ORIGINAL ARTICLE

Comparison of Two Fluid-Management Strategies in Acute Lung Injury

The National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network*

ABSTRACT

BACKGROUND

Optimal fluid management in patients with acute lung injury is unknown. Diuresis or fluid restriction may improve lung function but could jeopardize extrapulmonary-organ perfusion.

METHODS

In a randomized study, we compared a conservative and a liberal strategy of fluid management using explicit protocols applied for seven days in 1000 patients with acute lung injury. The primary end point was death at 60 days. Secondary end points included the number of ventilator-free days and organ-failure–free days and measures of lung physiology.

RESULTS

The rate of death at 60 days was 25.5 percent in the conservative-strategy group and 28.4 percent in the liberal-strategy group (P=0.30; 95 percent confidence interval for the difference, –2.6 to 8.4 percent). The mean (±SE) cumulative fluid balance during the first seven days was –136±491 ml in the conservative-strategy group and 6992±502 ml in the liberal-strategy group (P<0.001). As compared with the liberal strategy, the conservative strategy improved the oxygenation index ([mean airway pressure × the ratio of the fraction of inspired oxygen to the partial pressure of arterial oxygen] × 100) and the lung injury score and increased the number of ventilator-free days (14.6±0.5 vs. 12.1±0.5, P<0.001) and days not spent in the intensive care unit (13.4±0.4 vs. 11.2±0.4, P<0.001) during the first 28 days but did not increase the incidence or prevalence of shock during the study or the use of dialysis during the first 60 days (10 percent vs. 14 percent, P=0.06).

CONCLUSIONS

Although there was no significant difference in the primary outcome of 60-day mortality, the conservative strategy of fluid management improved lung function and shortened the duration of mechanical ventilation and intensive care without increasing nonpulmonary-organ failures. These results support the use of a conservative strategy of fluid management in patients with acute lung injury. (ClinicalTrials.gov number, NCT00281268.)

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Pulmonary edema resulting from increased capillary permeability, a hallmark of acute lung injury, worsens as intravascular hydrostatic pressure rises and oncotic pressure falls.[1,2] Although lung failure alone can be lethal, death in patients with acute lung injury is usually due to the failure of nonpulmonary organs.[1,3]

The optimal fluid management of acute lung injury is not settled.[4-7] The usual practice is wide-ranging, and many practitioners weigh the risks and benefits of strategies of conservative as compared with liberal fluid management. In the conservative approach, fluid intake is restricted and urinary output is increased in an attempt to decrease lung edema, shorten the duration of mechanical ventilation, and improve survival. A possible risk of this approach is a decrease in cardiac output and worsening of nonpulmonary-organ function. The liberal fluid approach essentially reverses these potential priorities and risks.

Current evidence is insufficient to support the use of either a liberal or conservative fluid strategy in patients with established acute lung injury.[8-11] We conducted a prospective, randomized clinical trial to investigate the risks and benefits of a fluid-management protocol with a lower (conservative use of fluids) or higher (liberal use of fluids) intravascular pressure (as defined by the pulmonary-artery occlusion pressure or central venous pressure) in patients with acute lung injury. Our primary outcome was death from any cause at 60 days.

METHODS

STUDY DESIGN

The complete protocol for this trial can be found in the Supplementary Appendix (available with the full text of this article at www.nejm.org). Patients were randomly assigned to a strategy involving either conservative or liberal use of fluids with concealed allocation in permuted blocks of eight with the use of an automated system. Participants were simultaneously randomly assigned to receive either a pulmonary-artery catheter or a central venous catheter in a two-by-two factorial design.[12]

INCLUSION CRITERIA

Eligible patients were intubated and received positive-pressure ventilation, had a ratio of the partial pressure of arterial oxygen (PaO_2) to the fraction of inspired oxygen (FIO_2) of less than 300 (adjusted if the altitude exceeded 1000 m), and had bilateral infiltrates on chest radiography consistent with the presence of pulmonary edema without evidence of left atrial hypertension.[13] If a potential participant did not have a central venous catheter, the primary physician's intent to insert one was required.

EXCLUSION CRITERIA

Reasons for exclusion are listed in the Supplementary Appendix. Major reasons for exclusion were the presence of a pulmonary-artery catheter after the onset of acute lung injury; the presence of acute lung injury for more than 48 hours; inability to obtain consent; the presence of chronic conditions that could independently influence survival, impair weaning, or compromise compliance with the protocol (e.g., severe lung or neuromuscular disease or dependence on dialysis); and irreversible conditions for which the estimated six-month mortality rate exceeded 50 percent, such as advanced cancer.

STUDY PROCEDURES

Ventilation according to the Acute Respiratory Distress Syndrome (ARDS) Network protocol of lower tidal volumes was begun within one hour after randomization and continued until day 28; a protocol was used to wean patients from mechanical ventilation.[14] The assigned catheter was inserted within four hours after randomization. Hemodynamic management was started within 2 hours after catheter insertion and continued for seven days or until 12 hours after a patient was able to breathe without assistance.[14] After day 3, a pulmonary-artery catheter could be replaced by a central venous catheter if hemodynamic stability (i.e., absence of the need for protocol-directed interventions on the basis of a measurement with a pulmonary-artery catheter for more than 24 hours) was achieved. We monitored compliance with protocol instructions twice each day: once during a morning reference period and again at a randomly selected time. A 100 percent audit of all instructions conducted after the first 82 patients were enrolled showed rates of protocol compliance similar to those obtained during the random checks (data not shown).

Study personnel underwent training in the con-

duct of the protocol (Fig. 1) and the measurement of vascular pressure. Vascular pressures were measured in supine patients at end expiration (identified with an airway pressure signal) but were not adjusted for airway pressure.[15]

SUBJECTS

A National Heart, Lung, and Blood Institute protocol-review committee, a data and safety monitoring board, and the institutional review board of each participating hospital approved the study.

Measured intravascular pressure (mm Hg)				MAP <60 mm Hg or a need for any vasopressor (except dopamine ≤5 μg/kg/min); consider correctable causes of shock first	MAP ≥60 mm Hg without vasopressors (except dopamine ≤5 μg/kg/min)			
CVP		PAOP[G]			Average urinary output <0.5 ml/kg/hr		Average urinary output ≥0.5 ml/kg/hr	
Conservative strategy	Liberal strategy	Conservative strategy	Liberal strategy		**Ineffective Circulation** Cardiac index <2.5 liters/min/m² or cold, mottled skin with capillary-refilling time >2 sec	**Effective Circulation** Cardiac index ≥2.5 liters/min/m² or absence of criteria for ineffective circulation	**Ineffective Circulation** Cardiac index <2.5 liters/min/m² or cold, mottled skin with capillary-refilling time >2 sec	**Effective Circulation** Cardiac index ≥2.5 liters/min/m² or absence of criteria for ineffective circulation
Range 1				1 Vasopressor[F] Fluid bolus[F]	3 KVO IV Dobutamine[A] Furosemide[B,1,2,4]	7 KVO IV Furosemide[B,1,2,4]	11 KVO IV Dobutamine[A] Furosemide[B,1,3,4]	15 KVO IV Furosemide[B,1,3,4]
>13	>18	>18	>24					
Range 2					4 KVO IV Dobutamine[A]	8 KVO IV Furosemide[B,1,2,4]	12 KVO IV Dobutamine[A]	16 KVO IV Furosemide[B,1,3,4]
9–13	15–18	13–18	19–24					
Range 3				2 Fluid bolus[F] Vasopressor[F]	5 Fluid bolus[C]	9 Fluid bolus[C]	13 Fluid bolus[C]	17 Liberal KVO IV
4–8	10–14	8–12	14–18					18 Conservative Furosemide[B,1,3,4]
Range 4					6 Fluid bolus[C]	10 Fluid bolus[C]	14 Fluid bolus[C]	19 Liberal fluid bolus
<4	<10	<8	<14					20 Conservative KVO IV

Figure 1. Overview of the Protocol for Conservative and Liberal Fluid Management in the Group Assigned to a Pulmonary-Artery Catheter (PAC) and the Group Assigned to a Central Venous Catheter (CVC).

At least every four hours, patients were assigned to 1 of 20 protocol cells (numbered in red in the top left-hand corner of each cell on the lower right-hand side of the figure) on the basis of four variables: central venous pressure (CVP) or pulmonary-artery occlusion pressure (PAOP), depending on catheter assignment; the presence or absence of shock (defined by the protocol as a mean systemic arterial pressure [MAP] below 60 mm Hg or the need for a vasopressor [except for a dose of dopamine of 5 μg per kilogram of body weight per minute or less]); the presence or absence of oliguria (defined by a urinary output of less than 0.5 ml per kilogram per hour); and the presence or absence of ineffective circulation (defined by a cardiac index of less than 2.5 liters per minute per square meter in the PAC group and by cold, mottled skin with a capillary-refilling time of more than 2 seconds in the CVC group). Each cell is associated with an intervention and a reassessment interval. A patient with effective circulation and normotension and without oliguria would be assigned to a cell in the far right-hand column (cells 15 to 20), depending on the intravascular pressure. These patients received furosemide or fluids to move their intravascular pressure toward the target range (in the liberal-strategy group, a CVP of 10 to 14 mm Hg and a PAOP of 14 to 18 mm Hg; in the conservative-strategy group, a CVP of less than 4 mm Hg and a PAOP of less than 8 mm Hg). For example, if such a patient had a CVP of 8 mm Hg, he or she would be assigned to cell 18 if assigned to the conservative strategy and to cell 19 if assigned to the liberal strategy. The protocol called for the conservative-strategy patient assigned to cell 18 to receive furosemide. (The footnote instructions determined the dose of furosemide on the basis of the prior response of this patient and for furosemide to be withheld if the patient had been in shock within the previous 12 hours.) In contrast, the liberal-strategy patient assigned to cell 19 would receive a fluid bolus. (The footnote instructions limited the daily fluid boluses and called for fluid to be withheld if the F_IO_2 was at least 0.7.) Lactate, oxygen delivery, and mixed venous and superior-vena-cava oxygen saturation were not used as protocol variables. For fluid boluses, clinicians were free to select isotonic crystalloid, albumin, or blood products, although the protocol dictated the volume of each administered. If patients were in shock (cells 1 and 2), treatment was left to the judgment of the physician except that after blood pressure stabilized, weaning from the vasopressor was conducted according to the protocol. Of roughly 27,000 assessments, about 19 percent resulted in the assignment of patients to cell 1 or 2 (shock), 75 percent to cells 15 through 20, 5 percent to cells 7 through 10, and 2 percent to other cells. KVO denotes keep vein open, and IV intravenous. The superscript letters and numbers refer to footnotes that may modify protocol instructions on the basis of an individual patient's physiology or response to prior instructions and are important for the safe implementation of the protocol. The protocol is described in detail in the Supplementary Appendix.

Written informed consent was obtained from participants or legally authorized surrogates. The data and safety monitoring board conducted interim analyses after the enrollment of 82 patients and then after the enrollment of approximately every 200 patients. Sequential stopping rules for safety and efficacy used the method of O'Brien and Fleming.[16]

ORGAN FAILURE

For 28 days, we monitored patients daily for cardiovascular, renal, and hepatic failure; coagulation abnormalities; and the need for assisted ventilation.[14] The severity of lung injury was scored according to the method of Murray et al.[17]; the scores can range from 0 to 4, with a lower score indicating better lung function.

STATISTICAL ANALYSIS

The study had a statistical power of 90 percent to detect a reduction by 10 percentage points (from 31 percent to 21 percent) in the primary end point, death before discharge home during the first 60 days after randomization, with the planned enrollment of 1000 patients. We assumed patients who went home without the use of assisted ventilation before day 60 were alive at 60 days. Data on patients who were receiving mechanical ventilation or in a hospital were censored on the last day of follow-up. The Kaplan–Meier method was used to estimate the mean (±SE) 60-day mortality rate at the time of the last death that occurred before 60 days. Differences in mortality between the groups were assessed by a z test. The primary analysis was conducted according to the intention to treat. We assessed differences in continuous variables with analysis of variance, differences in categorical variables with a Mantel–Haenszel test, and differences between continuous variables over time with repeated-measures analysis of variance. For continuous variables, means ±SE are reported. Two-sided P values of 0.05 or less were considered to indicate statistical significance. We used SAS software (version 8.2, SAS Institute) for the analysis.

RESULTS

ENROLLMENT AND EXCLUSIONS

We screened patients at 20 North American centers between June 8, 2000, and October 3, 2005. The trial was halted on July 25, 2002, for a review by the Office of Human Research Protection and resumed unchanged on July 23, 2003, except for the introduction of a modified consent form.[18-20] Figure 2 shows the most common reasons for exclusion for the 10,511 patients who were screened but not enrolled and the follow-up for the 503 patients who were randomly assigned to conservative fluid management and the 498 who were assigned to liberal fluid management (all reasons for

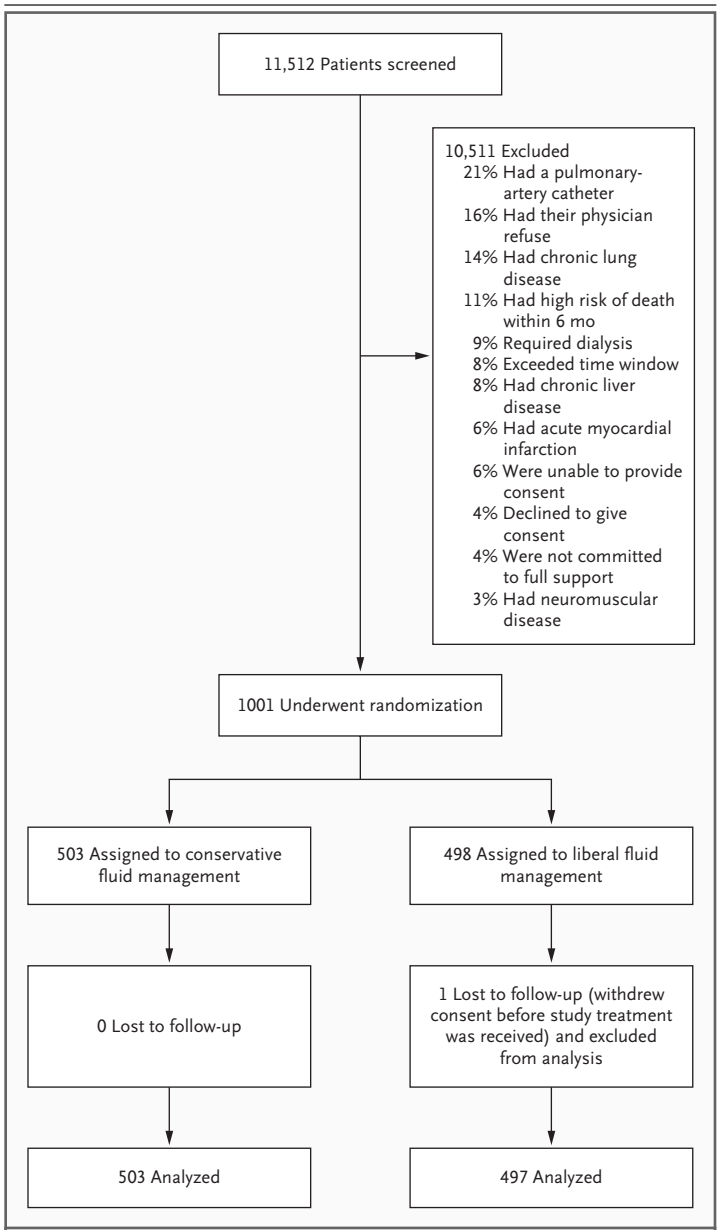

Figure 2. Enrollment and Outcomes.

Patients may have had more than one reason for exclusion. The full exclusion criteria are listed in Table 1 of the Supplementary Appendix.

Table 1. Baseline Characteristics.*

Characteristic	Conservative Strategy (N=503)	Liberal Strategy (N=497)	P Value
Age (yr)	50.1±0.7	49.5±0.7	0.57
Male sex (%)	52	55	0.48
Race or ethnic group (%)			0.66
White	65	63	
Black	20	24	
Hispanic	12	10	
Asian	2	2	
Other	1	1	
Primary lung injury (%)			0.33
Pneumonia	46	48	
Sepsis	22	25	
Aspiration	16	13	
Trauma	8	7	
Multiple transfusions	1	0	
Other	8	7	
Coexisting conditions (%)			
Diabetes	18	18	0.88
HIV infection or AIDS	7	8	0.68
Cirrhosis	3	3	0.89
Solid tumors	1	3	0.02
Leukemia	3	1	0.04
Lymphoma	2	1	0.42
Immunosuppression	9	7	0.27
APACHE III score†	93.1±1.4	95.2±1.4	0.28
Medical ICU (%)	66	66	0.95
Hemodynamic variables			
Mean arterial pressure (mm Hg)	77.1±0.6	77.2±0.6	0.99
CVP (mm Hg)	11.9±0.3	12.2±0.3	0.56
PAOP (mm Hg)	15.6±0.4	15.7±0.4	0.82
PAOP >18 mm Hg (%)	30	29	0.96
Cardiac index (liters/min/m^2)	4.2±0.1	4.3±0.1	0.46
Mixed venous oxygen saturation (%)	69±0.78	69±0.87	0.97
Met shock criteria (%)‡	33	36	0.21
Vasopressor use (%)	31	35	0.10
Prerandomization fluid balance (ml)	2655±156	2875±166	0.34

exclusion are listed in Table 1 of the Supplementary Appendix).

BASELINE CHARACTERISTICS

The two groups were similar with respect to demographic characteristics, type of intensive care unit (ICU), cause of lung injury, coexisting illnesses, severity of illness, organ function, fluid balance before the study began, vasopressor use, and presence of shock (Table 1).

PROTOCOL CONDUCT AND INSTRUCTIONS

The mean time from admission to the ICU to the first protocol instruction was 41.3±1.6 hours in

Table 1. (Continued.)

Characteristic	Conservative Strategy (N=503)	Liberal Strategy (N=497)	P Value
Respiratory variables			
Tidal volume (ml/kg of PBW)	7.4±0.1	7.4±0.1	0.93
Plateau pressure (cm of water)	26.2±0.4	26.2±0.4	0.99
PaO_2:FIO_2	157±3	153±3	0.45
Oxygenation index§	13.0±0.5	13.0±0.47	0.92
PEEP	9.4±0.2	9.5±0.2	0.63
Lung injury score¶	2.7±0.03	2.7±0.03	0.52
pH	7.36±0.00	7.36±0.00	0.46
Renal and metabolic variables‖			
Blood urea nitrogen (mg/dl)	23.2±0.8	24.1±0.8	0.44
Creatinine (mg/dl)	1.24±0.04	1.29±0.04	0.39
Bicarbonate (mmol/liter)	22.5±0.23	22.0±0.23	0.13
Hemoglobin (g/dl)	10.4±0.08	10.4±0.09	0.90
Glucose (mg/dl)	138±2.84	142±3.65	0.38

* Plus–minus values are means ±SE. Race was assigned by the coordinators on the basis of hospital records or information from the next of kin. Because of rounding, percentages may not total 100. HIV denotes human immunodeficiency virus, AIDS acquired immunodeficiency syndrome, CVP central venous pressure, PAOP pulmonary-artery occlusion pressure, PBW predicted body weight, and PEEP positive end-expiratory pressure.

† Scores for the Acute Physiology and Chronic Health Evaluation (APACHE III) can range from 0 to 299, with higher scores indicating a higher risk of death.

‡ Shock was defined by a mean arterial pressure of less than 60 mm Hg or the need for a vasopressor (except for a dose of dopamine of 5 μg per kilogram per minute or less).

§ The oxygenation index is calculated with the use of the following equation: (mean airway pressure × FIO_2:PaO_2) × 100. A lower number indicates better gas exchange.

¶ Scores can range from 0 to 4, with higher scores indicating more severe lung injury.

‖ To convert the values for blood urea nitrogen to millimoles per liter, multiply by 0.357. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for glucose to millimoles per liter, multiply by 0.05551.

the liberal-strategy group and 43.8±2.5 hours in the conservative-strategy group (P=0.42). The rate of compliance with instructions was similar in the two groups (91 percent in the liberal-strategy group and 88 percent in the conservative-strategy group, P=0.06), even though patients in the former group received more protocol instructions per day (5.1 vs. 4.1, P<0.001). Patients in the conservative-strategy group received furosemide more frequently than did patients in the liberal-strategy group (41 percent vs. 10 percent of instructions, P<0.001), whereas patients in the latter group more often received a fluid bolus (15 percent vs. 6 percent of instructions, P<0.001). More furosemide was given to the conservative-strategy group (Table 2). Dobutamine use was similar and uncommon in both groups (4 percent in the liberal-strategy group and 6 percent in the conservative-strategy group). At least one blood transfusion was given to 29 percent of patients in the conservative-strategy group and to 39 percent of patients in the liberal-strategy group (P<0.001). During the study, there was no significant difference in the use of drotrecogin alfa (19 percent in the conservative-strategy group vs. 21 percent in the liberal-strategy group, P=0.70) or systemic corticosteroids (32 percent vs. 37 percent, P=0.09).

FLUID BALANCE

Each study day the liberal-strategy group received more fluid than the conservative-strategy group and on days 1 through 4 had a lower urinary output, resulting in a higher cumulative fluid balance (Table 2). During the study, the seven-day cumulative fluid balance was –136±491 ml in the conservative-strategy group, as compared with 6992±502 ml in the liberal-strategy group (P<0.001) (Fig. 1 of the Supplementary Appendix). For pa-

Table 2. Furosemide Dose, Fluid Intake, Fluid Output, and Fluid Balance on Each Day during the Study.*

Day	Furosemide		Fluid Intake		Fluid Output		Fluid Balance	
	Liberal	Conservative	Liberal	Conservative	Liberal	Conservative	Liberal	Conservative
	mg/24 hr (no. of patients)		*ml/24 hr (no. of patients)*		*ml/24 hr (no. of patients)*		*ml/24 hr (no. of patients)*	
1	74.27±7.48 (133)	148.94±8.52 (312)	5029.8±132.98 (485)	4230.5±120.03 (491)	2501.9±73.23 (485)	3043.8±93.90 (491)	2529.5±148.99 (484)	1186.7±151.01 (491)
2	72.46±6.65 (146)	157.35±8.91 (304)	4467.4±136.11 (479)	3590.6±98.45 (480)	2824.5±101.44 (479)	3966.7±115.57 (480)	1642.9±151.71 (479)	−376.1±161.08 (480)
3	65.28±6.49 (140)	166.90±10.01 (269)	3997.1±103.40 (465)	3390.4±85.30 (464)	3060.9±103.23 (465)	3797.3±110.48 (465)	936.12±115.32 (465)	−408.5±135.90 (464)
4	80.74±10.23 (129)	154.25±10.61 (228)	3752.0±102.07 (444)	3430.8±96.49 (437)	3188.1±109.19 (444)	3606.1±113.38 (434)	563.88±100.98 (444)	−165.5±119.92 (434)
5	73.06±8.41 (119)	164.71±12.06 (197)	3825.3±110.62 (424)	3201.1±87.23 (411)	3358.7±115.49 (421)	3444.8±108.98 (408)	483.03±109.98 (421)	−226.3±115.22 (408)
6	58.20±6.68 (106)	158.87±13.45 (165)	3782.8±104.28 (411)	3159.4±88.12 (382)	3334.4±123.99 (411)	3316.9±103.81 (379)	508.04±111.75 (410)	−144.9±110.25 (378)
7	51.03±4.31 (87)	127.86±11.61 (137)	3639.7±93.96 (390)	3226.9±108.18 (355)	3216.8±98.36 (385)	3143.9±100.16 (346)	458.95±106.85 (385)	130.08±118.47 (346)

* Plus–minus values are means ±SE. Numbers in parentheses indicate the number of patients receiving at least one dose of furosemide on that day or the number of patients with a fluid measurement. P<0.001 for all comparisons except for fluid intake on day 4 (P=0.02) and day 7 (P=0.004); fluid output on day 4 (P=0.008), day 5 (P=0.58), day 6 (P=0.94), and day 7 (P=0.61); and fluid balance on day 7 (P=0.04). Negative fluid balance means that fluid output exceeded fluid intake.

tients who were in shock at baseline, the cumulative seven-day fluid balance was 2904±1008 ml in the conservative-strategy group and 10,138±922 ml in the liberal-strategy group (P<0.001). For patients who were not in shock at baseline, the cumulative fluid balance was −1576±519 ml in the conservative-strategy group and 5287±576 ml in the liberal-strategy group (P<0.001).

HEMODYNAMICS

Intravascular pressures declined in the conservative-strategy group but remained essentially unchanged in the liberal-strategy group (Fig. 2 in the Supplementary Appendix). The conservative-strategy group had a slightly lower mean arterial pressure, stroke volume, and cardiac index, but the heart rate, mixed venous oxygen saturation, and percentage of patients receiving vasopressors did not differ significantly between the two groups (Table 2A in the Supplementary Appendix). For patients in shock at randomization, approximately 40 percent of subsequent measurements met the criteria for shock in both treatment groups. For patients who were not in shock at baseline, there were no significant differences between groups in the incidence of shock during study (32 percent in the liberal-strategy group and 28 percent in the conservative-strategy group, P=0.29) or in the proportions of protocol reassessments classified as shock (6 percent and 7 percent, respectively; P=0.78).

LUNG FUNCTION

Ventilator settings and lung-function data are shown in Table 2B of the Supplementary Appendix. The conservative-strategy group had better lung injury scores and oxygenation indexes, as well as lower plateau pressures and positive end-expiratory pressures. The partial pressure of arterial carbon dioxide, arterial pH, and the PaO_2:FiO_2 were slightly higher in the conservative-strategy group on all study days, but this difference did not reach significance for the PaO_2:FiO_2 (P=0.07).

METABOLIC AND RENAL FUNCTION

The conservative-strategy group had slightly higher creatinine values than the liberal-strategy group during the study, but this difference did not reach significance (P=0.06) (Table 2C of the Supplementary Appendix). The conservative-strategy group had higher levels of blood urea nitrogen, bicarbonate, hemoglobin, albumin, and calculated colloid

osmotic pressure during the study.[21] There were no significant differences in mean serum sodium levels during the study.

SAFETY

Metabolic alkalosis and electrolyte imbalances were reported as an adverse event (none with associated arrhythmias) more frequently with the conservative strategy (42 events, 3 serious) than with the liberal strategy (19 events, 1 serious) (P=0.001). More patients in the conservative-strategy group than in the liberal-strategy group had at least one potassium value of 3.0 mmol per liter or less (26 percent vs. 22 percent, P<0.001), one sodium value of at least 150 mmol per liter (25 percent vs. 18 percent, P=0.009), or one bicarbonate value of more than 40 mmol per liter (6 percent vs. 2 percent, P<0.001). There was no significant difference in the percentage of patients with at least one potassium value of 2.5 mmol per liter or less (4 percent vs. 3 percent, P=0.23).

MAJOR OUTCOMES

Major outcomes are shown in Table 3 and Figure 3. There was no interaction between the interventions of the factorial design (type of fluid management and type of catheter, P=0.26). Therefore, results are reported according to the fluid-management strategy, irrespective of catheter assignment. The in-hospital death rate during the first 60 days after randomization was 25.5±1.9 percent in the conservative-strategy group and 28.4±2.0 percent in the liberal-strategy group (P=0.30; 95 percent confidence interval for the difference, –2.6 to 8.4 percent). The conservative-strategy group had more ventilator-free days, days free of central nervous system failure, and ICU-free days during the first 28 days. There were no significant differences in the number of failure-free days for other organs during the first 28 days, although there was a small (0.3 day) increase in the number of cardiovascular-failure–free days during the first 7 days with the liberal strategy. Within the first 60 days, there were no significant differences in either the percentage of patients receiving renal-replacement therapy (10 percent in the conservative-strategy group vs. 14 percent in the liberal-strategy group, P=0.06) or the average number of days of renal support (11.0±1.7 vs. 10.9±1.4, P=0.96). There were no significant interactions between baseline shock status and treatment with respect to the mortality rate or the number of ventilator-free days or ICU-free days (Table 3 of the Supplementary Appendix).

Table 3. Main Outcome Variables.*

Outcome	Conservative Strategy	Liberal Strategy	P Value
Death at 60 days (%)	25.5	28.4	0.30
Ventilator-free days from day 1 to day 28†	14.6±0.5	12.1±0.5	<0.001
ICU-free days†			
Days 1 to 7	0.9±0.1	0.6±0.1	<0.001
Days 1 to 28	13.4±0.4	11.2±0.4	<0.001
Organ-failure–free days†‡			
Days 1 to 7			
Cardiovascular failure	3.9±0.1	4.2±0.1	0.04
CNS failure	3.4±0.2	2.9±0.2	0.02
Renal failure	5.5±0.1	5.6±0.1	0.45
Hepatic failure	5.7±0.1	5.5±0.1	0.12
Coagulation abnormalities	5.6±0.1	5.4±0.1	0.23
Days 1 to 28			
Cardiovascular failure	19.0±0.5	19.1±0.4	0.85
CNS failure	18.8±0.5	17.2±0.5	0.03
Renal failure	21.5±0.5	21.2±0.5	0.59
Hepatic failure	22.0±0.4	21.2±0.5	0.18
Coagulation abnormalities	22.0±0.4	21.5±0.4	0.37
Dialysis to day 60			
Patients (%)	10	14	0.06
Days	11.0±1.7	10.9±1.4	0.96

* Plus–minus values are means ±SE. CNS denotes central nervous system.
† This was an a priori secondary outcome.
‡ For this analysis, cardiovascular failure was defined by a systolic blood pressure of 90 mm Hg or less or the need for a vasopressor (in contrast, shock was defined by a mean arterial pressure of less than 60 mm Hg or the need for a vasopressor [except a dose of dopamine of 5 μg per kilogram per minute or less]); a coagulation abnormality was defined by a platelet count of 80,000 per cubic millimeter or less; hepatic failure was defined by a serum bilirubin level of at least 2 mg per deciliter (34 μmol per liter); and renal failure was defined by a serum creatinine level of at least 2 mg per deciliter (177 μmol per liter). We calculated the number of days without organ or system failure by subtracting the number of days with organ failure from the lesser of 28 days or the number of days to death. Organs and systems were considered failure-free after patients were discharged from the hospital.

Black patients had a higher overall rate of death (37.3 percent of 118 black patients in the liberal-strategy group and 31.3 percent of 99 black patients in the conservative-strategy group) than white patients (22.7 percent of 313 white patients in the liberal-strategy group and 23.5 percent of 328 white patients in the conservative-strategy group) (P=0.002). Hispanic patients also had a higher mortality rate (38.5 percent of 52 Hispanic

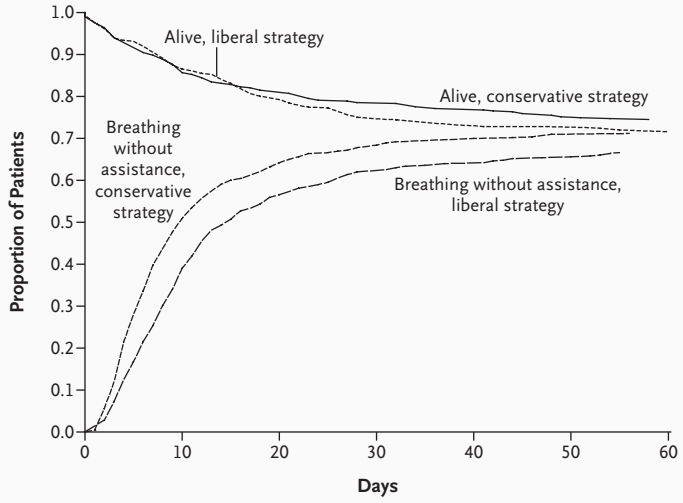

Figure 3. Probability of Survival to Hospital Discharge and of Breathing without Assistance during the First 60 Days after Randomization.

patients in the liberal-strategy group and 23.0 percent of 61 Hispanic patients in the conservative-strategy group) than whites, but this difference did not reach significance (P=0.10). After adjustment for baseline covariates, the hazard ratio for death among blacks as compared with whites was not significant (hazard ratio, 1.29; 95 percent confidence interval, 0.97 to 1.73), whereas it was significant for Hispanics (hazard ratio, 1.58; 95 percent confidence interval, 1.08 to 2.31). The interaction between treatment and race for whites as compared with nonwhites was not significant (P=0.10), nor was it significant in any of the racial or ethnic subgroups. There was also no significant interaction between treatment and sex.

DISCUSSION

Although we did not detect a significant difference between the conservative strategy and the liberal strategy of fluid management in the primary outcome of 60-day mortality, the conservative strategy improved lung function and shortened the duration of mechanical ventilation and intensive care without increasing nonpulmonary-organ failures. The overall difference in mortality according to race or ethnic group has previously been described in patients with acute lung injury[22] and could be due to several factors, including socioeconomic disparities or genetic determinants.[23]

The two strategies were designed to be prudent but distinctly different approaches to fluid therapy. To place the results of our study in context, it is useful to consider how these fluid strategies compare with usual practice. In this regard, it is of interest that the cumulative seven-day fluid balance in the liberal-strategy group (6992±502 ml) was similar to that among patients in ARDS Network studies in which the approach to fluid management was not specified[14,24] (Fig. 1 of the Supplementary Appendix). These findings are similar to those reported by Simmons et al.[8] in 1987, suggesting that the liberal approach to fluid management reflects long-standing practices. The usual practice resembles the liberal approach in another aspect: the prestudy baseline measurements for central venous pressure (12.2 mm Hg) and pulmonary-artery–occlusion pressure (15.7 mm Hg) were both within the target ranges for the liberal fluid strategy (10 to 14 mm Hg and 14 to 18 mm Hg, respectively).

Comparisons of our study to other studies of goal-directed management in critically ill patients are problematic because of differences in protocols, patient populations, and timing of the interventions. Whereas we targeted central venous pressure or pulmonary-artery occlusion pressure in patients with recent onset of acute lung injury, previous studies targeted the cardiac index, oxygen delivery, or mixed venous oxygen saturation in heterogeneous populations of critically ill patients.[25-31] Rivers et al.[32] demonstrated in patients with severe sepsis or septic shock the efficacy of six hours of early, goal-directed resuscitation in the emergency department before admission to the ICU. In contrast, our patients received their first protocol intervention an average of 43 hours after admission to the ICU and 24 hours after meeting the criteria for acute lung injury.

The conservative-strategy group had higher serum oncotic pressures and lower intravascular pressures — characteristics that would be expected to limit the development of pulmonary edema. With lung injury, small increases in the pulmonary-artery occlusion pressure are associated with large increases in extravascular lung water.[2] The higher albumin and hemoglobin levels in the conservative-strategy group appear to be primarily related to hemoconcentration (or less hemodilution), since the rate of albumin use was low and not significantly different between groups and red-cell transfusions were more frequent in the liberal-strategy group.

Our results are consistent with those obtained in studies in animals suggesting improved lung

function with diuretics and fluid restriction[33-37] and with the results of observational studies in humans indicating increased survival with a lower fluid balance and a reduction in the pulmonary-artery occlusion pressure.[6,8,9] Mitchell and colleagues[10] randomly assigned 89 patients with pulmonary edema to receive diuretics and fluid restriction based on extravascular lung water or routine fluid management; the group with fluid restriction had a lower fluid balance, fewer days of ventilator use, and fewer days in the ICU. Martin and coworkers[11] randomly assigned 37 patients with hypoproteinemia and acute lung injury to receive either a five-day specified regimen of furosemide and colloid replacement or placebo infusions. The treated group had an increase in the PaO_2:FiO_2 within 24 hours. We do not know whether using lung-water measurements to drive protocol instructions or increasing the use of colloid would have increased the benefits of the conservative strategy in our study.

The hemodynamic consequences of the conservative strategy were small and apparently of minimal clinical significance. Although the mean arterial pressure, stroke volume, and cardiac index were slightly lower in the conservative-strategy group than in the liberal-strategy group, there were no significant differences in mixed venous oxygenation or in the incidence or duration of shock. Although the conservative strategy was associated with a slightly higher blood urea nitrogen level, the creatinine level, the number of days without renal failure, and the need for dialysis were similar in the two groups. Possible reasons for the greater number of days without central nervous system failure in the conservative-strategy group include a reduced incidence of cerebral edema, differences in acid–base status, or a lower rate of use of sedation as improved lung function permitted earlier removal from the ventilator. The available data are not sufficient to distinguish among these or other potential explanations.

The protocols were designed to minimize risks. During shock, physicians treated patients according to their usual practice. Because of concern that a conservative approach might worsen cardiovascular or renal function, diuretic administration was suspended until 12 hours after a fluid bolus or the reversal of shock, and prompt fluid administration was provided in the event of oliguria or ineffective circulation. Diuretic therapy was titrated on the basis of the patient's response, avoided in patients with worsening renal function, and limited to a daily maximum. To minimize the risk of excessive fluid therapy, protocol-mandated fluid administration in patients without shock was limited to three boluses per day and was withheld in patients without shock who had severe hypoxemia ($FiO_2 \geq 0.7$) or a cardiac index of at least 4.5 liters per minute per square meter of body-surface area.

Electrolyte levels were managed by the clinician. The conservative-strategy group had a higher partial pressure of arterial carbon dioxide, arterial pH, and bicarbonate level than did the liberal-strategy group. Although mean differences between the groups in the serum sodium, potassium, and bicarbonate levels were small, a higher percentage of patients in the conservative-strategy group had at least one potassium value between 2.5 and 3.0 mmol per liter, at least one sodium value of 150 mmol per liter or more, and at least one bicarbonate value of 40 mmol per liter or more. Hence, close monitoring of electrolyte levels is warranted during diuretic therapy.

Since we tested specific management strategies that used several variables and safeguards, we do not know whether the safety and benefit of the conservative protocol could be realized by using the simplified target of a zero fluid balance. Departures from the specific hemodynamic and ventilator protocols used in this trial may lead to clinical outcomes that differ from those observed in this study.

In conclusion, we found that use of a conservative fluid-management protocol with a lower central venous pressure or pulmonary-artery occlusion pressure target resulted in a major reduction in net fluid balance without an increase in adverse events, as compared with a liberal fluid-management protocol targeting higher intravascular filling pressures. Although we did not detect a difference in the mortality rate between the two approaches, the conservative strategy improved lung function and shortened the duration of mechanical ventilation and intensive care, without increasing nonpulmonary organ failures. These results support the use of a conservative strategy of fluid management in patients with acute lung injury.

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APPENDIX

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