A high positive end-expiratory pressure, low tidal volume ventilatory strategy improves outcome in persistent acute respiratory distress syndrome: A randomized, controlled trial*

Jesús Villar, MD, PhD, FCCM; Robert M. Kacmarek, PhD, FCCM; Lina Pérez-Méndez, MD, PhD; Armando Aguirre-Jaime, PhD; for the ARIES Network

Objective: **It has been shown in a two-center study that high positive end-expiratory pressure (PEEP) and low tidal volume (LTV) improved outcome in ARDS. However, that study involved patients with underlying diseases unique to the study area, was conducted at only two centers, and enrolled a small number of patients. We similarly hypothesized that a ventilatory strategy based on PEEP above the lower inflection point of the pressure volume curve of the respiratory system (P_{flex}) set on day 1 with a low tidal volume would result in improved outcome in patients with severe and persistent acute respiratory distress syndrome (ARDS).**

Design: **Randomized, controlled clinical trial.**

Setting: **Network of eight Spanish multidisciplinary intensive care units (ICUs) under the acronym of ARIES (Acute Respiratory Insufficiency: España Study).**

Patients: **All consecutive patients admitted into participating Spanish ICUs from March 1999 to March 2001 with a diagnosis of ARDS were considered for the study. If 24 hrs after meeting ARDS criteria, the Pao_2/Fio_2 remained ≤200 mm Hg on standard ventilator settings, patients were randomized into two groups: control and P_{flex}/LTV.**

Interventions: **In the control group, tidal volume was 9–11 mL/kg of predicted body weight (PBW) and PEEP ≥5 cm H_2O. In the P_{flex}/LTV group, tidal volume was 5–8 mL/kg PBW and PEEP was set on day 1 at P_{flex} + 2 cm H_2O. In both groups, Fio_2 was set to maintain arterial oxygen saturation >90% and Pao_2 70–100 mm Hg, and respiratory rate was adjusted to maintain $Paco_2$ between 35 and 50 mm Hg.**

Measurements and Main Results: **The study was stopped early based on an efficacy stopping rule as described in the methods. Of 103 patients who were enrolled (50 control and 53 P_{flex}), eight patients (five in control, three in P_{flex}) were excluded from the final evaluation because the random group assignment was not performed in one center according to protocol. Main outcome measures were ICU and hospital mortality, ventilator-free days, and nonpulmonary organ dysfunction. ICU mortality (24 of 45 [53.3%] vs. 16 of 50 [32%], $p = .040$), hospital mortality (25 of 45 [55.5%] vs. 17 of 50 [34%], $p = .041$), and ventilator-free days at day 28 (6.02 ± 7.95 in control and 10.90 ± 9.45 in P_{flex}/LTV, $p = .008$) all favored P_{flex}/LTV. The mean difference in the number of additional organ failures postrandomization was higher in the control group ($p < .001$).**

Conclusions: **A mechanical ventilation strategy with a PEEP level set on day 1 above P_{flex} and a low tidal volume compared with a strategy with a higher tidal volume and relatively low PEEP has a beneficial impact on outcome in patients with severe and persistent ARDS. (Crit Care Med 2006; 34:1311–1318)**

Key Words: mechanical ventilation; positive end-expiratory pressure; acute respiratory distress syndrome; acute lung injury; lung protection; tidal volume; airway pressure; barotrauma; multiple organ failure

Acute respiratory distress syndrome (ARDS), a severe form of acute lung injury (ALI), is one of the most challenging problems in the intensive care unit (ICU) (1). The prognosis of patients with ARDS is poor, with death often attributed to the underlying disease and the presence of sepsis (1, 2). Amato et al. (3) demonstrated improved mortality by the use of a low tidal volume (Vt; 6 mL/kg) and positive end-expiratory pressure (PEEP) set on day 1 at the lower inflection point on the pressure-volume curve of the respiratory system (P_{flex}) plus 2 cmH_2O compared with a group with a large Vt (12 mL/kg) and a low PEEP. Amato et al. (3) were able to show a mortality difference (38% vs. 72%) by studying only 53 patients. However, in the Amato trial, many deaths in the control group occurred early in the course of mechanical ventilation, patients were enrolled with some underlying problems (Leptospirosis) unique to the study location, a number of iatrogenic deaths occurred during mechanical ventilation, and the study was

***See also p. 1540.**

From Canarian Institute for Biomedical Research, Canary Islands, Spain (JV, LPM, AAJ); Research Center, St. Michael's Hospital, Toronto, Canada (JV); Centro de Investigacion, Consejo Superior de Investigaciones Científicas, Madrid, Spain (JV); Harvard University and Massachusetts General Hospital, Boston, MA (RMK). Members of the Acute Respiratory Insufficiency: España Study (ARIES) network are listed in Appendix 1.

Current affiliation for Dr. Villar: Director, Canarian Institute for Biomedical Research, Tomás Morales, 6-1º, 35003 Las Palmas de Gran Canaria, Canary Islands, Spain. E-mail: jesus.villar@canarias.org

Supported, in part, by grants 97/0668 and 00/0564 from Fondo de Investigación Sanitaria of Spain.

The authors have no financial interests to disclose.

DOI: 10.1097/01.CCM.0000215598.84885.01

conducted at only two centers. Other trials conducted at the same time as the Amato trial (4–6) failed to demonstrate any significant impact on outcome. In these trials (4–6), little difference in V_T existed between groups, and PEEP was based only on oxygenation response and was essentially equal in both the low and high V_T groups. As a group, these studies (3–6) still left unanswered questions regarding the impact of lung-protective ventilation strategies on outcome in ARDS.

None of the clinical trials evaluating lung-protective ventilation published to date have enrolled only patients with persistent, established ARDS (3–8). Three recent reports (9–11) clearly demonstrated that alterations in ventilator settings can change a patient's conformance with the American-European Consensus Conference definitions of ARDS and ALI (12). It has also been shown that patients failing to meet ARDS criteria on standard ventilator settings (a specifically defined tidal volume, PEEP, and F_{IO_2}) have a much lower mortality rate than those fulfilling ARDS criteria on standard settings (9). Since the results of the Amato trial are consistent with experimental data (13–15) on the beneficial effects of high PEEP, we chose to repeat the Amato trial in a number of centers but with a V_T and PEEP level in the control group more consistent with levels recommended clinically at the time of the study (16). In addition, we chose to only study patients who demonstrated persistent ARDS 24 hrs after initially meeting ARDS criteria while on standard ventilator settings. In the present trial, we hypothesized that ventilation with PEEP above P_{flex} set on day 1 and a low V_T would result in reduced mortality rate in established ARDS compared with a mechanical ventilation strategy using higher V_Ts and lower levels of PEEP that were consistent with those used in clinical practice.

METHODS

Patients and Definitions. This protocol was approved by the Ethics Committee of the coordinating center and by the local institutional review boards in every participating hospital. This was a prospective, randomized, controlled study performed through a Network of Spanish, multidisciplinary ICUs under the acronym of ARIES (Acute Respiratory Insufficiency: España Study) (Appendix 1) from March 1999 to March 2001. All consecutive, mechanically ventilated patients admitted into the ICU who met the American-European Consensus Conference definition (12) for ARDS—$Pa_{O_2}/F_{IO_2} \leq 200$ mm Hg regardless of PEEP or F_{IO_2}, bilateral pulmonary infiltrates on an anterior/posterior chest radiograph, and a pulmonary artery occlusion pressure <18 mm Hg or no evidence of left ventricular failure—were considered for entry into the study. We excluded from this study patients younger than 15 yrs of age and those with acute cardiac clinical conditions, pregnancy, neuromuscular diseases, high risk of mortality within 3 months for reasons other than ARDS (severe neurologic damage, age >80 yrs, and cancer patients in the terminal stage of their disease), or more than two extrapulmonary organ failures. Definitions of organ failure were those described by Bell et al. (17) and Villar et al. (18) and used in previous clinical trials (8) (Appendix 2). Patients enrolled were not allowed to participate in any other experimental protocol.

Patients meeting these criteria were all ventilated with standard settings for 24 hrs, and only patients with a $Pa_{O_2}/F_{IO_2} \leq 200$ mm Hg on standard ventilator setting (V_T 10 mL/kg predicted body weight [PBW] with a square wave inspiratory flow, $F_{IO_2} \geq 0.5$, and PEEP ≥ 5 cm H_2O) 24 hrs after meeting the ARDS definition were enrolled. The specific F_{IO_2} and PEEP levels set were left to the judgment of the individual investigators. After patients met the inclusion criteria and informed consent was obtained from the patient or family, patients were randomized into two ventilatory strategies: conventional mechanical ventilation (control) or PEEP above P_{flex} with low V_T ventilation (P_{flex}/LTV). Randomization was performed by the coordinating center using blocks of ten opaque, identical, sealed envelopes, which were sent to participating ICUs. Inside each envelope was the treatment allocation for the patient. Blocks had equal numbers of treatment groups with the order of treatment within the block being randomly ordered to ensure that treatment group number were evenly balanced at the end of each block. Details of block distribution were not revealed to investigators. Additional sets of envelopes were sent to those institutions with a high rate of enrollment.

Experimental Ventilator Protocol. Patients allocated to the control group were ventilated with the volume assist/control mode without restrictions on the flow profile V_T of 9–11 mL/kg PBW, PEEP ≥ 5 cm H_2O, and an F_{IO_2} ensuring arterial oxygen saturation >90% and Pa_{O_2} of 70–100 mm Hg. PBW was estimated using height and weight tables derived from the equations published by Devine (19) (men weight in kg = 50 + 0.91 × [height in cm − 152]; women weight in kg = 45.5 + 0.91 × [height in cm − 152]). Patients in the control group developing an uncontrolled pneumothorax, despite the insertion of chest tubes, could be ventilated with the pressure-assist/control mode. Patients randomized to P_{flex}/LTV were ventilated with the volume assist/control mode V_T of 5–8 mL/kg PBW, PEEP level set on day 1 at P_{flex} + 2 cm H_2O, and an F_{IO_2} ensuring arterial oxygen saturation >90% and Pa_{O_2} of 70–100 mm Hg. In both groups, investigators were instructed to maintain P_{CO_2} between 35 and 50 cm H_2O by adjusting the ventilator rate. In the P_{flex}/LTV group, the investigators were instructed to decrease F_{IO_2} first followed by PEEP if above oxygenation range (Pa_{O_2} 70–100 mm Hg) and increase PEEP first followed by F_{IO_2} if below oxygenation range. However, the magnitudes of the F_{IO_2} and PEEP adjustments were left to the investigators' judgment. P_{flex} was only measured on day 1 of the protocol. Inspiratory pressure-volume curves of the respiratory system were constructed either with a super syringe or by using the ventilator. When using the ventilator, the V_T was progressively increased starting from 50 mL, while the patient received an $F_{IO_2} = 1.0$ and PEEP = 0, or a very slow constant inspiratory flow was provided by the ventilator with PEEP = 0 and $F_{IO_2} = 1.0$ while volume and pressure were automatically recorded. With the increasing volume approach, the respiratory rate was set at 6–8 breaths/min and an end-inspiratory pause (1–2 secs) was applied at each step. With the super syringe, each step was held appropriately 1–2 secs until airway pressure plateaued. With all approaches, peak pressures of up to about 35–40 cm H_2O were achieved. P_{flex} was determined by plotting the data and drawing tangents to the initial flat aspect of the curve and the segment of the curve with the maximum slope. The airway pressure corresponding to the point of intersection of these tangents was considered the P_{flex}. Patients were sedated and paralyzed for the performance of the pressure-volume curve and after its completion were allowed to spontaneously recover. P_{flex} was only measured once on day 1 of the protocol. If P_{flex} could not be identified, it was decided by the investigators based on their experience to set the PEEP equal to 15 cm H_2O. Management of pH was up to the individual clinician in both groups. There were no defined guidelines regarding weaning from mechanical ventilation.

Data Collection. Data compiled from each patient included the following: demographic information; clinical conditions associated with the development of ARDS; routine laboratory measurements; Acute Physiology and Chronic Health Evaluation II score (20); lung injury score (21); days on mechanical ventilation before and during the trial; days in the ICU; hospital length of stay; pulmonary physiologic and ventilatory measurements, including arterial blood gases, level of PEEP, end-inspiratory plateau pressure, F_{IO_2}, and V_T; cardiovascular data; complications and adverse events; number of extrapulmonary organ failures before and after randomization; and ICU and hospital outcome. The end-inspiratory plateau pressure was determined by application of an end-inspiratory pause of sufficient time, as determined by the investigators, to ensure airway pressure equilibration following increased sedation to ensure apnea. We considered cardiac failure, gastrointestinal

failure, renal failure, liver failure, coma, and disseminated intravascular coagulation as organ system failures in addition to lung failure. Organ failure definitions are contained in Appendix 2. Any organ failure occurring during the 6-hr period before death was considered part of the terminal event and, therefore, not considered in the analysis. Ventilator-free days were determined to day 28 (7) where all deaths were awarded zero days.

Data Analysis. Data were collected in each ICU using a standardized form. Data were transmitted to the coordinating center whenever a patient died or was discharged from the hospital. Before exporting the data into a computer program at the coordinating center, a trained data collector from the coordinating center checked the completeness and the quality of information. Logical checks were performed for missing data and to find inconsistencies, especially regarding clinical diagnosis, date, and severity scores. After speaking by phone with the investigator, the data collector reformatted the data and then entered them into the database. The primary endpoint was ICU mortality. Secondary endpoints were ventilator-free days, pulmonary complications (barotrauma), extrapulmonary organ failures, and hospital mortality. Our operating hypothesis was that the P_{flex}/LTV approach would produce a ≥20% reduction in ICU mortality vs. control. Power calculations assumed a 20% reduction in mortality rate from 50% in the control group (9, 16, 22, 23) to 30% in the P_{flex}/LTV group (with an α level of .05 at a power of 80%, requiring a sample size of 74 patients in each group). The 50% mortality figure was based on previously published epidemiologic data (9, 23) that has been validated recently (16, 22). A two-step stopping rule was used. To protect against an obvious lack of efficacy, failure to achieve a reduction of ICU mortality ≥10% when ≥15 patients per arm had been included justified stopping the trial. On the other hand, to protect against a clear improvement of efficacy, achieving a statistically significant absolute difference in ICU mortality ≥20% when ≥45 patients per arm had been included (two-tailed significant difference $p < .025$) justified stopping the trial. The differences in mortality rate between the two groups were evaluated at the coordinating center. Study members not enrolling patients consulted with an external observer to decide whether the stopping rule should be applied. Investigators enrolling patients were blinded to the results of this interim analysis if the stopping rule was not applied.

Descriptive statistics are expressed as mean ± SD or median and interquartile range depending on the nature and distribution of the variables. Inferential statistics used estimates of the mean of the differences and their 95% confidence intervals (CI). Variables normally distributed were compared with the Student's *t*-test. For variables without a normal distribution, the Mann-Whitney U rank test was used for comparison. Categorical variables were compared using Fisher's exact test. Probability of survival was analyzed according to the Kaplan-Meier method, and the results were compared with the log-rank test. The relative risks and their 95% CIs were estimated. For all these comparisons, we considered a difference to be statistically significant if $p < .05$ (SPSS 11.5.1 statistical packages, SPSS, Chicago, IL).

RESULTS

Study Population. During the 24-month study period, 311 patients who met the American-European consensus definition for ARDS and the rest of our inclusion criteria were considered for entry into the trial. According to our study design, 208 patients did not fulfill ARDS criteria after 24 hrs of standard ventilatory management and, therefore, a total of 103 consecutive ARDS patients were enrolled in the present study: 50 patients in the control group and 53 patients in the P_{flex}/LTV group (Fig. 1). None of the patients included or excluded based on standard ventilator settings died during the 24-hr evaluation period and no patients were dropped from the study after randomization. The trial was terminated early because the absolute mortality difference between control and P_{flex}/LTV groups satisfied the stopping rule. After completed data on 98 patients (51 patients in P_{flex}/LTV and 47 patients in control) were received by the coordinating center, mortality rate was 29.4% in the P_{flex}/LTV group and 53.2% in controls ($p = .024$). Centers were then notified to stop recruiting patients. Data on five additional patients, enrolled at the time of notification, were received by the coordinating center. The groups were balanced in terms of baseline characteristics at randomization (Table 1). Distribution of the 103 patients by risk factors or clinical conditions associated with the development of ARDS was similar in both groups (Table 1). The majority of patients developed ARDS secondary to pneumonia, sepsis, or trauma.

Primary and Secondary End Points. ICU mortality (27 of 50 [54%] vs. 16 of 53 [30.1%], $p = .017$; 95% CI for the 23.9% difference between groups, 5.3–42.3%) and hospital mortality (28 of 50 [56%] vs. 17 of 53 [32.1%], $p = .018$; 95% CI for the 23.9% difference between groups, 5.3–42.5%) were higher in controls than in the P_{flex}/LTV group. However, during the process of manuscript revision, it was determined that one center failed to adhere to the randomization methodology. As a result we were forced to eliminate the eight patients from this center (three P_{flex}/LTV and five controls) (Fig. 1). However, the exclusion of these eight patients did not significantly change the absolute ICU mortality difference (24 of 45 [53.3%] vs. 16 of 50 [32%], $p = .040$; 95% CI for the 21.3% difference between groups, 1.8–40.8%) and absolute hospi-

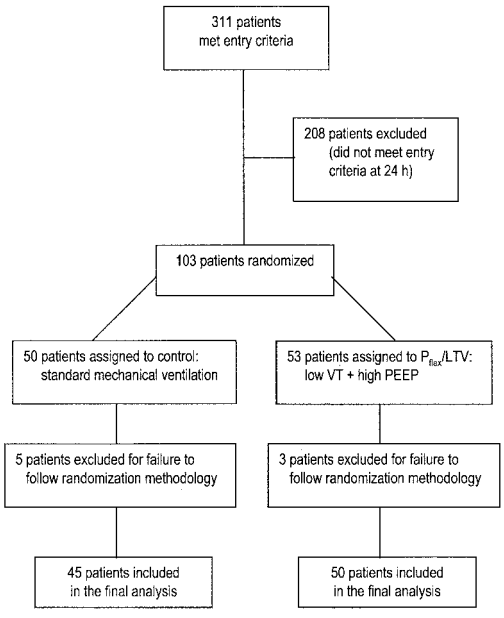

Figure 1. Flow diagram illustrating all patient initially meeting entry criteria to patients included in final analysis. *P_{flex}*, lower inflection point of the pressure volume curve of the respiratory system; *LTV*, low tidal volume; *VT*, tidal volume; *PEEP*, positive end-expiratory pressure.

Table 1. Patient demographics, physiologic variables, and clinical conditions associated with the development of acute respiratory distress syndrome (ARDS) at study entry, during the 24-hr period of standard ventilator settings

Variables, Units	Control (n = 45)	P_{flex}/LTV (n = 50)	*p* Value
Gender, male, n (%)	27 (60)	23 (40)	.218[a]
Age, yrs, median (P_{25}–P_{75})	52 (40–69)	48 (28–62)	.150[b]
APACHE II, mean ± SD	18 ± 6	18 ± 7	.980[c]
Plateau pressure, cm H_2O, mean ± SD	32 ± 6	32 ± 6	.757[c]
PEEP, cm H_2O, mean ± SD	7.6 ± 3	8.2 ± 3	.486[c]
Tidal volume, mL/kg PBW, mean ± SD	9.8 ± 0.6	9.9 ± 0.5	.672[c]
Respiratory rate, breaths/min, median (P_{25}–P_{75})	14 (12–16)	15 (13–17)	.276[b]
FIO_2, median (P_{25}–P_{75})	0.65 (0.5–0.9)	0.65 (0.5–0.9)	.118[b]
PaO_2, mm Hg, median (P_{25}–P_{75})	71 (58–84)	72 (67–85)	.149[b]
$PaCO_2$, mm Hg, median (P_{25}–P_{75})	44 (36–49)	40 (35–48)	.134[b]
pH, median (P_{25}–P_{75})	7.36 (7.31–7.41)	7.37 (7.30–7.41)	.426[b]
Pulmonary artery occlusion pressure, mm Hg, median (P_{25}–P_{75})	15 (13–16)	15 (13–16)	.972[b]
Cardiac index, L/min/m^2, median (P_{25}–P_{75})	4.5 (3.3–6)	5.5 (4–6.56)	.056[b]
Lung injury score, mean ± SD	2.8 ± 0.5	2.9 ± 0.4	.328[c]
Number, organ failures, mean ± SD	0.5 ± 0.6	0.8 ± 0.9	.101[c]
Days on mechanical ventilation at entry, mean ± SD	2.21 ± 0.31	2.66 ± 0.39	.307[c]
ARDS risk factors, n (%)			
Pneumonia	13 (28.9)	16 (32)	0.825[a]
Sepsis	12 (26.7)	14 (28)	0.887[a]
Trauma	10 (22.2)	11 (22)	1[a]
Aspiration	3 (6.6)	4 (8)	0.999[a]
Acute pancreatitis	4 (8.8)	2 (4)	0.418[a]
Other causes	4 (8.8)	4 (8)	1[a]

Control, conventional mechanical ventilation; P_{flex}, lower inflection point of the pressure volume curve of the respiratory system; LTV, low tidal volume; APACHE, Acute Physiology and Chronic Health Evaluation; PEEP, positive end-expiratory pressure; PBW, predicted body weight.

[a]Fisher's exact test; [b]Mann Whitney U rank test; [c]Student's *t*-test. One patient in each group had two main risk factors as primary diagnosis. Hemodynamic data at study entry from 47 patients (24 in the control group and 23 in the P_{flex}/LTV group) with pulmonary artery catheters in place before randomization. All differences between study groups were nonsignificant.

Table 2. Main outcome variables

	Control	P_{flex}/LTV	*p* Value
Ventilator-free days	6.0 ± 7.9	10.9 ± 9.4	.008
Barotrauma, n (%)	4 (8.4)	2 (4)	.418
No. of organ failures: post-pre randomization	1.2 (0.7–1.6)	0.3 (0–0.7)	<.001
ICU mortality rate, %	53.3	32.0	.040

P_{flex}, lower inflection point of the pressure volume curve of the respiratory system; LTV, low tidal volume; ICU, intensive care unit.

tal mortality difference (25 of 45 [55.5%] vs. 17 of 50 [34%], $p = .041$; 95% CI for the 21.5% difference between groups, 2–41%) between control and P_{flex}/LTV groups (Table 2). No patient was discharged while still mechanically ventilated. All of the data presented from this point forward are from the final 95 patients, although no substantial differences exist between these data and the data for the 103 patients. Most deaths occurred within the first 15 days of the study, 16 of 24 deaths (66.6%) in the control group and 11 of 16 deaths (68.8%) in the P_{flex}/LTV group. No deaths in either group occurred until day 4, when two deaths in control and three in P_{flex} occurred. By day 30 all but three deaths in the control group and three in P_{flex}/LTV had occurred. Only two patients (one in each group) died during hospitalization after being discharged from the ICU. Figure 2 shows the ICU probability of survival to 28 days. Multiple organ failure and septic shock were the most common causes of death in both groups. Less than one in five deaths were due to refractory respiratory failure (25% control vs. 12.5% P_{flex}, $p = .439$). Ventilator-free days at day 28 were 6.02 ± 7.95 in control and 10.90 ± 9.45 in P_{flex}/LTV ($p = .008$). A week after randomization, 78% of the patients on control still required mechanical ventilation, whereas 60% of patients on P_{flex}/LTV were still ventilated ($p = .062$). Both groups had additional organ failures after randomization (Table 3) but patients in the control group developed significantly more failing organs than those ventilated in the P_{flex}/LTV group (Table 2). No significant difference in pneumothorax rate was observed.

Table 4 shows selected values of gas exchange, ventilatory, and hemodynamic variables over the first week of the study. In general, during this period, patients in the control group were ventilated with a higher peak inspiratory pressure, a higher end-inspiratory plateau pressure, a lower level of PEEP, and a higher FIO_2 than patients in the P_{flex}/LTV group. During the first 6 days of the study, the maximum mean peak inspiratory and maximum mean end-inspiratory plateau pressures were higher in the control group than in the P_{flex}/LTV group (39.0 ± 8 vs. 32.0 ± 4.7 cm H_2O, $p < .001$; and 33.3 ± 7 vs. 28 ± 4.8 cm H_2O, $p = .045$, respectively), whereas maximum PEEP levels during the first 72 hrs were 3.6 cm H_2O lower on average in the control group (9.8 ± 2.8 cm H_2O) than in the P_{flex}/LTV group (13.4 ± 2.6 cm H_2O) ($p < .001$, 95% CI for the difference between groups, 2.6–5 cm H_2O). The value of maximum PEEP set on day 1 based on the lower inflection point for patients in the P_{flex}/LTV group ranged between 10 and 18 cm H_2O (mean 14.1 ± 2.8 cm H_2O). In five of the 50 patients in the P_{flex}/LTV group, the lower inflexion point on the pressure-volume curve could not be identified and no safety issues were identified with the performance of any pressure-volume curve. However, there was no difference in mortality between these patients and the remainder of the P_{flex}/LTV group. Patients in the control group were ventilated during the first week of the study with an average V_T of 2.8 mL/kg higher than the P_{flex}/LTV group (10 ± 1.1 vs. 7.2 ± 0.8 mL/kg PBW, $p < .001$), as defined by the study protocol. Compliance with the protocol was good in both groups. In the control group, compliance with PEEP setting was 97%, with V_T 80%, and with $PaCO_2$ 81%. In the P_{flex}/LTV group, compliance with

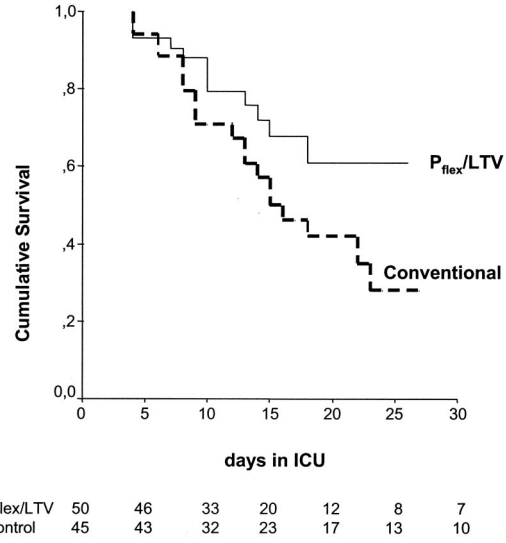

Figure 2. Kaplan-Meier 28-day probability of survival curve for patients with acute respiratory distress syndrome after randomization to conventional mechanical ventilation (control) and a group receiving lower inflection point of the pressure volume curve of the respiratory system (P_{flex})/low tidal ventilation (*LTV*) ($p = .05$, log rank test). Most deaths occurred within the first 15 days of the study: 16 of 24 deaths (66.6%) in the control group and 11 of 16 deaths (68.8%) in P_{flex}/LTV group. *ICU*, intensive care unit.

Table 3. Specific types of organ failure prerandomization and postrandomization

	Prerandomization		Postrandomization	
	P_{flex}/LTV	Control	P_{flex}/LTV	Control
CNS	10 (20)	12 (26.7)	5 (10)	8 (17.8)
Kidney	7 (14)	4 (8.9)	21 (42)	18 (40)
Liver	6 (12)	3 (6.7)	4 (8)	8 (17.8)
Cardio	5 (10)	3 (6.7)	9 (18)	28 (62.2)[a]
GI Tract	8 (16)	1 (2.2)[b]	8 (16)	8 (17.8)
DIC	4 (8)	1 (2.2)	8 (16)	7 (15.6)

P_{flex}, lower inflection point of the pressure volume curve of the respiratory system; LTV, low tidal volume; CNS, central nervous system; Cardio, cardiovascular; GI, gastrointestional; DIC, disseminating intravascular coagulation.

[a]$p < .001$; [b]$p = .033$. Values are n (%).

the initial PEEP setting was 100%, with VT 92%, and with $Paco_2$ 91%.

DISCUSSION

The main finding of this trial is the use of a small, physiologic VT and a PEEP level set on day 1 at P_{flex} + 2 cm H_2O in comparison with a ventilatory protocol with a higher VT and low PEEP level resulted in a 21.3% absolute improvement in ICU mortality. We speculate that the improved mortality observed in the P_{flex}/LTV group is a result of two mechanisms: a higher PEEP level and a lower VT and plateau pressure, the high PEEP preventing recruitment-derecruitment injury (3, 24) and the lower VT and plateau pressure avoiding overdistension injury (7, 13). Although the VT difference was small (about 2.8 mL/kg PBW), plateau pressures in the control group averaged >32 cm H_2O, whereas the plateau pressures in the P_{flex}/LTV group averaged ≤30 cm H_2O throughout the ventilation period. This low plateau pressure resulted in less end-inspiratory stress and strain on lung tissue and, as a result, less imposed lung injury.

There are major differences between our study and any of the other clinical trials (3–8) evaluating the impact of lung-protective strategies. First, none of those trials used the same definition for ARDS. Furthermore, those studies enrolled patients with less severe lung injury than in our trial. We ensured that all studied patients had established and persistent ARDS 24 hrs after meeting the American-European Consensus Conference definition of ARDS while on standard ventilator settings. As noted in Figure 1, 66% of patients meeting ARDS criteria on day 0 were excluded because they did not meet ARDS criteria 24 hrs later while on standard ventilator settings. Villar et al. (9) found that on standard ventilator settings the degree of hypoxemia improved significantly in >50% of patients within 24 hrs of meeting ARDS entry criteria. In that study, a PEEP trial with ≥5 cm H_2O PEEP at an FIO_2 of ≥0.5 and VT 10 mL/kg was able to identify ARDS patients with a higher mortality rate (68%) then those with ALI (23%, $p < .05$). Similarly, Ferguson et al. (10) demonstrated that <50% of patients initially meeting ARDS criteria continued to meet ARDS criteria when placed on standard ventilator setting (PEEP ≥10 cm H_2O, FIO_2 1.0, VT 7–8 mL/kg). They also found a large difference in mortality rate between groups. Those meeting ARDS criteria on standard ventilator settings had a mortality rate of 52.9%, and those with a PaO_2/FIO_2 >200 mm Hg on standard settings had a mortality rate of 12.5% ($p < .05$). In these studies, a PEEP trial was able to identify ARDS patients with a higher (>50%) or lower (<25%) mortality rate. Therefore, we must conclude that the patients we studied were different from those studied by the ARDSnet (7, 8). In addition the mortality rate in our control group was similar to the mortality rates reported in recent epidemiologic studies (9, 10, 16, 22, 23) and other clinical trials (25–27). We speculate that the use of PEEP = P_{flex} + 2 cm H_2O set on day 1 with a small VT in comparison with a ventilatory protocol with a higher VT and low PEEP level has the greatest impact on patients with persistent, established ARDS.

Second, the VT used in the control groups (10 ± 1.1 mL/kg PBW in our study vs. about 12 mL/kg in the ARDSnet) resulted in a 2.8 mL/kg vs. a 5.6 mL/kg difference between groups in the ARDSnet study. In our study, the application of PEEP > P_{flex} set on day 1 and a small VT was able to establish a 21.3% absolute ICU mortality difference between groups with a total of 95 patients enrolled. Amato et al. (3) required just 53 patients to show a 33% absolute ICU mortality difference when PEEP was > Pflex and a 6 mL/kg VT difference existed between groups. The ARDSnet trial (7), where only a very small but significant difference in PEEP (9.4 ± 3.6 cm H_2O low VT vs. 8.6 ± 3.6 cm H_2O high VT, $p < 0.05$) was reported between groups, required

Table 4. Respiratory and ventilatory variables during the first week of the study in the control and P_{flex}/LTV groups of patients

Variable, Units	Day 1		Day 3		Day 6	
	Control n = 45	P_{flex}/LTV n = 50	Control n = 45	P_{flex}/LTV n = 50	Control n = 42	P_{flex}/LTV n = 41
Tidal volume, mL/kg PBW	10.2 ± 1.2	7.3 ± 0.9[a]	10.0 ± 1.0	7.1 ± 0.9[a]	9.9 ± 1.2	7.1 ± 0.9[a]
PEEP, cm H_2O	9.0 ± 2.7	14.1 ± 2.8[a]	8.7 ± 2.8	11.2 ± 3.1[b]	8.3 ± 3.7	8.2 ± 3.5
Respiratory rate, breaths/min	15.0 ± 3.0	20.6 ± 4.0[b]	15.9 ± 2.9	19.8 ± 3.0[b]	16.1 ± 5	18 ± 4.0[c]
Peak inspiratory pressure, cm H_2O	37.1 ± 7.7	36.3 ± 5.9	38.0 ± 8.1	32.5 ± 6.6[b]	36.7 ± 8.6	29.2 ± 7.6[a]
Plateau pressure, cm H_2O	32.6 ± 6.2	30.6 ± 6.0	32.5 ± 7.5	28.4 ± 5.4[c]	32.4 ± 8.0	25.7 ± 7.2[a]
F_{IO_2}	0.70 ± 0.20	0.60 ± 0.15[c]	0.67 ± 0.19	0.55 ± 0.17[b]	0.61 ± 0.22	0.48 ± 0.15[b]
Pa_{O_2}/F_{IO_2}, mm Hg	124 ± 54	139 ± 43	134 ± 57	174 ± 61[b]	163 ± 93	208 ± 72[c]
Pa_{CO_2}, mm Hg	46.0 ± 11.1	42.7 ± 9.6	46.1 ± 10	42.9 ± 9.1	47.8 ± 13	41.7 ± 9.7[c]
pH	7.35 ± 0.07	7.35 ± 0.09	7.36 ± 0.07	7.37 ± 0.06	7.36 ± 0.07	7.40 ± 0.06[c]
Occlusion pressure, mm Hg	14.4 ± 2.8	14.9 ± 2.5	14.6 ± 3.9	13.0 ± 2.9	15.0 ± 3.6	11.8 ± 3.9
Cardiac index, L/min/m^2	4.7 ± 1.4	5.8 ± 1.5[c]	5.0 ± 1.5	5.2 ± 1.4	5.1 ± 1.8	5.4 ± 2.4

Control, conventional mechanical ventilation; P_{flex}, lower inflection point of the pressure volume curve of the respiratory system; LTV, low tidal volume; PBW, predicted body weight; PEEP, positive end-expiratory pressure.

[a] $p < .001$; [b] $p < .01$; [c] $p < .05$ (Student's *t*-test for each day). Hemodynamic data (occlusion pressure and cardiac index) were obtained from 47 patients on days 1 and 3 (24 CMV, 23 P_{flex}) and from 23 patients on day 6 (13 CMV, 11 P_{flex}). All values are mean ± SD. No statistically significantly differences were found (Student's *t*-test for each day).

861 patients to demonstrate an 8.9% absolute hospital mortality difference (ICU mortality not provided). As a result, we speculate that PEEP > P_{flex} has a synergistic effect on the Vt difference between groups increasing the overall lung-protective effect of a low Vt and improving outcome. This interpretation is consistent with experimental data (13–15, 28, 29). We assume that the application of PEEP > P_{flex} on day 1 reduced the lung injury associated with the repetitive opening and collapse of unstable lung units. Clearly, there is controversy over the significance of P_{flex} (30, 31), and P_{flex} may not be the best way to establish PEEP based on lung mechanics because of the problems associated with its significance, determination, reproducibility, and so on (30, 31). However, the use of the individual patient's lung mechanics does seem to be the most appropriate method of setting PEEP. We would suggest the use of a decremental PEEP trial, as suggested by Hickling (31), as a potentially more reproducible alternative for future studies.

Slutsky and Tremblay (32) postulated that mechanical ventilation may contribute to the development of a systemic inflammatory response and subsequent multiple system organ failure and death. In a randomized, controlled trial of 37 ARDS patients, Ranieri et al. (25) found that a protective ventilatory strategy very similar to our experimental group, using low Vt (7.6 ± 1.1 mL/kg) and PEEP 2–3 cm H_2O above P_{flex} (14.8 ± 2.7 cm H_2O) set on day 1, significantly attenuated the pulmonary and systemic cytokine responses within 36 hrs after randomization compared with a ventilatory strategy using relatively high Vt (11.1 ± 1.3 mL/kg) and low PEEP (6.5 ± 1.7 cm H_2O). In contrast, we found a reduction in organ failure after enrollment in patients in the P_{flex}/LTV group. In addition, Ranieri et al. (25) found that the 28-day mortality rate was 20% lower in the lung-protective group (38% vs. 58%) although this difference did not reach statistical significance due to a low sample size, whereas our data did demonstrate a significant reduction in mortality rate from 53.3% to 32% ($p = .040$). Our trial clearly supports the hypothesis that inappropriate mechanical ventilation leads to multiple system organ dysfunction and is associated with a worse outcome.

Third, contrary to the data in the ARDSnet trial (7) but consistent with the Amato et al. (3) data, Pa_{O_2}/F_{IO_2} was significantly greater after day 1 in patients in the P_{flex}/LTV group. As has been shown in both laboratory (33) and clinical studies (34), lung is recruited during tidal ventilation, and the greater the airway pressure obtained the greater the recruitment. However, if PEEP is inadequate, the lung collapses during expiration. We speculate that the oxygenation benefit in our trial was a result primarily of PEEP maintaining a greater end-expiratory lung volume, avoiding derecruitment. We also speculate that high PEEP used early in ARDS changes the course of ARDS, reducing the severity by day 6. It is interesting to compare day 1 data to day 6 data (Table 4). On day 1, a PEEP difference of about 5.1 cm H_2O existed; by day 6 PEEP levels were equal, but a consistent Vt difference of about 3.0 mL/kg was still present. However, large and significant F_{IO_2}, Pa_{O_2}/F_{IO_2}, and plateau pressure differences favoring P_{flex}/LTV existed on day 6. That is, the benefit of the PEEP and Vt differences on day 1 resulted in a benefit on day 6 despite the PEEP difference being eliminated by day 6. In the ARDSnet control group, the use of large Vt resulted in marked tidal recruitment but, because of inadequate PEEP, allowed derecruitment and caused ventilator-induced lung injury, losing the oxygenation benefit by 1 wk.

Our results differ from the recent ARDSnet ALVEOLI high-low PEEP trial (8), which reported no difference in outcome regardless of PEEP strategy. Three equally important reasons account for these differing results. First of all, we had a large Vt difference between groups (2.8 mL/kg), whereas in the ALVEOLI trial the Vts were essentially equal. Based on the results of the first ARDSnet trial (7), this Vt difference clearly had an impact on our mortality difference. Second was the fact that the patients in the ALVEOLI trial may not have had severe, persistent ARDS. The application of PEEP to the high-PEEP group (14.7 ± 3.5 cm H_2O PEEP, F_{IO_2} 0.44 ± 0.17) changed the majority of patients from ARDS (Pa_{O_2}/F_{IO_2} 168 ± 66 mm Hg at baseline) to ALI (Pa_{O_2}/F_{IO_2} 220 ± 89 mm Hg on day 1). This is contrary to what occurred with our patients on day 1, when a PEEP of 14.1 ± 2.8 cm H_2O and F_{IO_2} of 0.60 ± 0.15 resulted in a Pa_{O_2}/F_{IO_2} of 139 ± 43 cm H_2O, and with the patients in the P_{flex}/LTV group of the Amato (3) trial.

Finally, as discussed earlier, PEEP in the ALVEOLI trial was set by a PEEP/F_{IO_2} table not based on the individual patient lung mechanics. It may be that the impact of a higher PEEP level set based on lung mechanics on day 1 only affects outcome in severe established ARDS, not ALI.

Fourth, another difference between our study and that of Amato et al. (3) was the use of lung recruitment maneuvers. Before setting PEEP in the high-PEEP group, Amato et al. used 40 cm H_2O CPAP applied for 40 secs to recruit the lung, whereas we did not. However, the performance of a pressure-volume curve must be considered a lung recruitment exercise. In each patient, airway pressure was stepwise increased to 35–40 cm H_2O during the pressure-volume curve measurement. As shown by Pelosi et al. (33) and Crotti et al. (34), the process of increasing peak airway pressure recruits collapsed lung.

Our study is limited by a number of specific issues. First, the fact that our study used a different V_T in each group prevents us from being able to conclude that the addition of higher levels of PEEP to lower V_T ventilation is superior to lower V_T ventilation alone. Our data can only be generalized to those patients meeting the same entry criteria as used in this study. Additional multiple-center studies in patients with established ARDS, using lung mechanics to set PEEP in one group and a PEEP/F_{IO_2} table in the other group with a consistent V_T in each group, are needed to confirm these results. Second, although we originally appropriately stopped the study based on our stopping rule for efficacy, the subsequent elimination of patients from the one center and the change in *p* value as a result bring into question the early stopping of the study. However, because of timing of these two events, the study could not be continued. As a result, our outcomes should only be evaluated in light of this concern. Third, no weaning protocol was defined. This may have caused the length of mechanical ventilation to vary widely based on investigator or institutional basis. However, it would not have affected the primary end point of the study—mortality. Fourth, we did not define a precise protocol for the adjustment of PEEP or F_{IO_2} in either group, leaving the specific settings after day 1 to the judgment of the investigators. Fifth, we did not use a mathematical method to identify P_{flex}, and we did use multiple techniques to measure the pressure-volume curve. As a result, the specific value identified may have been biased by the investigators' skill at interpreting the pressure-volume curve and the potential for differing results based on the pressure-volume curve technique used. Also, in five patients P_{flex} could not be identified, causing us to set PEEP at 15 cm H_2O. PEEP of 15 cm H_2O was chosen based on the experience of the investigators in measuring P_{flex} in ARDS patients. This of course is a concern because there is a wide variability in P_{flex} among ARDS patients, and 15 cm H_2O may have over- or underestimated the correct PEEP level for any given patient. In addition, we cannot be assured that the unblinded nature of the study did not affect other aspects of care. However, our adherence to protocol data does indicate an average of 91% compliance. In summary, in patients with severe established ARDS, a ventilatory strategy using a smaller V_T and PEEP set on day 1 greater than P_{flex} results in marked improvement in mortality compared with a higher V_T and lower PEEP set solely on oxygenation criteria strategy.

REFERENCES

1. Villar J, Petty TL, Slutsky AS: ARDS in its middle age: What have we learned? *Appl Cardiopulm Pathophysiol* 1998; 7:167–172
2. Montgomery AB, Stager MA, Carrico J, et al: Causes of mortality in patients with the adult respiratory distress syndrome. *Am Rev Respir Dis* 1985; 132:485–489
3. Amato MBP, Barbas CSV, Medeiros DM, et al: Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. *N Engl J Med* 1998; 338:347–354
4. Stewart TE, Meade MO, Cook DJ, et al: Pressure- and Volume-limited Ventilation Strategy Group. Evaluation of a ventilatory strategy to prevent barotrauma in patients at high risk for acute respiratory distress syndrome. *N Engl J Med* 1998; 338:355–368
5. Brochard L, Roudot-Thoraval F, Roupie E, et al: Multicenter trial group on tidal volume reduction in ARDS. Tidal volume reduction for prevention of ventilator-induced lung injury in the acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1998; 158:1831–1838
6. Brower RG, Shanholtz CB, Fessler HE, et al: Prospective, randomised controlled clinical trial comparing traditional versus reduced tidal volume ventilation in acute respiratory distress syndrome. *Crit Care Med* 1999; 27: 1492–1498
7. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000; 342:1301–1308
8. Brower RG, Lanken PN, MacIntyre N, et al: National Heart, Lung, and Blood Institute ARDS Clinical Trials Network. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. *N Engl J Med* 2004; 351:327–336
9. Villar J, Pérez-Méndez L, Kacmarek RM: Current definitions of acute lung injury and the acute respiratory distress syndrome do not reflect their true severity and outcome. *Intensive Care Med* 1999; 25:930–935
10. Ferguson ND, Kacmarek RM, Chicke JD, et al: Screening of ARDS patients using standardized ventilator settings: Influence on enrolment in a clinical trial. *Intensive Care Med* 2004; 30:1111–1116
11. Estenssoro E, Dubin A, Laffaire E, et al: Impact of positive end-expiratory pressure on the definition of acute respiratory distress syndrome. *Intensive Care Med* 2003; 29: 1936–1942
12. Bernard GR, Artigas A, Brigham KL, et al: Consensus Committee. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med* 1994; 149:818–824
13. Dreyfus D, Soler P, Basset G, et al: High inflation pressure pulmonary edema: Respective effects of high airway pressure, high tidal volume and positive end-expiratory pressure. *Am Rev Respir Dis* 1988; 137:1159–1164
14. Muscedere JG, Mullen JBM, Gan K, et al: Tidal volume at low airway pressures can augment lung injury. *Am Rev Respir Dis* 1994; 149:1327–1334
15. Tremblay L, Valenza F, Ribeiro SP, et al: Injurious ventilatory strategies increase cytokines and c-*fos* mRNA expression in an isolated rat lung model. *J Clin Invest* 1997; 99:944–952
16. Esteban A, Anzueto A, Frutos F, et al: Mechanical Ventilation International Study Group. Characteristics and outcomes in adult patients receiving mechanical ventilation. A 28-day international study. *JAMA* 2002; 287:345–385
17. Bell RC, Coalson JJ, Smith JD, et al: Multiple organ system failure and infection in adult respiratory distress syndrome. *Ann Intern Med* 1983; 99:293–298
18. Villar J, Manzano JJ, Blazquez MA, et al: Multiple system organ failure in acute respiratory failure. *J Crit Care* 1991; 6:75–80
19. Devine BJ: Gentamicin therapy. *Drug Intell Clin Pharm* 1974; 8:650–655
20. Knaus WA, Draper EA, Wagner DP, et al: APACHE II: A severity of disease classification system. *Crit Care Med* 1985; 13:818–829
21. Murray JE, Matthay MA, Luce JM, et al: An expanded definition of the adult respiratory distress syndrome. *Am Rev Respir Dis* 1988; 138:720–723
22. Brun-Buisson C, Minelli C, Bertolini G, et al: ALIVE study group. Epidemiology and outcome of acute lung injury in European intensive care units. Results from the ALIVE study. *Intensive Care Med* 2004; 30:51–61
23. Lewandowski K, Metz J, Deutschmann C, et

al: Incidence, severity, and mortality of acute respiratory failure in Berlin, Germany. *Am J Respir Crit Care Med* 1995; 151:1121–1125
24. Webb H, Tierney D: Experimental pulmonary edema due to intermittent positive pressure ventilation with high inflation pressures. *Am Rev Respir Dis* 1974; 110:556–565
25. Ranieri VM, Suter PM, Tortorella C, et al: Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: A randomized controlled trial. *JAMA* 1999; 282:54–61
26. Derdak S, Mehta S, Stewart TE, et al: Multicenter Oscillatory Ventilation For Acute Respiratory Distress Syndrome Trial (MOAT) Study Investigators. High-frequency oscillatory ventilation for acute respiratory distress syndrome in adults: A randomized, controlled trial. *Am J Respir Crit Care Med* 2002; 166:801–808
27. Gattinoni L, Tognoni G, Pesenti A, et al: Prone-Supine Study Group. Effect of prone positioning on the survival of patients with acute respiratory failure. *N Engl J Med* 2001; 345:568–573
28. Takeuchi M, Gordon S, Dolhnikoff M, et al: Set positive end-expiratory pressure during protective ventilation affects lung injury. *Anesthesiology* 2002; 97:682–692
29. Herrera MT, Toledo C, Valladares F, et al: Positive end-expiratory pressure modulates local and systemic inflammatory responses in a sepsis-induced lung injury model. *Intensive Care Med* 2003; 29:1345–1353
30. Hickling KG: The pressure-volume curve is greatly modified by recruitment. A mathematical model of ARDS lungs. *Am J Respir Crit Care Med* 1998; 158:194–202
31. Hickling KG: Reinterpreting the pressure-volume curve in patients with acute respiratory distress syndrome. *Curr Opin Crit Care* 2002; 8:32–38
32. Slutsky AS, Tremblay L: Multiple system organ failure. Is mechanical ventilation a contributing factor? *Am J Respir Crit Care Med* 1998; 157:1721–1725
33. Pelosi P, Goldner M, McKibben A, et al: Recruitment and derecruitment during acute respiratory failure. An experimental study. *Am J Respir Crit Care Med* 2001; 164:122–130
34. Crotti S, Mascheroni D, Caironi P, et al: Recruitment and derecruitment during acute respiratory failure. A clinical study. *Am J Respir Crit Care Med* 2001; 164:131–140

APPENDIX 1: INVESTIGATORS AT PARTICIPATING CENTERS

Participating centers and investigators of the Acute Respiratory Insufficiency: España Study (ARIES) network, in addition to the authors, were as follows: *Hospital Morales Meseguer, Murcia* (Gumersindo González, MD, PhD; Francisco García-Córdoba, MD, PhD; Antonio Esquinas, MD, PhD; Andrés Carrillo, MD); *Hospital La Paz, Madrid* (Julia López, MD; María A. Arce, MD; Manuel Jiménez-Lendínez, MD, PhD); *Hospital Gregorio Marañón, Madrid* (Carmen Bouza, MD, PhD); *Hospital General de León, León* (José López, MD); *Hospital San Millán, Logroño* (Iñaki Saralegui, MD); *Hospital Insular de Gran Canaria, Las Palmas* (José J. Blanco, MD; Eva Treviño, MD; Manuel Sánchez-Palacios, MD); *Hospital General de La Palma, La Palma* (Luis A. Ramos, MD; Raquel Ortiz, MD; Trinidad Puente, MD); *Hospital Universitario N.S. de Candelaria, Tenerife* (José Sánchez-Godoy, MD).

APPENDIX 2: DEFINITIONS OF SEPSIS AND ORGAN FAILURES

Sepsis: Two or more of the following: a) a rectal or core temperature of $>39°C$; b) a total leukocyte count $>12{,}000/mm^3$ or with $>20\%$ immature forms; c) a blood culture positive for a recognized pathogen; d) gross pus in a closed space; or e) a positive culture from a known or strongly suspected source of systemic infection. In addition, the diagnosis requires any of the following systemic responses: a) unexplained systemic arterial hypotension (<85 mm Hg systolic) for >2 hrs; b) systemic vascular resistance or <800 dyne/sec/cm^5; or c) unexplained metabolic acidosis.

Pulmonary aspiration: Recent inhalation of gastric contents, documented by suctioning gastric contents from the endotracheal tube in a patient at high risk for aspiration.

Coma: Diminished level of consciousness with a Glasgow Coma Scale score 7 in the absence of therapeutic coma.

Acute heart failure: A clinical picture of left ventricular failure confirmed or not by a pulmonary artery occlusion pressure >18 mm Hg and a low cardiac output.

Acute renal failure: Defined by a serum creatinine level >2 mg/dL. In patients with preexisting renal disease, doubling of the admission creatinine level is considered an indication of acute renal failure.

Disseminated intravascular coagulation: A platelet count $<50{,}000/mm^3$, elevated fibrin degradation products, and a fibrinogen level <200 mg/dL with or without clinical evidence of spontaneous bleeding.

Hepatic failure: A serum bilirubin level >2 mg/dL with elevation of the transaminase and lactic dehydrogenase levels above twice normal values.

Acute gastrointestinal tract failure: A gastrointestinal bleeding requiring two or more units of blood replacement therapy within a 24-hr period.

Shock: A systemic systolic blood pressure <85 mm Hg for >2 hrs with evidence of organ hypoperfusion, or a systolic blood pressure of ≥ 85 mm Hg maintained by vasopressors.

Remarks: Any organ failure occurring during the 6-hr period before death is considered to be part of the terminal event.