

A Prospective Study of Lung Water Measurements during Patient Management in an Intensive Care Unit^{1,2}

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Introduction

One rationale for pulmonary artery catheterization (PAC) in critically ill patients is that the hemodynamic information obtained often differs from that predicted by clinical evaluation alone (1, 2). Even so, no study has ever explicitly shown that if hemodynamic parameters are used as end points for therapy, patient outcome is favorably altered (3). Thus, it is quite possible that PAC is overused (3).

Pulmonary artery catheterization is often performed to obtain pulmonary artery occlusion or wedge pressure (Ppaw) measurements (4-6), to guide fluid resuscitation during shock or diuretic therapy during pulmonary edema. However, in many critically ill patients, Ppaw interpretation is difficult because of numerous potential artifacts in the measurements (4-7). In such cases, treatment based on erroneous measurements could be hazardous.

An alternative approach might incorporate direct measurements of the extravascular water content of the lung as a therapeutic end point. Experimental and clinical studies (8-11) have shown that the thermal green dye, double-indicator dilution technique of measuring extravascular thermal volume (ETV) accurately reflects the quantity of extravascular lung water (EVLW). However, the technique has never been tested as an adjunct or alternative to the Ppaw measurement. Accordingly, we designed a prospective randomized study to evaluate whether EVLW could be safely used as an end point for therapeutic intervention when PAC was performed for the diagnosis or management of hypotension or pulmonary edema. We compared the results of therapy in patients managed with a protocol based on EVLW measurements with those of a control group of patients managed conventionally without knowledge of the EVLW value.

Methods

Conduct of the Study

Study eligibility was defined by hypotension

SUMMARY We prospectively evaluated a protocol that included extravascular thermal volume (ETV) as a measure of extravascular lung water (EVLW) instead of pulmonary artery wedge pressure (Ppaw) measurements to guide the hemodynamic management of 48 critically ill patients. Patients were randomized to either a protocol management (PM), or to a routine management (RM) group. In the RM group, EVLW measurements were unknown to the primary care physicians. The 2 groups were similar with respect to age, gender, and severity of illness. In patients with initially high EVLW, EVLW fell to a greater extent in PM than in RM patients (18 ± 5 versus $4 \pm 8\%$ decrease, $p < 0.05$). This difference was even greater in patients with heart failure. No adverse effects on oxygenation or renal function occurred in following the protocol. Mortality for the groups as a whole was similar, but was significantly better ($p < 0.05$) for PM patients with initially high EVLW and normal Ppaw (predominantly patients with sepsis or the adult respiratory distress syndrome). For both groups, patients with an initial EVLW > 14 ml/kg had a significantly greater mortality than did those with a lesser amount of EVLW: 13 of 15 (87%) versus 13 of 32 (41%), $p < 0.05$. We conclude that management based on a protocol using EVLW measurements is safe, may hasten the resolution of pulmonary edema, and may lead to improved outcome in some critically ill patients.

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(systolic blood pressure < 90 mm HG) prior to PAC, or after PAC if for any reason a Ppaw > 14 mm Hg was found. These criteria were arbitrarily selected since in our ICU in appropriate clinical circumstances, these values often represent threshold values for initiating therapy to either increase or decrease intravascular volume. Patients with an allergy to iodine-containing contrast material were excluded. In all cases, the attending and/or intensive care unit staff decided if PAC was clinically indicated. Then, after obtaining informed consent, patients were randomized to either an EVLW protocol management (PM) or a routine management (RM) group. Treatment of PM patients was based on a specified algorithm that included EVLW measurements (figure 1). Treatment proceeded without regard to EVLW measurements in the RM group. The EVLW protocol mandated, in some instances, therapies that differed significantly from routine practices in our ICU. For example, if EVLW was normal, intravascular volume expansion was continued for hypotensive patients, even if the Ppaw was ≥ 18 mm Hg. On the other hand, if EVLW was abnormally elevated, intravascular volume expansion was restricted in hypotensive patients, even if the Ppaw was < 18 mm Hg. Because of such departures from "conventional" or routine management, this initial study was specifically designed to exclude an adverse outcome caused by following the management protocol (see statistical considerations, below).

In both groups, EVLW measurements were obtained on average every 6 to 8 h by one of a group of trained nurses. In the RM 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 for 72 h (or less, if the clinical indication for PAC was no longer present, or if the patient died).

Each day, one of the investigators documented adherence to the EVLW treatment protocol in PM patients, and evaluated whether any adverse outcome had occurred because of the prescribed management. A physician not directly involved in the study was empowered to withdraw a patient from the EVLW protocol if in his judgment clinical progress was being adversely affected. This occurred only once among all 48 study patients. All fluid intake (including colloid, crystalloid, and blood products) and output (all sources, including dialysis losses) during the study were recorded. Vital signs were recorded according to ICU routine (usually every hour in hypotensive patients); routine laboratory tests, including hemoglobin/hematocrit and creatinine, were recorded at least on a daily

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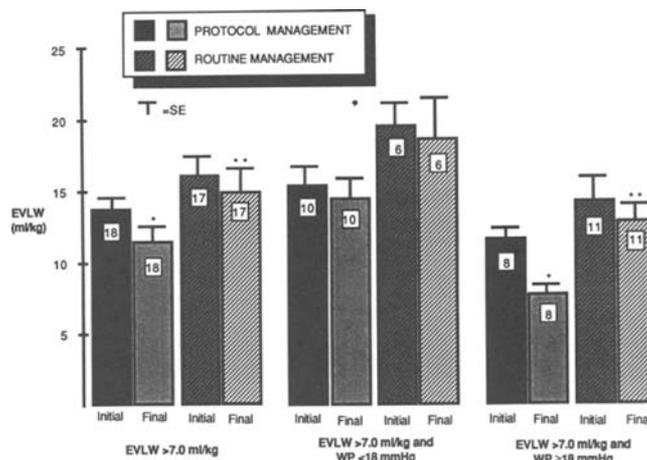
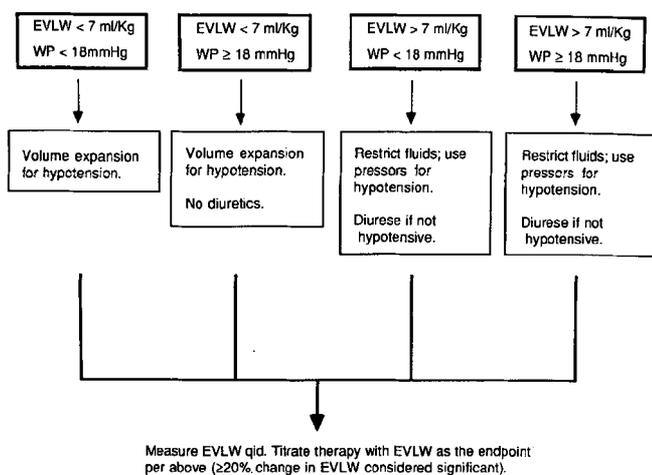


Fig. 1(left). Extravascular lung water (EVLW) measurement based protocol (WP = wedge pressure). See METHODS for discussion of how protocol differed from routine management. Fig. 2(right). Resolution of extravascular lung water (EVLW) during study period among various groups. The decrease in EVLW is greater in protocol-managed than in routinely managed patients, especially in patients where EVLW and WP (wedge pressure) were both elevated initially. Single asterisks = $p < 0.01$; double asterisks = $p < 0.05$.

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, Ppaw, and cardiac output (CO). For study purposes, changes in oxygenation were evaluated every 24 h by noting any alteration in inspired oxygen concentration ($F_{I_{O_2}}$) or positive end-expiratory pressure (PEEP) required to maintain the $P_{a_{O_2}} > 60$ mm Hg.

Each patient was followed for the duration of his hospitalization. In addition to the patient's final disposition, the number of days the patient received mechanical ventilation and supplemental oxygen were recorded.

This study was approved by the institution's Human Studies Committee.

Measurement of Lung Water and Other Hemodynamic Parameters

Extravascular thermal volume was measured by the thermal indocyanine green dye, double-indicator dilution method (8), using a commercially available computer (Model 9310; Edwards Laboratories, Santa Ana, CA). The value obtained was taken as equivalent to EVLW (8). Indocyanine green dye injectate was prepared every 8 h and stored at 4° C on ice in the dark. All injections were made by hand after rapid transfer of the syringe from the ice bath. A 1-mg test dose of indocyanine green dye was injected intravenously prior to the first measurement. In the absence of any allergic reaction, the EVLW measurement was obtained with a full 10-mg dose, and CO was determined simultaneously by the standard thermodilution technique. The value recorded for EVLW and CO was the average of at least 3 measurements that varied < 20%. No more than 5 measurements were made at one time. The EVLW values were expressed in milliliters per kilogram. We used 7 ml/kg as the upper limit of normal (11).

All pressure measurements, including Ppaw, were made with fluid-filled transducers, zeroed and mechanically calibrated at the midthoracic level. Zero reference level and calibration were checked at least once per nursing shift (8 h) or when the patient's position changed. Pressures were recorded and read from wave forms made on a strip chart recorder. The Ppaw measurements were made at end-expiration. No correction was made for levels of positive end-expiratory pressure. All Ppaw tracings were kept and reviewed by one of the investigators for accuracy at a later time.

Chest Radiographs

All chest radiographs were obtained whenever possible with patients in the semierect position, using routine mobile unit radiography. Radiographs were interpreted by one of the investigators (DA) without knowledge of the patients' randomization or EVLW measurement. The radiographs were graded on a four-point scale: 0 = no acute infiltrates to suggest an increased EVLW, 1 = pulmonary vascular redistribution and/or mild diffuse interstitial infiltrates, 2 = moderate diffuse in-

terstitial infiltrate, 3 = diffuse interstitial and focal alveolar infiltrate, and 4 = diffuse alveolar infiltrate.

Estimation of Severity of Illness

Severity of illness (which might affect outcome independent of any hemodynamic management protocol) was evaluated by summing the number of failed organ systems upon entry to the study, and by determining the patient's health status prior to ICU admission. Criteria used to define organ system failure are given in table 1. Prior health status was graded on a four-point scale; 1 = no impairment, 2 = mild limitation of activity, 3 = severe restriction of activity, and 4 = bedridden or institutionalized. Both parameters have been shown to be of prognostic value in ICU patients (12-15).

Statistical Considerations and Methods

In deciding on study size, we estimated that 60% of patients would deteriorate regardless of therapy (including the protocol) (12, 13). A sample size, then, of 50 patients had a power of 0.72 at the $p = 0.05$ alpha level to detect at least a 10% difference in the mean change

TABLE 1
CRITERIA USED TO DEFINE ORGAN-SYSTEM FAILURE*

Renal failure: creatinine > 3 mg/dl
Respiratory failure: $P_{a_{O_2}} < 50$ mm Hg (room air)
Hepatic or digestive failure (must include at least 2): macroscopic GI bleeding, bilirubin > 10 mg/dl, alkaline phosphatase > 200 IU/L, amylase > 700 units
Hematologic failure (must include at least 1): hematocrit < 30%, white cell count < 2,000 or > 30,000 cells/ml, platelets < 80,000/ml
Cardiovascular failure (must include at least 2): heart rate > 140 beats/min, systolic blood pressure < 80 mm Hg, any arrhythmia or myocardial infarction < 3 days old
Sepsis (must include at least 1): positive blood culture, proved abscess, temperature > 39° C for 3 consecutive days
Neurologic failure: Glasgow coma scale < 10

* All abnormalities had to be newly present.

in F_{iO_2} (from admission to the ICU to the end of the study period) between the PM and RM groups.

Data are presented as the mean \pm SEM. Statistical analysis included chi-square or Fisher's exact test analyses for dichotomous variables, and paired or unpaired t-tests or analysis-of-variance techniques, as appropriate, for continuous variables. Correlations between variables were obtained by standard least-squares linear regression methods. Mortality and the number of days receiving mechanical ventilation were analyzed by life table methods using a Cox multivariate analysis (16) that took into account the influence of age, prior health status, number of failed organ systems, and the presence of hypotension on admission to the ICU on mortality. Statistical analysis was performed with the SAS statistical software system (SAS Institute, Cary, NC) using the facilities of the Washington University Biomedical Computing Laboratory.

Results

Patient Demographics

Forty-seven patients were entered into the study, 25 into the EVLW protocol group (PM) and 23 into the nonprotocol, i.e., routinely managed group (RM). One patient was admitted to the study on 2 different occasions and was randomized once to each management group. For purposes of mortality statistics, however, she is considered as part of her first randomization group (RM). A total of 351 EVLW measurements were made over 99 patient-days. The 2 groups (PM and RM) were not significantly different with respect to age, gender, prior health status, or number of failed organ systems (table 2). The most common indication for PAC was hypotension (73% of all patients) (table 2). The number of patients who were hypotensive on admission was similar between the 2 groups: 17 of 25 (68%) in the PM group compared with 18 of 23 (63%) in the RM group. The distribu-

tion of underlying illnesses was also similar for both groups.

Four hemodynamic subsets based on the initial Ppaw and EVLW measurement were defined. The distribution of patients into these subsets was similar for both PM and RM groups (table 3). For both groups, patients with an initially elevated EVLW, but a Ppaw $<$ 18 mm Hg, were more likely to have clinical diagnoses of sepsis or the adult respiratory distress syndrome (9 of 16) than patients in whom both parameters (EVLW and Ppaw) were initially elevated (4 of 19) ($p <$ 0.05). The converse was true for the diagnosis of congestive heart failure (4 of 16 versus 12 of 19) ($p <$ 0.05).

On admission, approximately three quarters of patients in each group had an abnormally high EVLW ($>$ 7.0 ml/kg). In this subset, the initial EVLW was not significantly different between RM and PM groups (16.1 ± 1.9 versus 13.7 ± 1.2 ml/kg, $p =$ NS) (figure 2). Interestingly, patients with EVLW $>$ 7 ml/kg but a Ppaw $<$ 18 mm Hg from both groups together (average Ppaw of 11.7 ± 1.1 mm Hg) had significantly greater elevations of EVLW on entry into the study (16.9 ± 1.6 ml/kg, $n = 16$) than did those with both elevated EVLW and

TABLE 3

DISTRIBUTION OF PATIENTS INTO HEMODYNAMIC SUBSETS

Subset	Group	
	Protocol Management (n = 25)	Routine Management (n = 23)
EVLW \leq 7 ml/kg, Ppaw $<$ 18 mmHg	4	4
EVLW \leq 7 ml/kg, Ppaw \geq 18 mmHg	3	2
EVLW $>$ 7 ml/kg, Ppaw $<$ 18 mmHg	10	6
EVLW $>$ 7 ml/kg, Ppaw \geq 18 mmHg	8	11
EVLW \leq 7 ml/kg	7	6
EVLW $>$ 7 ml/kg	18	17

Definition of abbreviations: EVLW = extravascular lung water; Ppaw = pulmonary artery wedge pressure.

Ppaw (13.1 ± 1.4 ml/kg, $n = 19$) ($p <$ 0.05) (average Ppaw of 27.0 ± 2.5 mm Hg).

Radiographic and Hemodynamic Correlations

The correlation of the chest radiographic score with EVLW measurements is shown in figure 3. Although 125 chest radiographs were obtained, only 85 were obtained within 4 h of an EVLW measurement. Our analysis, therefore, is limited to this subgroup. The lack of correlation between EVLW and chest radiographic interpretation is obvious from figure 3. Therefore, we also separated the radiographs into 2 groups: clearly "normal" (radiographic score = 0) and all other radiographs (scores 1 to 4) and correlated them with a dichotomous analysis of EVLW (i.e., values greater or less than 7 ml/kg). By this analysis all radiographs were concordant with the EVLW measurement in 48% of the patients (22 of 46), and all were discordant in 26% (12 of 46). In 76% (35 of 46), at least 1 radiographic interpretation was concordant with an EVLW measurement.

As would be expected for this diverse group of patients with multiple etiologies for pulmonary edema, the correlation between EVLW and Ppaw measurements ($n = 290$) was poor (coefficient of determination = 0.026).

At the time of the first EVLW measurement, CO was similar for both groups (6.6 ± 3.0 versus 5.7 ± 2.5 L/min, $p =$ NS, PM group versus RM group, respectively). Likewise, no significant change occurred in CO ($p =$ NS) between the first and last EVLW measurement in either group (final CO = 6.5 ± 2.4 versus 5.8 ± 2.9 L/min, $p =$ NS, PM group versus RM group, respectively).

Initial EVLW Measurement versus Subsequent Management

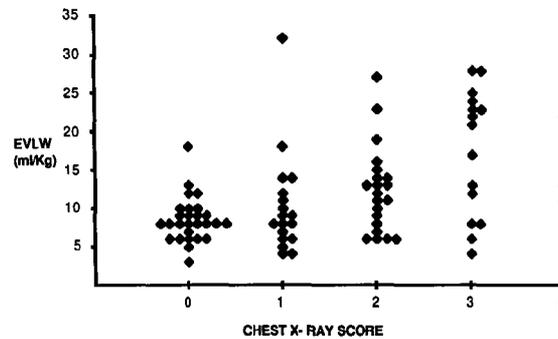
To provide some objective evidence that the protocol indeed resulted in different

TABLE 2
PATIENT DEMOGRAPHICS

Variable	Group	
	Protocol Management (n = 25)	Routine Management (n = 23)
Age, yr	56.9 ± 3.2	61.0 ± 3.2
Sex, male/female	15/10	14/9
Failed organ systems, n*	2.1 ± 1.3	2.1 ± 1.4
Prior health status*	2.1 ± 0.3	2.5 ± 0.2
Entry criteria		
Hypotension (systolic BP \times 90 mm Hg)	14	12
Wedge pressure $<$ 14 mm Hg	8	5
Both criteria	3	6
Total duration of the study, hr	47.6 ± 18.8	41.6 ± 17.7

* See METHODS for criteria.

Fig. 3. Correlation of extravascular lung water measurements (EVLW) with radiographic scores obtained on 85 radiographs performed within 4 h of the EVLW measurements. Although there is a tendency for radiographic score to increase as EVLW increases, there is also considerable overlap.



management for PM and RM patients, we compared the amount of fluid used for intravascular volume expansion during the first 24 h of therapy in patients with an initial EVLW > 7 ml/kg (35 of 48 patients) (figure 4). On average, less fluid was given to PM patients with a Ppaw < 18 mm Hg (treated primarily with vasopressors) than to similar patients in the RM group in the first 24 h (figure 4). Net fluid balance (all input minus output) was similarly reduced in the protocol patients (data not shown). Because of the small number of patients and the wide variability in amounts of fluid administered, this difference was not significant. One patient, who was hypotensive with an EVLW > 7 ml/kg on admission, was withdrawn from the protocol. This patient continued to receive fluids aggressively because of concomitant acute renal failure, which in the opinion of the responsible clinician might have responded to fluid administration. This patient, however, is still included in the PM group for any determination of outcome. Protocol patients received pressors for a shorter period of time (1.4 ± 0.1 days) than did patients managed routinely (2.9 ± 0.7 days), although this difference was not statistically significant.

The remaining patients with EVLW > 7 ml/kg had an initial Ppaw ≥ 18 mm Hg. As would be expected (because both EVLW and Ppaw were elevated), there was little difference in the amount of fluid used for intravascular volume expansion between hypotensive PM and RM patients (figure 4).

Effect of Management Protocol on Accumulation of EVLW

By the end of the study, EVLW decreased by $18 \pm 5\%$ in PM patients with an initially elevated EVLW (> 7 ml/kg), but by only $4 \pm 8\%$ in similar patients in the RM group ($p < 0.05$) (figure 2). The EVLW did not change significantly in either group during the course of the study

in patients with an initially elevated EVLW and Ppaw < 18 mm Hg (figure 2), despite the previously noted differences in fluid administration (figure 4). Among patients in which both EVLW and Ppaw were elevated initially (primarily patients with heart failure), EVLW fell $58 \pm 14\%$ by the end of the study in the PM group of patients compared with $13 \pm 11\%$ in patients in the RM group (figure 2) ($p < 0.05$).

Only 1 of the 7 patients in the PM group with a normal EVLW on admission had an elevated EVLW by the conclusion of the study period; this patient never developed an elevated Ppaw. By comparison, 2 of 6 patients managed conventionally had an EVLW > 7 ml/kg by the conclusion of the study; in both cases, Ppaw also increased above 18 mm Hg.

Effect of EVLW Protocol on Short-Term Outcome

As already noted, despite relative fluid restriction in hypotensive PM patients, the number of patient days that pressors were required was not greater in PM than in RM patients. In addition, the number of patients who developed an increased

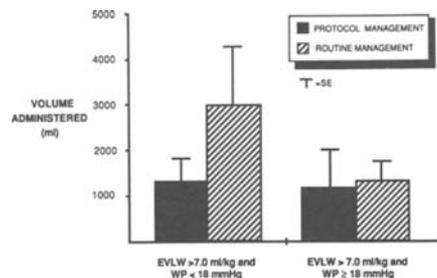


Fig. 4. Comparison of total amount of fluid used for intravascular volume expansion (blood, colloids, or isotonic crystalloid solutions) during the first 24 h of therapy in patients with initially elevated extravascular lung water (EVLW). On average, more fluid was given to patients in the routinely managed group with an initially low wedge pressure (WP) than to comparable patients in the protocol-managed group, although the difference was not statistically significant.

serum creatinine during the study period was similar in the 2 groups (7 of 25 in the PM group versus 7 of 23 in the RM group).

Oxygen and/or PEEP requirements changed to a similar degree during the study period in both PM and RM patients. Overall, 64% of the protocol patients and 78% of the conventionally treated patients were in respiratory failure on admission to the study. After the first day, improvements in oxygenation were similar for both groups, although the trend was for PM patients to do better than RM patients. By the end of the study, 36% of the patients in the protocol group compared with 22% of the conventionally treated patients required either less supplemental oxygen or PEEP ($p = \text{NS}$). Oxygenation improved in 5 of 9 patients with an elevated EVLW and normal Ppaw in the PM group compared with only 1 of 6 in the RM group ($p = \text{NS}$). Similarly, no difference occurred between the 2 groups in the number of patient-days of mechanical ventilation (14 ± 3 days for PM patients versus 12 ± 3 days for the RM group).

Comparison of Mortality

Patients were followed in hospital for 18 ± 2 versus 27 ± 6 days for the PM and RM groups, respectively. For both groups, there was a trend for the total number of failed organ systems to be significantly related to the probability of death ($p = 0.08$, Wilcoxon's rank test), but not to age, prior health status, or hypotension on ICU admission. For both groups, EVLW measurements were related to mortality only at extreme elevations of EVLW (13 of 15 patients with EVLW > 14 ml/kg died versus 13 of 32 with EVLW ≤ 14 ml/kg, $p < 0.05$).

Overall, 46% (54% inhospital) of the patients managed using the EVLW protocol died in the ICU compared with 65% (74% inhospital) of those managed conventionally ($p = \text{NS}$). The ICU mortality was similar in all hemodynamic subsets, except for patients with an initially elevated EVLW but a Ppaw < 18 mm Hg. Here only 33% (3 of 9) died in the protocol group (56% inhospital) compared with 100% (6 of 6) of the conventionally managed patients (all in the ICU) ($p < 0.05$). This difference in mortality was also significant when life table analysis was employed ($p = 0.036$, Wilcoxon's rank test) (figure 5) even accounting for differences in age, number of failed organ systems, and prior health status. It is also apparent from this analysis (figure 5) that virtually the entire difference

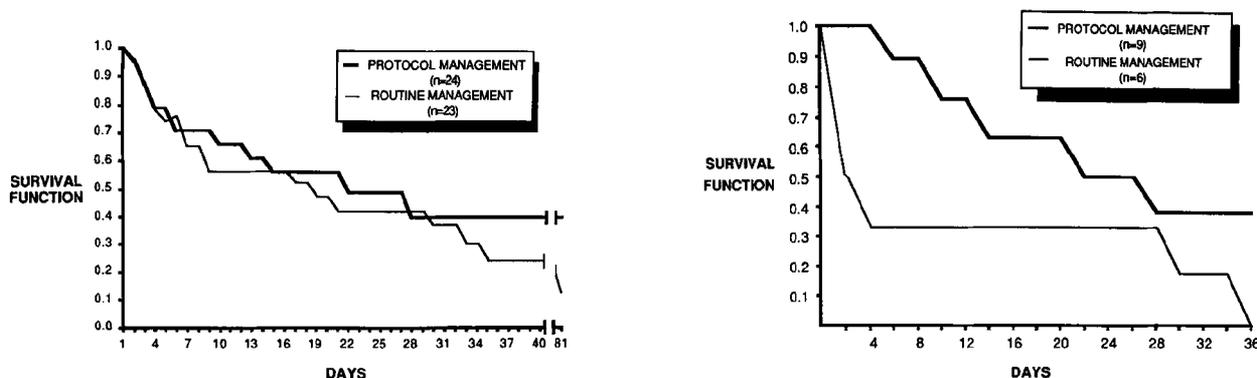


Fig. 5. Survival plots for both protocol and routinely managed groups (5a, left) and for the subset of patients with initially elevated extravascular lung water (EVLW) and low wedge pressure (WP) (5b, right). For the latter group of patients only, survival is significantly better in the protocol-managed patients ($p < 0.05$) even after accounting for age and severity-of-illness score.

in mortality in this subgroup became apparent during the first 72 h of treatment. Cardiac output also was similar in this subgroup, both at the outset of the study (6.4 ± 2.0 versus 5.9 ± 1.7 L/min, PM group versus RM group) and at the end of the study (5.9 ± 1.7 versus 5.7 ± 1.2 L/min, PM group versus RM group).

Discussion

Approximately 16 yr have passed since the introduction of PAC as a routine procedure for managing critically ill patients. Despite frequent use, no study has ever specifically shown that using the information obtained by this procedure favorably affects patient outcome. Because a preceding clinical evaluation often differs from the "objective" data obtained by PAC (1, 2), few clinicians have been willing to routinely treat critically ill patients without such information. Even so, the hazards of relying too heavily on data that are often of questionable validity are obvious (3–6).

We believe this to be the first study to prospectively evaluate the value of a therapeutic strategy based on measurements obtained during invasive hemodynamic monitoring. We hypothesized that EVLW might be a better endpoint than Ppaw during the management of fluid resuscitation for shock or diuretic therapy for pulmonary edema. Five conclusions seem warranted from our data. (1) The EVLW measurement provides independent, clinically useful information from that obtained by Ppaw measurement or chest radiographic interpretation. (2) Following our protocol for hemodynamic management based on EVLW measurements is safe and can be ethically applied to a larger group of ICU patients. (3) Resolution of pulmonary edema may be more

rapid when EVLW is used as a therapeutic endpoint (especially when the cause of pulmonary edema is congestive heart failure). (4) Prognosis of patients with extreme elevations in EVLW is significantly worse than for those with lesser increases. (5) Patient outcome might be improved by restricting excessive intravascular volume expansion in hypotensive patients with the adult respiratory distress syndrome (ARDS).

We found, as have others, that there is a poor correlation between chest radiographic interpretation or Ppaw and EVLW measurements (17–20). In our "real-life" clinical study, mobile unit radiography was hampered by performing studies with different x-ray units, along with inconsistencies in patient position. Furthermore, radiographic interpretation of pulmonary edema was hampered by the frequent occurrence of underlying lung disease or changes in ventilator settings. For these reasons, we did not find that adopting the criteria of Pistolesi and coworkers (21) improved our radiographic interpretation of pulmonary edema.

Because our study design included a treatment protocol that at times mandated a nonconventional approach to management, we made safety considerations paramount. It is important to point out that although fluids were restricted in some PM patients (i.e., patients with initially elevated EVLW and Ppaw < 18 mm Hg), these same patients were not hypovolemic, since their initial mean Ppaw was approximately 12 mm Hg. Thus, we are not advocating fluid restriction in hypotensive, hypovolemic patients. Furthermore, if PAC is already clinically indicated, obtaining the EVLW measurement itself provides little addi-

tional risk. To measure EVLW, a femoral arterial catheterization must be performed, but this procedure is also quite safe (22) and is routinely performed in most critically ill, hypotensive patients. In our study, there were no acute complications (e.g., serious bleeding, sepsis, arterial occlusion, or embolus) attributed to femoral arterial catheterization per se. The EVLW measurement also carries a slight risk from potential adverse reactions to indocyanine green dye, but no such reactions were observed in our study, despite more than 350 measurements.

Of course, the safety of a protocol based on EVLW measurements depends in part of the accuracy of the measurement. The accuracy of the EVLW technique used in this study has been demonstrated in multiple experimental and clinical studies (8–11), in a wide variety of forms of pulmonary edema, and over a wide range of actual EVLW contents. The technique may be inaccurate in certain forms of regional pulmonary edema, or when vascular obstruction is prominent (11, 23). However, these factors do not seem to be important during most cases of diffuse pulmonary edema, as were encountered in our study. Although a concern has been expressed that the EVLW measurement might paradoxically increase as perfusion to edematous areas improved during the resolution of pulmonary edema (11), we never noted this kind of disparity.

We believed that the greatest risk of our EVLW protocol was that we might cause or exacerbate pulmonary edema if intravascular volume expansion was continued when it might otherwise have been stopped, or that we might exacerbate renal failure by withholding fluids and using vasopressors when volume expan-

sion might otherwise have been continued. Accordingly, we monitored effects on oxygenation by noting changes in F_{IO_2} or PEEP to maintain the $P_{aO_2} > 60$ mm Hg, and on renal function by monitoring the daily serum creatinine. Although other indices of oxygenation could have been used, they offer little advantage when the F_{IO_2} , PEEP, and hemodynamic state are being manipulated. We found no systematic difference for any outcome between the PM and RM groups as a whole. On the other hand, favorable trends were almost always in the PM instead of the RM group. Thus, we believe our conclusion concerning the safety of the EVLW protocol is reasonable and warranted.

The resolution of pulmonary edema was more rapid in patients managed by the EVLW protocol than in those managed by routine measures (figure 2). This difference was greater still in patients in whom both EVLW and Ppaw were initially elevated (primarily patients in congestive heart failure). This latter finding probably reflects continued aggressive diuretic therapy in the PM patients even after the WP fell below 18 mm Hg. On the other hand, whether outcome is affected (i.e., time receiving mechanical ventilation, duration of ICU stay, hospital duration, or mortality) by this shortened resolution time remains to be determined.

Our most striking finding was the improved survival of PM patients with initially elevated EVLW but a Ppaw < 18 mm Hg compared with patients in the RM group. This improvement in survival persisted even after accounting for factors such as age, severity of illness, and primary indication for PAC (figure 5) or cardiac output. It is possible that patients in the nonprotocol group were actually more severely ill than those in the protocol group, despite our attempts to demonstrate otherwise. In retrospect, the protocol patients in this subgroup required pressors for a shorter period of time and had a slightly lower initial EVLW than did PM patients, although neither difference was statistically significant. Other systems of quantitating severity of illness (14, 24, 25) might have revealed a difference between PM and RM patients, but these systems have never actually been tested for use in studies like ours. On the other hand, the reason for the difference in mortality is not clear since we were unable to demonstrate a difference in the response of EVLW or CO to protocol

management during the first 24 to 48 h compared with routine management. However, several experimental studies (26–28) have emphasized that measures (such as fluid restriction) will minimize EVLW accumulation and it is possible that in a larger group of patients, changes in EVLW would more closely relate to mortality.

It might also be argued that had "routine management" been different, our results would have been less striking. For instance, in some ICUs, it may be common practice to use a lower target Ppaw than 18 mm Hg during therapy. This type of criticism begs the question, however, since the goal of a study such as ours is to help define which approaches to management are optimal, and therefore which should become "routine".

For the study group as a whole, EVLW correlated poorly with mortality, as noted by others (29). However, mortality was significantly higher (87%) if EVLW was > 14 ml/kg than if EVLW was less than this amount (41%). This finding may simply reflect the poor prognosis of patients with ARDS or sepsis, since 87% of patients with EVLW > 14 mm Hg had one of these admitting diagnoses. The prognostic value of this finding, therefore, will require further study.

In summary, management based on EVLW measurements is safe, practical, and has been successfully applied in a group of critically ill ICU patients. Outcome is at least comparable to conventional approaches based on Ppaw measurements alone, and may be superior in selected patient subgroups. This study demonstrates the feasibility of performing studies of this type, even in critically ill ICU patients, and can be used as a model for future studies.

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