for at least 48 h after extubation. Weaning failure was defined as a failed SBT or extubation requiring reintubation or any form of ventilatory support within 48 h after extubation. Ventilatory support included noninvasive ventilation for postextubation acute respiratory failure but not prophylactic noninvasive ventilation.[17] Prophylactic noninvasive ventilation was used with physician discretion in patients at risk of extubation failure based on the following criteria: age older than 65 yr, underlying respiratory or cardiac dysfunction, and hypercapnia during the SBT.[17] The use of high-flow oxygen through a nasal cannula was allowed with physician discretion without any predefined criteria. The physician in charge of the patient was blinded to the ultrasound examination results, and the investigators were not involved in the extubation decision.

Pleural Ultrasound

To standardize and simplify ultrasound examinations, all patients were examined while lying in bed in the ICU. Pleural ultrasound examination was performed after completion of the SBT. To avoid any potential bias, investigators were asked to perform the ultrasound a few minutes after the end of the SBT while patients were still connected to the ventilator and before the physician in charge decided whether the patient would be extubated. Both hemithoraces were examined during the procedure. The intercostal spaces were used as ultrasound windows. In all hemithoraces, at least two intercostal ultrasound windows were used to scan the dorsal and lateral areas of the basal pleural space for the presence of pleural effusion. Different ultrasound systems were used according to availability in each ICU: Sparq ultrasound system (Phillips, USA) in La Pitié Salpêtrière Hospital and Philips HD11XE (Phillips, USA) in the other two centers. In each center, the ultrasound system was connected to a 3.5-MHz cardiac transducer. In each ICU, ultrasonography was performed by one designated investigator (M.D., D.R., or T.P.). All investigators were qualified ICU physicians with at least 5 yr of experience.

Detection of Pleural Effusion

Pleural ultrasound was performed with the patients in the semirecumbent position. The transducer was positioned on the posterior axillary line between the ninth and eleventh ribs to identify the liver on the right side and the spleen on the left side. The transverse section perpendicular to the body axis was obtained with pleural separation visible as an anechoic or hypoechoic layer between two pleural layers. If a pleural effusion was detected

(see below description of quantification of pleural effusion), the investigator subsequently moved the transducer sequentially through superior intercostal spaces to define the full extent of the effusion. To visualize the effusion, the transducer was then advanced cephalad, and a longitudinal view was chosen. The positive diagnosis of pleural effusion was based on the combination of the following four findings: (1) presence of an anechoic image above the liver on the right side or above the spleen on the left side; (2) image lined by the superficial parietal pleura and the deeper visceral pleura; (3) identification of the lung behind the effusion; and (4) the visceral layer moved during respiratory cycles with an inspiratory decrease of the interpleural separation.

Quantification of Pleural Effusion

When a pleural effusion was detected, the volume of fluid was first estimated according to the British Thoracic Society classification[18]: small, if the anechoic space extended over the costophrenic angle but was still within a one-probe range; moderate, if the space was between a one- and two-probe range; and large, if the space was bigger than a two-probe range (fig. 1). In addition, according to the equation proposed by Balik *et al.*,[19] we also quantified the fluid volume according to the following formula: volume (*V*) of pleural fluid (ml) = 20 × Sep (mm), where Sep is the maximal end-expiratory pleural distance between the parietal and visceral pleura. Sep was measured off-line after freezing the image in end expiration. Three measurements were performed, and their mean was used for the final analyses. In the presence of loculated pleural effusion, the largest loculated space was used to measure the volume of effusion.

Clinical Data Collection

Demographic data, comorbidities, severity scores, organ dysfunction–related variables, physiologic data, weight gain between inclusion and admission (weight on the day of inclusion minus weight on the day of admission), arterial blood gasses before SBT, and duration of mechanical ventilation and ICU stay were prospectively recorded. Whenever available, findings from echocardiography performed at admission and at the end of the weaning trial were also recorded. In particular, we looked for dilated, hypertrophic, or hypokinetic cardiopathy or significant valvular disease (aortic or mitral insufficiency grade of at least 2, mild or severe aortic and mitral stenosis). Structural cardiopathy was defined as dilated and/or hypertrophic and/or hypokinetic cardiopathy and/or significant valvular disease. Increase in cardiac filling pressures was defined by either increases in the ratio of the E and A waves of the mitral flow and/or of the ratio of the E wave of the mitral flow over the E′ wave of the mitral annulus.[20]

Reproducibility of Ultrasound Findings

Interobserver reproducibility of ultrasound findings was assessed in an additional set of 15 consecutive patients between October 17 and November 8 in 2016. Pleural ultrasound was done, and video recordings were saved for off-line analysis. Then the three main investigators blindly analyzed video recordings. Each investigator rated visual estimation of pleural effusion volume and measured Sep. Intraobserver reproducibility was then assessed for all three investigators with the same sample of video-recorded data by repeating the measurements (visual estimation of pleural effusion volume and Sep) on two occasions (10 days after initial examination).

Statistical Analysis

Continuous variables are expressed as median and interquartile range, and categorical variables are expressed as absolute and relative frequencies. Patients were categorized *a priori* into two groups according to the findings of the visual estimation: small or no pleural effusion *versus* moderate to large pleural effusion. In patients with bilateral effusion, the larger effusion was used to classify the patient. Patients were also categorized within two groups according to the weaning outcome: success *versus* failure. Continuous variables were tested for normality using the Shapiro–Wilk test. Gaussian variables were compared using a Student's *t* test and nonnormally distributed variables using a Mann–Whitney test. Categorical variables were compared with a χ^2 test. The volume of pleural effusion calculated by the formula proposed by Balik *et al.*[19] was compared with visual estimation of the fluid volume (small, moderate, and large) with a Kruskal–Wallis test. The primary endpoint was the prevalence of pleural effusion (small or no pleural effusion *versus* moderate to large pleural effusion) in patients with weaning failure and weaning

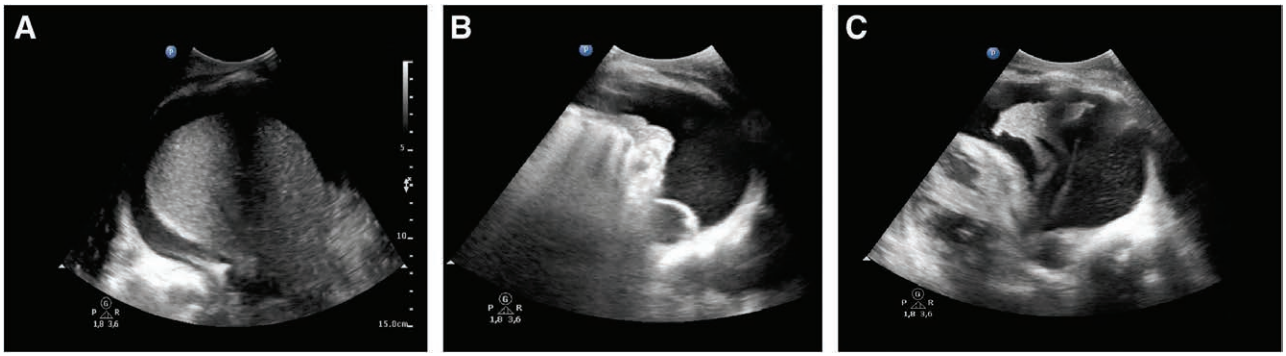

Fig. 1. Estimation of the volume of pleural fluid according to the classification of the British Thoracic Society.[17] The volume of fluid was estimated as small in (*A*), moderate in (*B*), and large in (*C*).

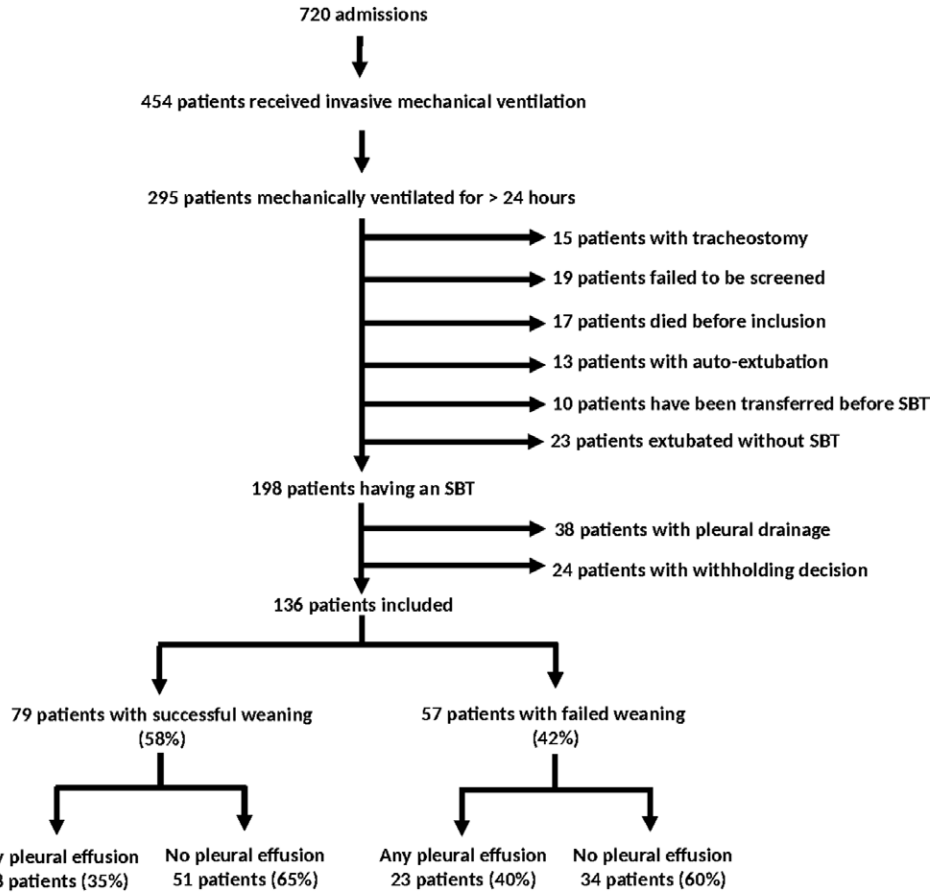

Fig. 2. Study flow chart. SBT = spontaneous breathing trial.

success. Two sensitivity analyses were performed. The first one looked at the primary outcome after exclusion of patients with small and moderate pleural effusion (restricted to only patients with none and large pleural effusions). The second one assessed the outcomes according to the measured volume of pleural effusion with 500 ml as the cutoff.

The sample size was calculated by considering a weaning failure rate of 30%,[16] an expected prevalence of pleural effusion of 25% in the successful group, and a twofold higher expected prevalence of pleural effusion in the failure group. Based on these considerations, 133 patients were included.

Agreement between observers regarding the visual estimation of pleural effusion volume was calculated with κ coefficient. Reproducibility in the measurement of Sep was calculated with intraclass correlation coefficients.

For all final comparisons, a two-tailed *P* less than or equal to 0.05 was considered statistically significant. Analyses were performed using Prism 4.01 software (GraphPad Software, USA) and SPSS, version 21 (IBM, USA).

Results

Patients

During the study period, 720 patients were admitted to the three participating ICUs, 295 were eligible, and 136 were finally enrolled (fig. 2). The characteristics of the population at inclusion are detailed in table 1 and in table 1 of the Supplemental Digital Content (http://links.lww.com/ALN/B408, which is a table listing primary and associated diagnoses). Most were medical ICU patients receiving invasive mechanical ventilation for acute respiratory failure or shock for 6 days (range, 3 to 11 days).

Prevalence and Volume of Pleural Effusion

A pleural effusion was diagnosed in 51 (37%) patients and was bilateral in 29 (21%) patients. Altogether, 18 (13%) patients had a moderate (12 patients) to large (6 patients) pleural effusion, and 118 (87%) patients had no (85 patients) or small (33 patients) pleural effusion. On average, the mean fluid volume was 509 ± 408 ml on the left side and 411 ± 329 ml on the right side. The corresponding calculated volumes of each category of pleural effusion (small, moderate, and large) are displayed in figure 3.

Patient Characteristics According to Volume of Pleural Effusion

The characteristics of the 18 patients with moderate to large pleural effusion were compared with their counterparts (no or small pleural effusion). Demographic variables, body

Table 1. Patient Characteristics According to the Presence and Volume of Pleural Effusion

	All Patients (n = 136)	None or Small PE (n = 118)	Moderate to Large PE (n = 18)	*P* Value	OR (95% CI)
Demographic data					
Males, n (%)	75 (55)	63 (53)	12 (67)	0.29	0.57 (0.20–1.63)
Age, yr	64 (54–74)	64 (52–73)	64 (58–76)	0.22	0.98 (0.94–1.01)
Body mass index, kg/m^2	24 (21–28)	24 (21–29)	23 (22–26)	0.40	1.04 (0.95–1.12)
Medical conditions, n (%)					
Chronic hypertension	66 (49)	58 (49)	8 (44)	0.71	1.21 (0.45–3.28)
COPD	33 (24)	28 (24)	4 (22)	0.83	1.14 (0.35–3.74)
Diabetes	29 (21)	24 (20)	5 (28)	0.47	0.66 (0.22–2.04)
Chronic left ventricular failure	22 (16)	18 (15)	4 (22)	0.45	0.63 (0.19–2.13)
Chronic respiratory failure	26 (19)	25 (21)	1 (5)	0.15	0.22 (0.03–1.72)
Chronic renal failure	15 (11)	8 (7)	7 (39)	0.01	8.75 (2.66–28.73)
Cirrhosis	17 (13)	13 (11)	4 (22)	0.18	0.43 (0.12–1.51)
Active neoplasm	15 (11)	13 (11)	2 (11)	0.99	0.99 (0.20–4.80)
At admission					
SOFA score	8 (6–11)	8 (5–10)	10 (8–13)	0.08	0.85 (0.71–1.02)
SAPS2 score	50 (40–63)	48 (39–63)	54 (45–63)	0.28	0.98 (0.93–1.03)
Main reason for mechanical ventilation, n (%)					
Acute respiratory failure	69 (51)	63 (53)	6 (33)	0.12	0.44 (0.15–1.24)
Septic/hemorrhagic shock	31 (23)	23 (19)	8 (44)	0.02	3.3 (1.17–9.3)
Cardiogenic shock	6 (4)	6 (4)	0 (0)	1.00	—
Coma	20 (15)	17 (14)	3 (17)	0.80	1.19 (0.31–4.55)
Cardiac arrest	2 (1)	2 (1)	0 (0)	1.00	—
Postsurgery	8 (6)	7 (6)	1 (6)	0.95	0.93 (0.11–8.06)
On inclusion					
Weight gain before inclusion, kg	0.0 (–0.5–5.0)	0.0 (–1.0–4.7)	4.0 (0.0–6.5)	0.02	0.91 (0.85–0.98)
Duration of MV before inclusion, days	6 (3–11)	6 (3–11)	6 (4–12)	0.69	0.99 (0.93–1.06)
PE calculated volume, ml	—	80 (0–150)	900 (600–1,200)	0.01	0.99 (0.98–0.99)

Continuous data are expressed as median (interquartile range), and categoric data are expressed as number of events (percentages). OR (95% CI) values are calculated with none/small PE as reference.

COPD = chronic obstructive pulmonary disease; ICU = intensive care unit; MV = mechanical ventilation; OR = odds ratio; PE = pleural effusion; SAPS = Simplified Acute Physiology Score; SOFA = Sequential Organ Failure Assessment.

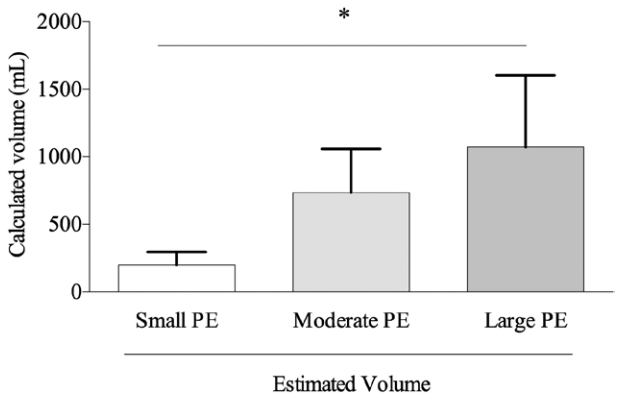

Fig. 3. Calculated volume of pleural fluid (equation proposed by Balik *et al.*[19]) according to categories of estimated volume of pleural effusion (PE; small, moderate, or large). **P* < 0.0001 for the overall comparison between the three groups (Kruskal–Wallis test).

mass index, cirrhosis, chronic left ventricular failure, diabetes, chronic respiratory failure, and active neoplasm were similar in patients with no or small pleural effusion and in those with moderate to large pleural effusion (table 1). However, moderate to large pleural effusion was more frequently observed in patients with chronic renal failure ($P = 0.01$) and in those with septic/hemorrhagic shock as the main reason for mechanical ventilation ($P = 0.02$). Patients with moderate to large pleural effusion also presented with higher weight gain between ICU admission and readiness to wean ($P = 0.03$).

Weaning Outcomes

Among the 136 patients, 91 (67%) succeeded the SBT and were subsequently extubated. Ten of these patients were reintubated during the following 48 h, and two received nonprophylactic noninvasive ventilation for postextubation acute respiratory failure. Three patients passed the SBT but were not extubated because of a low level of consciousness. These three patients were considered as SBT failure. A total of 57 (42%) patients were classified as a weaning failure. Table 2 displays patient characteristics according to the outcome of the weaning process. As compared with their counterparts, patients who failed the weaning process were more likely to have chronic obstructive pulmonary disease but had similar duration of mechanical ventilation before SBT. The

Table 2. Patient Characteristics According to the Results of Weaning

Variables	Weaning Success (n = 79)	Weaning Failure (n = 57)	*P* Value	OR (95% CI)
Demographic data				
Males, n (%)	42 (53)	33 (58)	0.58	0.83 (0.41–1.64)
Age, yr	60 (54–72)	67 (57–77)	0.11	0.98 (0.96–1.01)
Body mass index, kg/m^2	24 (22–29)	23 (21–28)	0.98	1.00 (0.95–1.05)
Comorbidities, n (%)				
Chronic hypertension	41 (51)	25 (45)	0.20	1.56 (0.78–3.10)
COPD	14 (18)	19 (34)	0.01	0.31 (0.14–0.69)
Chronic left ventricular failure	14 (17)	8 (14)	0.56	1.32 (0.51–3.39)
Patients characteristics before SBT				
Duration of MV before SBT, days	5 (2–10)	7 (3–12)	0.33	0.98 (0.93–1.02)
Weight gain since admission, kg	0.0 (–0.5–5.0)	1.0 (–0.5–4.7)	0.75	0.99 (0.94–1.04)
Pressure support, cm H_2O	10 (9–12)	10 (8–12)	0.07	0.89 (0.79–1.01)
PEEP, cm H_2O	5 (5–6)	5 (5–6)	0.85	0.98 (0.83–1.17)
Presence of cough, n (%)	77 (97)	52 (91)	0.13	0.27 (0.05–1.44)
Glasgow score	15 (11–15)	15 (12–15)	0.81	0.98 (0.82–1.17)
Respiratory rate, min^{-1}	21 (17–24)	22 (20–25)	0.08	0.95 (0.89–1.01)
Heart rate, min^{-1}	92 (75–104)	87 (78–105)	0.83	0.99 (0.98–1.02)
Systolic arterial pressure, mmHg	126 (114–142)	133 (116–145)	0.60	0.99 (0.98–1.01)
Diastolic arterial pressure, mmHg	68 (60–81)	66 (57–73)	0.06	1.03 (0.99–1.06)
Echocardiography at the end of the SBT, %*	34	46		
Left ejection fraction, %	60 (45–60)	60 (50–60)	0.89	1.00 (0.98–1.02)
Left ejection fraction < 45%, n (%)	9 (33)	18 (32)	0.16	2.44 (0.69–8.56)
Structural cardiopathy, n (%)	9 (30)	5 (19)	0.76	1.20 (0.36–3.99)
Increase in cardiac filling pressures, n (%)	11 (41)	12 (46)	0.74	0.85 (0.31–2.31)
Significant valvular disease, n (%)	4 (15)	5 (19)	0.48	1.72 (0.38–7.77)
Arterial blood gasses				
pH	7.43 (7.40–7.46)	7.45 (7.42–7.47)	0.98	1.11 (0.01–1,250.51)
$Paco_2$, mmHg	38 (34–44)	40 (34–47)	0.34	1.02 (0.98–1.06)
Pao_2/Fio_2	273 (232–354)	252 (196–327)	0.06	1.00 (1.00–1.00)
HCO_3^-, mM	25 (23–28)	27 (23–30)	0.09	0.94 (0.88–1.01)
Pleural effusion, n (%)				
Any, n (%)	28 (35)	23 (40)	0.56	1.23 (0.61–2.49)
Bilateral, n (%)	17 (21)	12 (22)	0.59	1.26 (0.55–2.91)
None or small, n (%)	69 (87)	49 (86)	0.81	0.89 (0.33–2.41)
Moderate to large, n (%)	10 (13)	8 (14)	0.81	0.89 (0.33–2.41)
Calculated volume, ml	400 (240–800)	550 (200–1,300)	0.48	1.00 (0.99–1.00)

Continuous data are expressed as median (interquartile range), and categorical data are expressed as number of events (percentages). OR (95% CI) are calculated with weaning success as reference.

*Echocardiography was available in 53 patients at the end of the SBT.

COPD = chronic obstructive pulmonary disease; MV = mechanical ventilation; OR = odds ratio; PEEP = positive end-expiratory pressure; SBT = spontaneous breathing trial.

prevalence and volume of pleural effusion were similar in the two groups (fig. 4; table 2; table 2 of the Supplemental Digital Content [http://links.lww.com/ALN/B408, which is a table showing outcomes according to the measured volume of pleural effusion]). The extubation failure rate, the total duration of mechanical ventilation, and the ICU length of stay were similar whether the pleural effusion was moderate to large or absent or small (table 3).

Drainage of Pleural Effusion

Two patients underwent pleural drainage: the first patient was extubated 4 days after drainage, whereas the other patient died before he could be weaned from the ventilator.

Sensitivity Analysis Restricted to Patients with No Pleural Effusion and Large Pleural Effusion

A sensitivity analysis eventually compared patients without pleural effusion (n = 85) to patients with large pleural effusion (n = 6), according to the result of SBT (SBT success *vs.* SBT failure; table 3 of the Supplemental Digital Content [http://links.lww.com/ALN/B408, which is a table showing outcomes according to the presence of large pleural effusion *vs.* none]). This sensitivity analysis showed a similar SBT success ratio but a longer duration of mechanical ventilation after the SBT and a longer ICU stay in patients with large pleural effusion. However, after exclusion of an outlier (a patient who had a total duration of ICU stay of 59 days

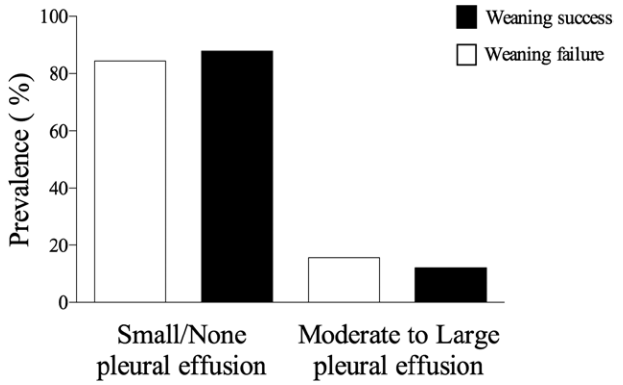

Fig. 4. Prevalence of pleural effusion (none or small *vs.* moderate to large) in patients with weaning success and weaning failure.

in the large pleural effusion group and a total duration of mechanical ventilation of 56 days), this sensitivity analysis did not show any more difference between the two groups.

Reproducibility of Ultrasound Findings

The interobserver agreement for visual estimation of pleural effusion volume was found to be $\kappa = 0.79$ (between T.P. and D.R.; $P < 0.01$), 0.70 (between M.D. and T.P.; $P < 0.01$), and 0.89 (between M.D. and D.R.; $P < 0.01$). Intraclass correlation coefficient regarding the measurement of Sep was 0.84 (0.67 to 0.94; $P < 0.01$) between all three investigators. The intraobserver agreement of visual estimation of pleural effusion volume was found to be $\kappa = 0.69$ (for M.D.; $P < 0.01$), $\kappa = 0.70$ (for T.P.; $P < 0.01$), and $\kappa = 0.69$ (for D.R.; $P < 0.01$). Intraclass correlation coefficients regarding the measurement of interpleural distance were 0.95 (0.87 to 0.98 for M.D.; $P < 0.01$), 0.88 (0.68 to 0.96 for T.P.; $P < 0.01$), and 0.98 (0.95 to 0.99 for D.R.; $P < 0.01$).

Discussion

Because pleural effusion can theoretically contribute to weaning failure, this multicenter observational study was designed to determine the prevalence, features, and clinical impact of pleural effusion at the time of liberation from mechanical ventilation. The main findings of our study can be summarized as follows: (1) the prevalence of pleural effusion at the time of liberation from mechanical ventilation was 37%, but only 13% of patients had moderate to large pleural effusion; (2) three factors (chronic renal failure, septic and hemorrhagic shock as the main reason for intubation, and higher weight gain) were associated with the presence of pleural effusion; and (3) pleural effusion had no significant impact on weaning outcome or on the duration of mechanical ventilation.

Prevalence and Causes of Pleural Effusion

To our knowledge, this is the first study to investigate pleural effusion at the time of liberation from mechanical ventilation. Observational series focusing on pleural effusion in the ICU have reported a wide range of prevalence, depending on the timing of detection during the ICU stay, on the diagnostic methods used, and on the case mix. The prevalence of pleural effusion may range from 8% when detected by physical examination and chest radiographs[12] to 60% when routine ultrasonography is performed.[11] In a study based on computerized tomography scans, pleural effusion was detected in 83% of patients with acute respiratory distress syndrome.[13] In our series of unselected mechanically ventilated ICU patients at the time of weaning, the prevalence of clinically significant (*i.e.* moderate to large) pleural effusion was only 13%.

Although our study was not designed to determine the precise cause of pleural effusion, three factors were found to be associated with moderate to large pleural effusion: shock as the main reason for mechanical ventilation, chronic renal failure, and positive weight gain between ICU admission and inclusion. Shock is associated with fluid expansion during the initial phase of resuscitation, and chronic renal failure is associated with decreased fluid removal. Consequently, these two factors may lead to fluid overload, positive weight gain, and eventually pleural effusion. These findings are consistent with experimental data from hydrostatic and permeability pulmonary edema models, showing that almost one third of the overall excess fluid formed exited the lung *via* the visceral pleura into the pleural space.[21,22]

Impact of Pleural Effusion

Time devoted to weaning accounts for approximately 40% of the total duration of mechanical ventilation.[23] It is therefore

Table 3. Outcomes According to the Presence of Pleural Effusion

Outcomes	All Patients (n = 136)	None or Small PE (n = 118)	Moderate to Large PE (n = 18)	*P* Value
SBT success, n (%)	91 (67)	80 (69)	11 (61)	0.31
SBT failure, n (%)	45 (33)	38 (31)	7 (39)	—
Extubation failure, n (%)	12 (9)	11 (9)	1 (6)	0.27
MV duration after SBT, days	0 (0–1)	0 (0–1)	0 (0–2)	0.23
Total duration of MV, days	7 (3–12)	7 (3–12)	7 (4–14)	0.62
ICU length of stay, days	11 (6–17)	11 (6–17)	13 (6–18)	0.51

Continuous data are expressed as median (interquartile range), and categorical data are expressed as number of events (percentages).
ICU = intensive care unit; MV = mechanical ventilation; PE = pleural effusion; SBT = spontaneous breathing trial.

of critical importance to identify factors that may contribute to weaning failure. Pleural effusion may be involved in weaning failure *via* three mechanisms. The first of these mechanisms is related to the effect of pleural effusion on respiratory mechanics. Unilaterally infused pleural effusion in dogs is associated with a decrease in lung volume.[8] Accordingly, in mechanically ventilated patients, it has been reported that drainage of large pleural effusion (at least 500 ml) increased end-expiratory lung volume and improved gas exchange.[24] In contrast, in patients with acute respiratory distress syndrome, it has been shown that pleural effusion led to greater chest wall expansion than lung reduction without affecting gas exchanges or respiratory mechanics.[13] Because our study was not mechanistic, we can only speculate that the same phenomenon occurred in our patients. The second mechanism is linked to the potential impairment of gas exchange. Lung collapse caused by the pleural effusion induces hypoxemia caused by ventilation-perfusion mismatch or intrapulmonary shunt. However, clinical findings regarding this mechanism by which pleural effusion may cause weaning failure remain conflicting. For instance, chest tube drainage of an average of 1,050 ml of pleural effusion was associated with a significant increase in $Pa_{O_2}/F_{I_{O_2}}$ ratio from 206 to 251 mmHg in mechanically ventilated patients.[25] In contrast, another study found no correlation between the volume of pleural fluid removed and improvement of oxygenation.[10] Last, pleural effusion may increase cardiac filling pressures,[7] a factor that contributes to weaning-induced pulmonary edema, a well-established cause of weaning failure.[26] Nevertheless, in a study performed in mechanically ventilated patients, no change in cardiac output or even in cardiac filling pressures was observed after pleural drainage.[9]

Only one study has reported an association between pleural effusion and a longer duration of mechanical ventilation and ICU stay.[11] However, in this study, pleural effusion was detected on chest radiography, a method that has been shown to be less reliable than ultrasound.[27,28] In contrast, we found that pleural effusion was not associated with a higher prevalence of weaning failure. As previously established,[2] the success of weaning is determined by several factors in which the presence and volume of pleural effusion may only play a minor role. First, pleural effusions develop progressively during the ICU stay and not acutely during the SBT. It explains the clinical tolerance of the patients at inclusion as shown by the presence of SBT readiness criteria. Second, unlike common mechanisms of weaning failure that stem from physiologic changes induced by the SBT, pleural effusion is already present at the beginning of the SBT. Finally, the fact that two thirds of pleural effusions in our series were classified as small pleural effusion may attenuate these findings.

Strengths and Limitations

This is the first multicenter prospective study observational on this topic. This approach should limit the bias related to case mix. Second, we used a standardized method to detect and quantify pleural effusion by ultrasound. Pleural ultrasound is considered to be the most reliable technique to detect and evaluate the volume of pleural effusion.[19,20,25,27,29] Finally, this study is seemingly the first to provide insight into pleural effusion at the time of liberation from mechanical ventilation.

Our study has several limitations. First, the limited subset of moderate to large pleural effusions may limit generalization of our findings. Second, although weaning failure is mostly related to multiple mechanisms,[3,30] we did not investigate the specific reason for weaning failure apart from looking for pleural effusion. However, the observational design of the study did not allow us to precisely assess the reasons for weaning failure in each patient. From a therapeutic point of view, the presence of pleural effusion associated with echo markers of cardiac dysfunction would suggest the use of diuretics to shorten weaning. Third, we could not assess the potential benefit of pleural drainage in the event of weaning failure. It is noteworthy that pleural drainage was performed in only 2 of the 136 patients, suggesting that pleural drainage is not part of routine clinical practice at the time of weaning from mechanical ventilation.

Conclusions

Significant pleural effusion is observed in approximately 13% of patients at the time of liberation from mechanical ventilation and is not associated with any significant impact on the results of weaning. Other mechanisms should be carefully excluded before attributing weaning failure to pleural effusion.

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Competing Interests

Dr. Demoule has signed research contracts with Covidien (Dublin, Ireland), Maquet (Rastatt, Germany), and Philips (Amsterdam, The Netherland) and has also received personal fees from Covidien (Dublin, Ireland), Maquet (Rastatt, Germany), and MSD (Courbevoie, France). Dr. Dres received personal fees from Pulsion Medical System (Feldkirchen, Germany) and Astra Zeneca (Cambridge, United Kingdom). Dr. Ricard received travel expenses from Fisher & Paykel (Kingston, Milton Keynes, United Kingdom) to attend scientific meetings. Dr. Roux received personal fees from Astellas (Levallois-Perret, France). The other authors declare no competing interests.

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