Improved Outcome Based on Fluid Management in Critically Ill Patients Requiring Pulmonary Artery Catheterization

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Introduction

Theoretically and experimentally, fluid balance can affect the development, accumulation, and resolution of severe pulmonary edema (1-6). Even so, other concerns are often invoked as more important in the clinical setting, leading to fluid management strategies that could be counterproductive to the resolution of pulmonary edema. For instance, in hypotensive patients, clinicians often try to balance the potential benefits of intravascular volume expansion on cardiac and renal function against the potentially negative effect of causing or worsening pulmonary edema. Measuring the pulmonary capillary wedge pressure (WP) is usually a central feature in designing these approaches to patient care.

The relative benefits or disadvantages of any one strategy have never been tested prospectively. In a previous study (7), we reported that a strategy that emphasized intravascular volume restriction for hypotensive patients in severe pulmonary edema was still safe and well tolerated, despite "deviations" from conventional practice. The sample size, however, was too small to detect differences in outcome. Two other recent studies (8, 9), however, neither of which was designed to prospectively study the impact of fluid balance, nevertheless provide evidence that outcome in severe pulmonary edema can be affected by fluid management.

In the present study, we evaluated whether an alternative protocol to "routine" management would favorably affect the development or resolution of pulmonary edema per se (as the primary outcome variable) as well as other relevant outcome variables (to assess clinical significance). The main feature of this alternative approach was to use direct measurements of extravascular lung water (EVLW) instead of WP measurements to guide fluid management. These measurements were made possible by the development of the thermal-indocyanine green dye double-indicator dilution method as a bedside technique (10, 11). The data strongly suggest that alternatives to "routine" management that stress diuresis and fluid restriction in patients with pulmonary edema can affect the development or resolution of extravascular lung water (EVLW), as well as time on mechanical ventilation and time in the intensive care unit (ICU), in critically ill patients requiring pulmonary artery catheterization (PAC). PAC was performed on 101 patients. A total of 52 patients were randomized to an EVLW management group using a protocol based on bedside indicator-dilution measurements of EVLW. The other 49 patients were randomized to a wedge pressure (WP) management group in whom fluid management decisions were guided by WP measurements. A total of 89 patients had pulmonary edema (defined as EVLW > 7 ml/kg ideal body weight). Except for a clinically unimportant difference in mean age, the two groups were entirely comparable at baseline. The study groups were managed differently, as evidenced by cumulative input-output of 2,239 ± 3,695 ml (median = 1,600 ml) in the WP group versus 142 ± 3,632 ml (median = 754 ml) in the EVLW group (p = 0.001). EVLW decreased significantly, and ventilator-days and ICU days were significantly shorter only in patients from the EVLW group. No clinically significant adverse effect occurred as a result of following the EVLW group algorithm. Thus, a lower positive fluid balance, especially in patients with pulmonary edema regardless of cause, is associated with reduced EVLW, ventilator-days, and ICU days.

Conduct of the Study

Patients were recruited from June 14, 1987 to June 22, 1989. All patients admitted to the medical intensive care unit (ICU) requiring PAC were eligible for this study if the investigators were notified within 2 h of performing PAC. PAC was always performed for clinical reasons, not for this study alone. During the recruitment period, PAC was performed on 302 patients. As shown in the appendix, 201 patients were excluded for various reasons. Thus, the study group analyzed in this report consists of 101 critically ill patients.

After obtaining informed consent and for the purposes of randomization only, the patients were divided into two groups on the basis of the current chest radiograph (figure 1): one group with clear lung fields and the other with new, bilateral interstitial and/or alveolar infiltrates consistent with acute pulmonary edema. The latter group was also divided into two subgroups based on whether the initial WP was less than or greater than 18 mm Hg. The purpose of this prerandomization stratification was to increase the likelihood that equal numbers of patients with "low-pressure" pulmonary edema (the adult respiratory distress syndrome, ARDS) or "high-pressure" pulmonary edema (usually congestive heart failure [CHF] or intravascular volume overload) would be randomized to the two prospective management groups. The patients were then randomized to either an EVLW management or a WP management group.

Treatment in the EVLW management group was based on a specified algorithm that included serial EVLW measurements; no management decisions were actually made based on WP. In the WP management group, treatment proceeded without knowledge of the

SUMMARY

We performed a randomized, prospective trial to evaluate whether fluid management that emphasized diuresis and fluid restriction in patients with pulmonary edema could affect the development or resolution of extravascular lung water (EVLW), as well as time on mechanical ventilation and time in the intensive care unit (ICU), in critically ill patients requiring pulmonary artery catheterization (PAC). PAC was performed on 101 patients. A total of 52 patients were randomized to an EVLW management group using a protocol based on bedside indicator-dilution measurements of EVLW. The other 49 patients were randomized to a wedge pressure (WP) management group in whom fluid management decisions were guided by WP measurements. A total of 89 patients had pulmonary edema (defined as EVLW > 7 ml/kg ideal body weight). Except for a clinically unimportant difference in mean age, the two groups were entirely comparable at baseline. The study groups were managed differently, as evidenced by cumulative input-output of 2,239 ± 3,695 ml (median = 1,600 ml) in the WP group versus 142 ± 3,632 ml (median = 754 ml) in the EVLW group (p = 0.001). EVLW decreased significantly, and ventilator-days and ICU days were significantly shorter only in patients from the EVLW group. No clinically significant adverse effect occurred as a result of following the EVLW group algorithm. Thus, a lower positive fluid balance, especially in patients with pulmonary edema regardless of cause, is associated with reduced EVLW, ventilator-days, and ICU days.

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EVLW measurement itself, and the specified algorithm included serial WP measurements. Of the 101 study patients 89 had an EVLW > 7 ml/kg, the algorithm mandated, in some instances, therapies that differed significantly from "routine" practice. For instance, in hypotensive patients, intravascular volume expansion was restricted even if the WP was < 18 mm Hg, in contrast to patients in the WP management group.

Management of patients without pulmonary edema (although only 12 such patients were included in the study) could also be significantly different between the two management groups. For instance, if a patient in the EVLW management group had an EVLW < 7 ml/kg and was hypotensive or oliguric, intravascular volume expansion was provided until EVLW was > 7 ml/kg (unless WP became > 25 mm Hg or the alveolar-arterial oxygen pressure (aApo) gradient deteriorated without other apparent etiology). However, if a patient was hypotensive in the WP management group without radiographic pulmonary edema, volume resuscitation was provided (in addition to vasopressors) until WP reached 18 mm Hg, at which time intravenous vasopressors only were used.

Except for decisions about fluid management and the support of blood pressure with vasoactive medications (table 1), all other clinical decisions, including those concerning mechanical ventilation or cardioactive medications or transfer from the ICU were left to the team caring for the patient.

In both management groups, EVLW measurements were obtained, on average, every 6 h by one of a group of trained nurses. In the EVLW management group, the nurse obtaining the EVLW measurement was not involved in the patient's care and the measurement was kept from the physicians or nurses responsible for the patient's management. The EVLW measurements were obtained until the patient died or PAC was discontinued. The decision to discontinue PAC was again based entirely on the clinician's perception of whether continued PAC was useful.

At least twice each day, one of the investigators discussed treatment goals for each subject with the clinical team caring for the patient, as dictated by the protocol to which they were assigned. In only one case did the team ever refuse to follow the protocol. For purposes of analysis, this patient was still analyzed according to his originally randomized group. All fluid intake (including colloid, crystalloid, and blood products) and output (all sources, including dialysis losses) during the study were recorded. Fluid balance was simply obtained by subtracting inputs from outputs (or intake) and expressed as I–O measurements. Vital signs were recorded according to ICU routine (usually every hour in hypotensive patients); routine laboratory tests, including hemoglobin, hematocrit, serum creatinine, and blood urea nitrogen (BUN), were recorded at least on a daily basis. All vasoactive medications and diuretic therapy were recorded hourly. Invasive hemodynamic measurements were obtained with each EVLW measurement, including systemic blood pressure, right atrial pressure, pulmonary artery pressure, WP, and thermodilution cardiac output (CO). Changes in oxygenation were evaluated by recording arterial blood gas results each time they were obtained (as clinically indicated), along with the fraction of inspired oxygen (FiO2) and mechanical ventilator settings.

Each patient was followed for the duration of hospitalization. In addition to the patient's final disposition, the number of days the patient received mechanical ventilation, vasopressor, or inotropic support or was in the ICU was recorded.

This study was approved by the institution's human studies committee.

Measurement of Lung Water and Other Hemodynamic Parameters

The extravascular thermal volume was measured by the thermal-indocyanine green dye, double-indicator dilution method (10) using a commercially available computer (Model 9310; Edwards Laboratories, Santa Ana, CA). The value obtained was taken as equivalent to EVLW (10). Indocyanine green dye was pre-

### TABLE 1

**MANAGEMENT ALGORITHMS FOR PATIENTS WITH RADIOGRAPHIC PULMONARY EDEMA**

<table>
<thead>
<tr>
<th>EVLW Management Group (Known EVLW &gt; 7 ml/kg)</th>
<th>WP Management Group (Radiographic Pulmonary Edema)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypotensive</strong></td>
<td><strong>Normotensive</strong></td>
</tr>
<tr>
<td>Use vasopressors</td>
<td>Diurese†</td>
</tr>
<tr>
<td>Restrict intravascular volume expansion</td>
<td>Use vasodilators, as indicated (to improve cardiac output)</td>
</tr>
<tr>
<td>Measure EVLW, CPA every 6 h (all groups)</td>
<td></td>
</tr>
</tbody>
</table>

Definition of abbreviations: CPA = cardiopulmonary analysis: systemic blood pressure, right atrial and pulmonary artery pressures; pulmonary capillary wedge pressure (WP); cardiac output; EVLW = extravascular lung water.

† Goal is 750 ml net diuresis every 12 h; stop diuresis if EVLW < 7 ml/kg, serum creatinine increases > 0.5 mg/dl per day, or patient becomes hypotensive.

‡ Avoid normal saline, maximally concentrate all intravenous medications and use "keep vein open" rates when possible.

§ Add vasopressors for sudden, large decrease in blood pressure or failure to improve blood pressure after 250 to 500 ml fluid (but continue intravenous volume expansion).
pared every 8 h and stored in prepared syringes in an ice slush in a refrigerator. All injections were made by hand after rapid transfer of the syringe from the ice bath. A 1-ng test dose of indocyanine green dye was injected intravenously before the first measurement. In the absence of any allergic reaction, the EVLW measurement as obtained with a full 5-ml dose, and CO was determined simultaneously by the standard thermodilution technique. Five injections were made and the highest and lowest values discarded. The value recorded for EVLW and CO was the average of the remaining three measurements. The EVLW values were expressed in milliliters and ml/kg ideal body weight, based on the patient’s height. We used 7 ml/kg as the upper limit of normal (7).

All pressure measurements, including WP, were made with fluid-filled transducers, zeroed and mechanically calibrated at the midthoracic level. Zero resonance level and calibration were checked with each measurement. Pressures were recorded at least once per nursing shift (8 h) and read from waveforms made on a strip-chart recorder. The WP measurements were made at end expiration. No correction was made for levels of positive end-expiratory pressure (PEEP). All WP tracings were kept and reviewed by one of the investigators for accuracy at a later time.

**Estimation of Severity of Illness and Clinical Definitions**

Severity of illness was evaluated by using the APACHE II scoring system (12) and by summing the number of failed organ systems upon entry into the study (7).

Data were also analyzed for both hemodynamic and clinical subgroups. Most of our patients had sepsis syndrome, ARDS, or CHF. Definitions are provided in the Appendix; for sepsis syndrome and ARDS we used definitions already published by others (13). ARDS patients were a subgroup of patients with “low-pressure pulmonary edema” (defined as patients with EVLW > 7 ml/kg and a WP < 18 mm Hg). Others in this group did not meet all the critical criteria for ARDS. “High-pressure pulmonary edema” patients had EVLW > 7 ml/kg and a WP ≥ 18 mm Hg. Most of these patients had CHF. Others with high-pressure pulmonary edema had sepsis syndrome but did not meet all the criteria for ARDS (e.g., because the WP was not < 18 mm Hg).

**Statistical Considerations and Methods**

In deciding on study size, we used the standard deviation of EVLW measurements in our previous study and determined that, assuming an α error of 0.05, 80 to 100 patients would be required to ensure a study power of 0.7 to 0.8 to detect at least a 15% difference in the change in EVLW between groups. Thus, a difference in the change in EVLW, if any, was used as the primary outcome variable for this study.

We evaluated both ICU and hospital mortality as outcome variables. We used 48 h after ICU discharge as our definition of ICU survival. We reasoned that patients who died many weeks after ICU discharge often died for reasons unrelated to the original ICU admission. In contrast, patients who died shortly after ICU discharge may have been discharged for the purpose of terminal care on the general ward. We reviewed the charts of all patients who died in the hospital after ICU discharge and found that nine of 25 such patients died within 48 h, all for reasons related to their original need for ICU care. We counted these as ICU deaths. Only four additional patients died within the following week.

All baseline features, fluid balance (I-O), and all secondary outcome variables were analyzed statistically for the study group as a whole, unless otherwise indicated. Changes in EVLW were analyzed for all subgroups of the two management groups (WP < 18 mm Hg, WP ≥ 18 mm Hg, ARDS, and CHF). However, only in the subgroups with an initial EVLW > 7 ml/kg (with pulmonary edema) could one reasonably expect EVLW to decrease as a result of following either protocol.

Because fluid balance (I-O), EVLW, and WP measurements could not be made strictly at the same time in every patient studied, we divided each patient’s I-O into 6-h periods from the time of entry. The I-O, EVLW, and WP measurements closest to the relevant 6-h interval were used for data analysis. When a measurement was not obtained during a particular 6-h period, we interpolated the values obtained in the preceding and subsequent periods (about 8% of all measurements).

Data are presented as the mean ± SD for normally distributed data. The median is also given for nonnormally distributed data. Statistical analysis was performed with the SAS statistical software system (SAS Institute, Cary, NC) for the IBM PC. Statistical analysis included chi-square or Fisher’s exact test analysis for dichotomous variables (the FREQ procedure). The Wilcoxon test was used for paired comparisons of the first and last measurements obtained during each patient’s study period (UNIVARIATE procedure), or for unpaired comparisons of measurements obtained in each management group at a particular time (e.g., at baseline) (NPARIWAY procedure). Repeated-measures analysis of variance (GLM procedure) was performed as appropriate for more complex paired comparisons. Because nonnormal distributions can significantly affect the interpretation of the GLM procedure, we also evaluated the impact that seven outliers, which were principally responsible for the nonnormal distribution, had on the statistical results. We found that none of our statistical inferences were changed when the outliers were deleted (indeed, in each case, they were actually strengthened). Therefore, we believed we were justified in using the GLM procedure for the group as a whole.

The number of days that patients required mechanical ventilation, were in the ICU, or were in the hospital was also analyzed by the GLM procedure, we also evaluated the impact that seven outliers, which were principally responsible for the nonnormal distribution, had on the statistical results. We found that none of our statistical inferences were changed when the outliers were deleted (indeed, in each case, they were actually strengthened). Therefore, we believed we were justified in using the GLM procedure for the group as a whole.

Results

**Demographic and Baseline Data**

Baseline characteristics for the two management groups are compared at the time of study entry in table 2. Except for a slightly lower age in the EVLW management group, randomization was effective and the two groups were not different statistically. Importantly, all the indices of severity of illness were similar for the two management groups.

**Baseline hemodynamic, EVLW, and laboratory data for the two management groups are shown in table 3. Once again, the two groups are entirely comparable at the time of randomization into the study.**

Among the 101 patients who were randomized, 12 patients entered the study with an initial EVLW < 7 ml/kg. These patients were distributed equally between the two management groups. Their initial WP ranged from 11 to 30 mm Hg, and clinical diagnoses included sepsis syndrome (5) and CHF (4).

Of the 89 other patients with an initial EVLW > 7 ml/kg, 50 had an initial WP ≤ 18 mm Hg (mean ± SD = 12 ± 3 mm Hg). These patients also were equally distributed between the two management groups (24 in the EVLW management group and 26 in the WP management group). As expected, most such patients carried a clinical diagnosis of ARDS (24) and/or sepsis syndrome (25); 10 patients had CHF.

A total of 39 patients had an initial
ARDS or sepsis syndrome) than in those patients with an initial WP less than 7 mm Hg (n = 50) (most of whom had chronic heart failure or intravascular volume overload). The mean initial EVLW was 18 mm Hg (mean ± SD = 24 ± 6 mm Hg). Of these patients 22 were in the EVLW management group, and 17 were in the WP management group. Of the 39 patients, 24 carried a clinical diagnosis of CHF, 13 had a clinical diagnosis of ARDS, and 10 had a clinical diagnosis of sepsis. For the patients with an initial EVLW > 7 ml/kg and initial WP > 18 mm Hg for or for those patients with a clinical diagnosis of CHF, the overall I-O was similar between management groups (as expected, because among normotensive patients with pulmonary edema, fluid management algorithms did not differ significantly between the two management groups; see table 1).

Despite the relative fluid “restriction” in the patients from the EVLW management group as a whole, the number of patients requiring vasopressors or inotropic support or the number of days these patients were on such drugs was not different compared with patients from the WP management group (table 5). Consistent with the differences in I-O, a small but statistically significant increase in the mean serum creatinine and blood urea nitrogen occurred in patients from the EVLW management group. The mean increases in serum creatinine and BUN were 0.4 ± 1.0 mg/dl (p < 0.02) and 13 ± 27 mg/dl (p < 0.0007), respectively. Changes in both creatinine (0.2 ± 0.9 mg/dl) and BUN (6 ± 18 mg/dl) were not significant in the patients from the WP management group.

**Effect on Pulmonary Edema**

The initial EVLW was not significantly different between the two management groups (table 3). Among the 89 patients with an initial EVLW > 7 ml/kg, EVLW was significantly less at each time point after 24 h in patients from the EVLW management group (table 5). The patients in the EVLW management group remained in the study for a slightly but statistically longer time than did patients in the WP management group (median of 60 versus 47 h, respectively).

**Effect on Fluid Balance**

The principal evidence that the groups were managed differently as a whole is the difference in cumulative I-O, which was less in the patients from the EVLW management group than in the patients from the WP management group (median of 60 versus 47 h, respectively).

**Effect on Hemodynamics and Oxygenation**

Consistent with the differences in fluid balance and changes in creatinine, the WP fell slightly but significantly over the

\[ EVLW > 7 \text{ml/kg} \text{ and an initial WP } > 18 \text{ mm Hg (mean } \pm \text{ SD } = 24 \pm 6 \text{ mm Hg). Of these patients 22 were in the EVLW management group, and 17 were in the WP management group. Of the 39 patients, 24 carried a clinical diagnosis of CHF or intravascular volume overload, and 14 had a diagnosis of sepsis syndrome. Consistent with previous findings by us and others (7, 14), the mean initial EVLW of patients with an initial EVLW > 7 ml/kg (n = 89) tended to be greater in those patients with an initial WP < 18 mm Hg (n = 50) (most of whom had ARDS or sepsis syndrome) than in those patients with an initial WP > 18 mm Hg (n = 39): 1,326 ± 774 ml versus 1,031 ± 496 ml, respectively (p = 0.10). The patients in the EVLW management group remained in the study for a slightly but statistically longer time than did patients in the WP management group (median of 60 versus 47 h, respectively).**
course of the study in patients from the EVLW management group as a whole (mean change = $-2.5 \pm 8 \text{ mm Hg}$, $p = 0.03$) but not in patients from the WP management group (mean change = $-0.5 \pm 7 \text{ mm Hg}$). This decrease in WP in patients from the EVLW management group was actually accompanied by a small but statistically significant increase in cardiac output (mean change = $0.4 \pm 2.2 \text{ L/min}$, $p = 0.045$), whereas there was no significant change in the patients from the WP management group.

Oxygenation for the patients who were supported by mechanical ventilation, as evaluated by the arterial/alveolar $P_0_2$ ratio, did not change in a statistically significant manner in either group. The trend (first versus last measurement), however, was favorable for patients from the EVLW management group (0.33 ± 0.17 to 0.38 ± 0.16, $p = 0.12$) and was inapparent in the other group (0.29 ± 0.15 to 0.29 ± 0.13, $p = 0.76$).

**Effect on Other Outcome Variables**

Patients from the EVLW management group required mechanical ventilation and were in the ICU for a significantly shorter period of time than patients from the WP management group (figure 5). The median time on mechanical ventilation for patients from the EVLW management group was only 9 days compared with 22 days for patients from the WP management group ($p = 0.047$). The median ICU stay was only 7 days for patients from the EVLW management group versus 16 days for patients from the WP management group ($p = 0.05$, figure 6).

There was no significant difference between the two management groups in duration of mechanical ventilatory support or in ICU stay for patients with a clinical diagnosis of CHF or volume overload. For patients with a clinical diagnosis of ARDS, the median duration of mechanical ventilation was about 9 days for patients from the EVLW management group versus 28 days for patients from the WP management group ($p = 0.084$). For duration of ICU stay, patients with ARDS had similar lengths of stay in the two management groups.

The overall ICU mortality for both
Theoretically, fluid management should have a significant impact on pulmonary edema formation and resolution (1). As a model for the forces governing transvascular fluid flux, the familiar Starling equation predicts that any measure that would reduce pulmonary microvascular hydrostatic pressures should reduce pulmonary edema accumulation. Experimentally, there is little question that fluid management affects the development and resolution of pulmonary edema, whether the principal cause is increased microvascular hydrostatic pressures (CHF) or increased vascular permeability (ARDS) (2-6). Indeed, when vascular permeability is abnormal, the accumulation of extravascular water in the lung is exquisitely sensitive to hydrostatic pressure (4, 16-18). Based on such data, Wood and Prewitt (19) were among the first to articulate a strategy for the cardiovascular management of patients with severe pulmonary edema, emphasizing that one should try to achieve “the lowest pulmonary wedge pressure consistent with an adequate cardiac output.” Humphrey and colleagues (9) reaffirmed this position in a recent retrospective analysis.

Despite this theoretical and experimental foundation, clinicians have often been reluctant to employ diuresis or fluid restriction for patients in pulmonary edema, especially those with noncardiogenic pulmonary edema, for several reasons. (1) Many such patients are in shock, and diuresis or fluid restriction might worsen shock, whereas intravascular volume expansion might improve cardiac function. (2) Survival has been linked to increased peripheral oxygen delivery (largely related to cardiac function (20, 21)) but not to lung water accumulation or pulmonary function (22). (3) Fluid restriction or diuresis might worsen renal function, with its independent negative impact on outcome (23, 24). (4) A bias exists that, all other variables being equal, it is “better” (that is, the risk-benefit ratio is more favorable) to increase cardiac output by intravascular volume expansion than with inotropic or vasoactive drugs.

As a result, fluid management, as commonly practiced in many patients with ARDS, often represents a compromise between the desire to maintain cardiac function while minimizing the hydrostatic forces favoring fluid extravasation in the lung. Specific guidelines are often lacking in the literature, but we have observed that many physicians attempt to keep the WP between 14 and 18 mm Hg. The justification for these specific pressure end points is obscure. Perhaps the observation that cardiac output is frequently optimized when the wedge pressure reaches this level in patients with acute myocardial infarction has been instrumental in forming this opinion (25). Regardless, because WP in this range seems to be a commonly accepted benchmark and because a WP of 18 mm Hg is a commonly used cutoff for the diagnosis of ARDS (13, 26-28), we used a WP of 18 mm Hg in the WP management algorithm (table 1) and in some of our statistical analyses.

Nevertheless, alternative strategies might be reasonable and testable. For instance, in an early study of only 12 patients with ARDS, Bone found that 10 responded to diuretics or dialysis with improvements in oxygenation and respiratory system compliance (29). Costello and coworkers (15), in a preliminary report, described a reduction in weight, mean level of PEEP required for adequate oxygenation, final WP, and mortality in 15 ARDS patients undergoing aggressive diuresis compared with 10 patients undergoing conventional fluid management. In addition, Simmons and colleagues (8) also showed that survival in patients with ARDS was related to negative fluid balance during their hospitalization, although it is uncertain from their data whether the groups were comparable at baseline. And importantly, in our own previous study (7), diuresis or fluid restriction in such patients was not...
associated with adverse side effects, such as worsening renal function, hypotension, or need for vasopressor agents. This lack of a harmful effect was verified again in the current study (table 5). Finally, several studies have suggested that vasoactive agents can be used to maintain blood pressure or cardiac output in patients with sepsis or after moderate volume depletion in patients with severe pulmonary edema without worsening end-organ function (30–33).

**Technical Issues**

For a variety of reasons, about two-thirds of all patients receiving PAC were excluded from entering this study (Appendix). None of the reasons suggest that a systematic bias occurred in patient recruitment, however, and the ICU and hospital mortality were similar for the experimental group and a comparable group of excluded patients (Appendix). The only significantly different variable between the management groups, among 27 examined baseline features, was a slightly lower mean age in patients from the EVLW management group. We doubt that this 8-yr difference has any biologic or clinical significance, nor do we believe that it accounts for the differences we observed in EVLW, ventilator-days, or ICU days.

Since this study involved the impact of a fluid management algorithm, we used fluid balance (I-O) as the principal evidence for differences in management between the two patient randomization groups. Since pulmonary edema is often the major physiologic abnormality of concern (either actual or impending), we chose a direct, bedside (34) measure of pulmonary edema (the thermal indocyanine green dye estimate of EVLW) as the primary outcome variable. Although the thermal indocyanine green dye technique is quite accurate when compared with the classic gravimetric measurement of EVLW (11), it is also clear that technical considerations, such as catheter positioning, regional heterogeneity in pulmonary perfusion, or changes in PEEP, can affect accuracy (35). In this regard, it is useful to recall that technical difficulties are also common and important in WP measurement and interpretation (36–39). EVLW measurements also have the virtue of being immediately available as often as needed during the day. In contrast, radiographic evaluation is not immediately available, is costly and cumbersome to repeat more than once per day, and correlates poorly with EVLW (6), except obviously at the extremes or in the long term.

To judge clinical significance, we chose to review several other outcome variables: ventilator-days, ICU days, and hospital days. Ventilator-days should be the most relevant variable, as increased development or hastened resolution of EVLW should translate into less need for mechanical ventilatory support. In this study, the decrease in ventilator-days was also accompanied by a decrease in ICU length of stay. Hospital length of stay, as well as mortality, is also important, of course, but is clearly affected to an even greater extent than ventilator-days or ICU days by factors other than fluid management or a change in EVLW.

Although the study group was not homogeneous with regard to underlying cause for pulmonary edema (for instance, either ARDS or CHF), the Starling equation model of pulmonary edema, as already noted, predicts a favorable effect on EVLW when fluid balance is used to lower the WP, regardless of the state of the membrane permeability. Thus, once pulmonary edema has occurred, physiologic principles related to resolving or slowing the accumulation of EVLW by altering fluid balance per se are similar in ARDS and CHF. This does not mean, of course, that the impact is the same in both patient populations. Interestingly, in this study, fluid balance in the two management groups was most different in patients with ARDS, as was duration of ventilatory support.

Although the data in figure 2 clearly show that fluid management in fact differed between the two management groups (and this is the main purpose of presenting these data), fluid balance per se cannot be expected to have any direct correlation with changes in EVLW. Clearly, net I-O represents the fluid balance from all body compartments, not only the lung. There is no a priori reason, for instance, why a given amount of diuresis in a patient with peripheral edema (indicating total body salt and water overload) should lead to the same change in EVLW as in a patient without peripheral edema. Similarly, in the injured lung, it is not clear how changes in EVLW would follow I-O changes.

**Clinical Impact**

Although mortality was not different between the two management groups, the study size was too small (by design) to detect such a difference reliably. Although the trend in mortality was favorable for patients from the EVLW management group, a much larger study (by a factor of 3) would be necessary to avoid a Type II form of statistical error on this point.

The beneficial clinical outcome associated with fluid management in patients from the EVLW management group (reduced ventilator and ICU days) might have several causes: hastened resolution of EVLW, decreased gut edema with reduced bacterial translocation, or other unknown reasons. Improved resolution of EVLW might reduce ventilator-days, thereby reducing the risks of infection, barotrauma, and O₂ toxicity associated with prolonged mechanical ventilatory support. The changes in EVLW in the patients from this group with pulmonary edema (figures 3 and 4), although statistically significant, may seem small and therefore unlikely to have been biologically important. This observation could be misleading. If 500 ml is an approximate upper limit for normal EVLW content (about 7 ml/kg) (4), then a change from, say, 1,000 to 900 ml really represents a 20% change toward the normal state. Furthermore, the clinical consequences of an increased EVLW may not be linearly related to the absolute value for EVLW but related to some threshold value instead. Indeed this seems likely, since gas exchange does not deteriorate until EVLW approximately doubles (40). Therefore, relatively small differences in EVLW, between 750 and 1,500 ml, for instance, may have greater clinical impact than similar changes at values for EVLW above or below this range.

Although no unexpected or clinically significant deterioration in cardiovascular or renal function occurred in patients in the EVLW management group compared with the patients in the WP management group, we underscore that we are not recommending fluid restriction or diuresis for frankly hypervolemic patients. Indeed, the average initial WP even in the patients with a WP < 18 mm Hg (which included the 24 strictly defined ARDS patients in the EVLW management group) was still 12 mm Hg.

Hemodynamic monitoring in critically ill patients continues to be a subject of considerable controversy (41–43). A call has even been made for a moratorium on invasive monitoring until a randomized, prospective trial can be designed and completed (42). We doubt that such a trial is really feasible, as it is our impression that most physicians who are involved in the care of critically ill patients on a daily basis believe such
monitoring to be crucially important to their decision making. Nevertheless, this does not mean that the procedure is used optimally.

The current study, although not strictly speaking a randomized study of hemodynamic monitoring per se, may shed some light on this issue. In our view, the results of this study suggest that the real benefit of hemodynamic monitoring may be to avoid the complications of therapy (e.g., allowing the WP to fall below 5 to 10 mm Hg with a fall in cardiac output or blood pressure or to rise above 20 to 25 mm Hg with an increase in EVLW). This goal seems both reasonable and achievable given the numerous sources of artefact that complicate a more precise measurement of the wedge pressure in the clinical setting (36–39). With wedge pressures of intermediate value, which is the most common finding (44), our data suggest that for critically ill patients requiring PAC, especially if they suffer from severe pulmonary edema, careful attention to fluid balance, perhaps with the additional information provided by EVLW monitoring, may significantly shorten ventilator and ICU days.

**Reasons for and Outcome of Patients Excluded from Study Entry**

Of the 302 patients who underwent pulmonary artery catheterization over the approximately 2-yr period of patient recruitment, 201 were excluded for the following reasons (number of patients in parentheses):

1. **Patient-related technical problems** (69)
   - a. Arterial catheter contraindicated (34)
   - b. Not notified within 2 h of placement of the PAC (24)
   - c. PAC performed for preoperative assessment only (11)

2. **Patient-unrelated technical problems** (42)
   - a. Investigative staff unavailable (23)
   - b. Equipment malfunction or supply shortage (19)

3. **Technique unreliable** (38)
   - a. Focal infiltrate (in which the thermal dye EVLW technique is often inaccurate) (30)
   - b. PAC performed for evaluation of hemodynamics after pulmonary embolism (5)
   - c. Documented severe mitral regurgitation (3)

4. **Refused** (28)
   - a. Patient (25)
   - b. Attending physician (3)

5. **Other** (14)

6. **Contraindicated** (10)
   - a. History of allergy to iodinated dyes (7)
   - b. PAC performed in a pregnant or lactating patient (3)

Of these 201 patients, only patients excluded for reasons 2 and 4 might legitimately have been included in this study. However, the ICU and hospital mortality of these patients (33 and 53%, respectively) was not significantly different from those in the study group as a whole (41 and 60%; see Results).

**Definitions**

**Criteria used to define organ system failure** (all abnormalities had to be newly present): (1) renal failure: serum creatinine > 3 mg/dl; (2) respiratory failure: PaO₂ < 50 mm Hg (on room air); (3) hepatic failure or digestive failure (must include at least two): macroscopic gastrointestinal bleeding, bilirubin > 10 mg/dl, alkaline phosphatase > 200 IU/L, amylase > 700 units; (4) hematologic failure (any one): hematocrit < 30%, white cell count < 2,000 or > 30,000 cells/ml, platelets < 80,000/ml; (5) cardiovascular failure (must include at least two): heart rate > 140 beats/min, systolic blood pressure < 90 mm Hg, any arrhythmia, or myocardial infarction < 3 days old; (6) sepsis syndrome; (7) neurologic failure: Glasgow coma scale < 10.

**Criteria used to define the sepsis syndrome** (9). Must include two of the following findings: (1) temperature > 39°C or < 36°C; (2) white blood cell count > 3,000 or < 12,000 cells/ml; or with (3) > 10% immature granulocytes; (4) positive blood culture of a commonly accepted pathogen; (5) localized abscess plus unexplained metabolic acidosis; (6) unexplained hypotension (systolic blood pressure < 90 mm Hg) for more than 2 h; (7) systemic vascular resistance < 800 dyne/s/cm².

**Definition of adult respiratory distress syndrome** (9). At the time of onset, each patient fulfilled all four criteria for ARDS: (I) severe refractory hypoxemia (PaO₂/FIO₂ < 150); (2) diffuse radiographic pulmonary infiltrates involving all lung fields; (3) PCWP < 18 mm Hg; and (4) no other etiology to explain 1 to 3, or the presence of a recent medical history of ARDS-associated risk factor(s), including sepsis syndrome, witnessed aspiration, drug overdose, overwhelming pneumonia, prolonged hypotension, pancreatitis, disseminated intravascular coagulation, multiple emergency transfusions, or multiple major fractures.

**Definition of congestive heart failure.** A clinical diagnosis made with any combination of the following: history (in medical record) of CHF or cardiomyopathy, presence of a third heart sound (S₃), objective evidence of poor inotropy (e.g., from PAC, radionuclide scintigraphy, echocardiography, or angiography), and large radiographic cardiac silhouette (in the absence of suspected pericardial disease).

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**References**

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