Chapter 8

Predictors of pulmonary edema formation during fluid loading in the critically ill with presumed hypovolemia

Authors

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ABSTRACT

Introduction It is largely unknown why extravascular lung water (EVLW) may increase during fluid loading in the critically ill with presumed hypovolemia. In this study we evaluated the hemodynamic predictors of such an increase.

Design A prospective, observational study.

Patients Sixty-three presumed hypovolemic, mechanically ventilated patients (22 septic and 41 non-septic patients).

Intervention Fluid loading with saline or colloid fluids guided by (changes in) cardiac filling pressures.

Measurements and Main Results Before and after fluid loading hemodynamic and respiratory variables were recorded, including variables obtained by transpulmonary dilution such as cardiac index (CI), pulmonary blood volume index (PBVI) and EVLW. Baseline parameters and change in parameters (Δ) were compared between patients with a ΔEVLW <10% and patients with a ΔEVLW ≥10%. Predictive values for a ΔEVLW ≥10% were evaluated. Baseline CI and PBVI were higher, whereas ΔCI, ΔPBVI and $\Delta P_aO_2/F_iO_2$ ratio were lower in patients with a ΔEVLW ≥10% than in patients with a ΔEVLW <10%. The ΔEVLW correlated to baseline CI (r^2=0.17, P=0.001), baseline PBVI (r^2=0.15, P=0.001), ΔPBVI (r^2=0.16, P<0.001) and $\Delta P_aO_2/F_iO_2$ ratio (r^2=0.13, P=0.004). In multiple logistic regression analysis baseline CI, baseline PBVI, the ΔCI, ΔPBVI and $\Delta P_aO_2/F_iO_2$ ratio individually contributed to prediction of a ΔEVLW ≥10%, independent of the presence of sepsis, pulmonary vascular permeability and cardiac filling pressures. A ΔEVLW ≥10% was predicted by baseline CI (77% sensitivity, 98% specificity) and PBVI (92% sensitivity, 68% specificity), and by ΔCI (69% sensitivity, 59% specificity), ΔPBVI (77% sensitivity, 82% specificity) and $\Delta P_aO_2/F_iO_2$ ratio (77% sensitivity, 66% specificity).

Conclusion EVLW increase during fluid loading in the critically ill is predicted by a plateau of cardiac function and pulmonary vascular filling at baseline, rather than by pulmonary vascular permeability and filling pressures. Increasing EVLW is further reflected by a decrease of P_aO_2/F_iO_2 ratio. These observations may help preventing pulmonary fluid overloading.

INTRODUCTION

Fluid management is an essential part of the care for hypovolemic, critically ill patients, but may cause or aggravate pulmonary edema if cardiopulmonary function cannot compensate for the increase in preload. Fluid responsiveness is defined as an increase in cardiac output upon a fluid challenge. Prediction and monitoring hereof may prevent harmful fluid overloading [1,2] since loading in non-responders is thought to contribute to pulmonary edema and to prolong mechanical ventilation [3,4].

Extravascular lung water (EVLW) can be determined at the bedside, together with cardiac output and blood volumes, by transpulmonary dilution techniques [5]. Previous studies have shown that EVLW changes during fluid loading do not relate to pulmonary vascular permeability, as measured by a radionuclide technique, and hardly to cardiac filling pressures and colloid osmotic pressure (COP) [6,7]. Although the latter factors, according to the Starling equation, should predict an increase of EVLW, their predictive value in clinical practice is thus poor, partly because of increased lymph flow offsetting increased microvascular fluid filtration in the lung [8], and partly because of confounding of measured filling pressures by airway pressures in mechanically ventilated patients. Together with the unknown magnitude and effects of interstitial fluid pressures, this may, for instance, explain the ongoing controversy on the value of the COP-filling pressure gradient for predicting pulmonary edema formation in the critically ill [9-11]. In contrast, increase of EVLW may inversely relate to recruitable cardiac output and – since fluid extravasation is mostly preceded by pulmonary venous congestion [12-14] – pulmonary vascular filling. We therefore hypothesized that a plateau in cardiac function and pulmonary vascular filling, rather than permeability, cardiac filling pressures and COP, is associated with an increase of EVLW during fluid loading.

The aim of the current study was to identify predictors, including hemodynamics, blood volumes and permeability, for pulmonary edema development during crystalloid and colloid fluid loading in the presumably hypovolemic, critically ill patient.

METHODS AND PATIENTS

This was a prospective, observational study including 63 hypovolemic patients (22 septic and 41 non-septic patients) admitted to the Intensive Care Unit (ICU). Patients were involved in prior fluid loading trials, and randomizingly received saline, gelatin 4%, hydroxyethyl starch 6%, or albumin 5% [6,7]. Together these trials involved 112 patients. From this cohort 38 cardiac surgery patients were excluded, because of utilisation of cardiopulmonary bypass and priming solution, which may

confound EVLW increase before fluid loading in the ICU. Subsequently, 11 patients were excluded because no transpulmonary variables were obtained. The current study is a post hoc analysis of the remaining 63 patients. Written informed consent was obtained from patients or relatives. The study was approved by the ethical committee of the VU University Medical Center.

Patient enrolment

Presumed hypovolemia was arbitrarily defined as a systolic arterial pressure <110 mmHg, with either a pulmonary capillary wedge pressure (PCWP) ≤10 mmHg (in the presence of a pulmonary artery catheter, n=9), or a central venous pressure (CVP) ≤12 mmHg when positive end-expiratory pressure (PEEP) ≤15 mmHg, or ≤16 mmHg when PEEP >15 mmHg (in the presence of a central venous catheter, n=54). Non-septic patients were included within 3 h after major surgery, trauma or gastro-intestinal bleeding; septic patients were included within 12 h after meeting criteria for sepsis. Sepsis was diagnosed in the presence of two or more of the following criteria: abnormal body temperature (<36 °C or >38 °C), abnormal white blood cell counts (<4 or >12 x10^9/L), tachycardia (>90/min) and tachypnea (>20/min or a partial pressure of arterial carbon dioxide (P_aCO_2) <32 mmHg [4.3 kPa]), combined with a microbiologically proven or clinical source of infection. Exclusion criteria were age >79 years, a life expectancy <24 h and pregnancy. Patients were intubated upon arrival at the ICU or before initiation of surgery, and mechanically ventilated with a pressure-controlled (septic patients) or a volume-controlled (non-septic patients) ventilation regimen, aiming at tidal volumes of 6-8 mL/kg and normocapnia.

Study protocol

After measurement of baseline study variables, patients received saline, gelatin 4%, hydroxyethyl starch 6%, or albumin 5% during an interval of 90 min, until predefined increases in CVP/PCWP were achieved [15]. Fluid loading rate did not exceed 200 mL per 10 min and therefore amounted to 1800 mL at maximum. At t=90 min, measurement of study variables was repeated. Patients were otherwise treated by attending ICU physicians according to institutional guidelines, and followed until death or discharge from the ICU.

Measurement of study variables

After inclusion, demographic data were recorded. Pulmonary or central venous catheters had been inserted as part of routine management of these patients. Measurement of transpulmonary hemodynamic variables involved venous injection of 15 mL ice-cold indocyanine green (1 mg/mL 5% dextrose in water), after introduction of a 3F catheter (PV 2024, Pulsion Medical Systems, Munich, Germany) in the femoral artery. Dilutional curves were obtained (COLD Z-021, Pulsion

Medical Systems); the average of triplicate measurements is given. The cardiac index (CI), global end-diastolic volume index (GEDVI), pulmonary blood volume index (PBVI) were measured and indexed for body surface area. For techniques we refer to [16,17]. The EVLW was indexed for predicted body weight (PBW) [18]. Reproducibility is typically within 10% [5]. The global ejection fraction (GEF, normal 20-30%) is an index of cardiac function. It is calculated from stroke volume and global end-diastolic volume (stroke volume x 4 / global end-diastolic volume), where stroke volume is CI/ heart rate, taken from continuous electrocardiograms. In the absence of right ventricular overload or dysfunction, the GEF is an index of left ventricular systolic function. Pressures were measured after calibration and zeroing to atmospheric pressure at the midchest level with patients in supine position (Monitor Tramscope^{R}, Marquette Electronics, Milwaukee, USA). Mean pulmonary artery pressure (MPAP) and CVP were measured at end-expiration. After balloon inflation, the PCWP was recorded. Arterial blood samples were taken to assess partial pressure of oxygen (P_aO_2) and P_aCO_2 (Rapidlab 865, Bayer Diagnostics, Tarrytown, USA). The plasma COP was measured using a membrane osmometer (Osmomat 050, Gonotex, Berlin, Germany). The fluid balance was recorded by the ICU staff. Ventilation settings including fraction of inspired oxygen (F_iO_2) were obtained from the ventilator. Duration of mechanical ventilation was determined as the time from ICU admission to extubation. The lung injury score (LIS) was calculated from: a) P_aO_2/F_iO_2, b) number of alveolar consolidations on the chest radiograph, c) PEEP and d) pulmonary compliance [19]. The pulmonary leak index (PLI) was calculated by measuring extravasation of ^{67}Gallium (^{67}Ga)-labelled transferrin. Administration of autologous, ^{99m}Technetium-labelled erythrocytes (^{99m}Tc, 11MBq, physical half-life 6 h; Mallinckrodt Diagnostica, Petten, The Netherlands) and *in vivo* labelling of transferrin by intravenous injection of ^{67}Ga-citrate (4.5MBq, physical half-life 78 h; Mallinckrodt Diagnostica) was followed by 30 min of radioactivity detection over both lung apices (counts per minute [CPM] per lung field) with two scintillation detection probes (Eurorad C.T.T., Strasbourg, France), and in 2 mL blood samples (CPM/gram) taken every 4 min (LKB Wallac 1480 Wizard, Perkin Elmer, Life Science, Zaventem, Belgium). The radioactivity ratio was calculated (^{67}Ga lung/^{99m}Tc lung)/(^{67}Ga blood/^{99m}Tc blood) and plotted against time. Average PLI values for both lung fields were taken. Reproducibility for measurement is 14%. The upper limit of normal for PLI is 14.7 •10^{-3}/min [20].

Statistics

Since this is a substudy, it was not powered for a change in EVLW. The latter was used to divide patients into two groups (ΔEVLW <10% versus ΔEVLW ≥10%) for the purpose of this study. The 10% cut-off value was chosen as this represents the measurement error of EVLW, so that an increase ≥10% was considered as a significant increase in pulmonary edema. Variables were tested for normal distribution (Kolmogorov-Smirnov test), and presented as mean ± standard deviation (SD),

median (interquartile range) or number (percentage), when appropriate. Groups were compared for baseline variables (t=0) and changes in variables during fluid loading (Δ) using a Students t-test or Mann-Whitney U test, when appropriate. For correlations, coefficients of determination (r^2) are given. A multiple logistic regression analysis with a stepwise backward method was performed introducing ΔEVLW ≥10% as the dependent variable. The presence of sepsis, the baseline CVP, COP, CI, PBVI, P_aO_2/F_iO_2 ratio, LIS, PLI, EVLW and the type and volume of loading fluid were included as covariates in a regression model for baseline values (Model A); the ΔCVP, ΔCOP, ΔCI, ΔPBVI, $\Delta P_aO_2/F_iO_2$ ratio and the ΔGEDVI in a regression model for delta values (Model B). Odds ratios with 95% confidence interval are given. Areas under the receiver operating curves (AUC) were calculated; the maximal sum of sensitivity and 1-sensitivity determined optimal cut-off values. P-values <0.05 were considered statistically significant. Exact values are given unless <0.001.

RESULTS

Study population

Fifty patients (79%) showed a ΔEVLW <10%, and 13 patients (21%) had a ΔEVLW ≥10% during fluid loading. Groups were comparable with respect to age, underlying condition, APACHE II score, mortality, fluid balance, volume and type of loading fluid (Table 1).

Sepsis versus non-sepsis

Although septic patients had a higher baseline EVLW than non-septic patients (10.5±6.1 versus 7.4±3.0 mL•kg^{-1}, P=0.03), the ΔEVLW was similar (Supplementary Figure 1). At baseline, septic patients had a lower P_aO_2/F_iO_2 ratio (207±53 in septic versus 322±130 in non-septic patients, P<0.001), a higher LIS (2.25 [1.75;2.75] in septic versus 1.00 [0.63;1.50] in non-septic patients, P<0.001), and a higher PLI (50.3 [37.6;72.1] •10^{-3}/min in septic versus 22.0 [12.0;32.0] •10^{-3}/min in non-septic patients, P<0.001). No differences in $\Delta P_aO_2/F_iO_2$ ratio, ΔLIS and ΔPLI were observed between septic and non-septic patients.

Study variables

Hemodynamic and respiratory variables during fluid loading are presented in Table 2A and Table 2B, respectively. Groups were comparable for baseline EVLW. At baseline patients with a ΔEVLW ≥10% had a higher heart rate, stroke volume index, CI, PBVI and LIS, and a lower P_aO_2/F_iO_2 ratio than patients with a ΔEVLW <10% during fluid loading. The PBVI increased in patients with a ΔEVLW <10%, but decreased when ΔEVLW ≥10% (P<0.001 for ΔPBVI, Table 2A), whereas the ΔCI also

differed between groups (P=0.01, Table 2A). Among patients with a ΔEVLW <10% 25 out of 50 (50%) patients were fluid responsive (ΔCI ≥15%), whereas among patients with a ΔEVLW ≥10% 5 out of 13 (38%) patients were fluid responsive.

Table 1 - Demographic variables

	ΔEVLW <10% n=50	ΔEVLW ≥10% n=13	P-value
Age, y	61 ± 11	53 ± 18	0.16
Sex, m/f	37/13	9/4	0.73
BMI, kg•m^{-2}	24.9 ± 4.4	26.0 ± 4.4	0.44
APACHE II score	11.4 ± 4.9	11.4 ± 5.4	0.99
Major surgery	35 (70)	6 (46)	0.11
Thoracic vascular surgery	3	-	
Abdominal vascular surgery	13	1	
Abdominal general surgery	15	-	
Orthopedic surgery	3	1	
Trauma	1	3	
Gastro-intestinal bleeding	-	1	
Sepsis	15 (30)	7 (54)	0.11
Pulmonary	7	5	
Abdominal	2	1	
Blood/catheter	2	0	
Urinary	1	0	
Other	3	1	
Microbiology			
Gram positive bacteria	9	1	
Gram negative bacteria	6	3	
Fungi	4	1	
No microorganisms cultured	-	3	
Volume of fluid loaded, mL	1607 ± 257	1435 ± 390	0.15
Type of resuscitation fluid			0.29
NaCl 0.9%	13 (26)	6 (46)	
Gelatin 4%	10 (20)	2 (15)	
HES 6%	12 (24)	4 (31)	
Albumin 5%	15 (30)	1 (8)	
Fluid balance, mL	1164 ± 405	1084 ± 698	0.59
Vasopressor dependency	36 (72)	8 (62)	0.46
Duration of mechanical ventilation, hours	168 ± 238	226 ± 334	0.48
Mortality	9 (18)	2 (15)	0.83

Mean±SD or number (%), when appropriate. EVLW=extravascular lung water; APACHE=acute physiology and chronic health evaluation; BMI=body mass index; HES=hydroxyethyl starch.

Table 2A - Hemodynamic variables

	Time (min)	ΔEVLW <10% n=50	ΔEVLW ≥10% n=13	P-value
Heart rate, min^{-1}	t=0	76 ± 22	92 ± 28	0.03
	t=90	75 ± 22	91 ± 23	0.02
	Δ	0 ± 8	-1 ± 11	0.88
MAP, mmHg	t=0	80 ± 13	76 ± 10	0.35
	t=90	92 ± 14	85 ± 14	0.11
	Δ	12 ± 13	9 ± 9	0.37
CVP, mmHg	t=0	5.2 ± 3.4	6.6 ± 3.6	0.19
	t=90	8.2 ± 4.0	8.8 ± 4.5	0.67
	Δ	3.0 ± 2.0	2.2 ± 2.4	0.18
MPAP, mmHg	t=0	20.4 ± 9.1	17	0.70
	t=90	25.5 ± 10.9	21	0.68
	Δ	5.1 ± 3.4	4	0.76
PCWP, mmHg	t=0	6.3 ± 2.8	4.0	0.48
	t=90	11.0 ± 2.9	9.0	0.53
	Δ	4.8 ± 1.4	5.0	0.87
Cardiac index, $L•min^{-1}•m^{-2}$	t=0	3.3 ± 0.8	5.1 ± 1.6	0.002
	t=90	3.8 ± 1.0	5.1 ± 1.1	<0.001
	Δ	0.5 ± 0.6	0.0 ± 0.8	0.01
Stroke volume index, $mL•m^{-2}$	t=0	46 ± 14	57 ± 18	0.02
	t=90	53 ± 15	58 ± 16	0.29
	Δ	7 ± 8	0 ± 6	0.01
GEF, %	t=0	23 ± 8	26 ± 7	0.25
	t=90	24 ± 7	25 ± 6	0.89
	Δ	1 ± 3	-1 ± 2	0.005
GEDVI, $mL•m^{-2}$	t=0	849 ± 234	916 ± 207	0.36
	t=90	909 ± 250	971 ± 250	0.43
	Δ	59 ± 94	55 ± 82	0.88
PBVI, $mL•m^{-2}$	t=0	182 ± 67	266 ± 59	<0.001
	t=90	211 ± 65	252 ± 63	0.05
	Δ	30 ± 37	-13 ± 34	<0.001
COP, mmHg	t=0	16.0 ± 2.3	14.8 ± 2.9	0.12
	t=90	18.1 ± 3.4	15.7 ± 3.1	0.02
	Δ	2.2 ± 3.1	0.9 ± 1.9	0.18
CVP-COP, mmHg	t=0	-10.8 ± 4.1	-8.2 ± 3.6	0.04
	t=90	-9.9 ± 4.2	-6.9 ± 3.7	0.02
	Δ	0.9 ± 2.9	1.2 ± 2.1	0.67

Mean ± SD. EVLW=extravascular lung water; MAP=mean arterial pressure; CVP=central venous pressure; MPAP=mean pulmonary arterial pressure; PCWP=pulmonary capillary wedge pressure; GEF=global ejection fraction; GEDVI=global end-diastolic volume index; PBVI=pulmonary blood volume index; COP=colloid osmotic pressure. Δ's are the differences between t=90 and t=0min. NS=not significant.

Table 2B - Respiratory variables

	Time (min)	ΔEVLW <10% n=50	ΔEVLW ≥10% n=13	P-value
P_aO_2/F_iO_2 ratio	t=0	297 ± 119	221 ± 117	0.04
	t=90	321 ± 117	203 ± 107	0.002
	Δ	23 ± 44	-17 ± 37	0.003
Tidal volume, mL	t=0	586 ± 81	619 ± 112	0.26
	t=90	583 ± 110	600 ± 114	0.65
	Δ	-4 ± 51	-20 ± 60	0.37
PEEP, cmH_2O	t=0	8.8 ± 4.4	8.9 ± 4.5	0.92
	t=90	8.8 ± 4.4	9.3 ± 4.8	0.74
	Δ	0.0 ± 0.4	0.4 ± 1.6	0.17
Compliance, $mL•cmH_2O^{-1}$	t=0	53 ± 19	46 ± 17	0.32
	t=90	50 ± 19	40 ± 11	0.12
	Δ	-3 ± 8	-6 ± 10	0.21
Plateau pressure, cmH_2O	t=0	21.2 ± 7.7	23.5 ± 7.1	0.38
	t=90	22.0 ± 7.7	25.3 ± 7.7	0.21
	Δ	0.8 ± 1.6	1.8 ± 3.8	0.39
LIS	t=0	1.38 ± 0.84	2.12 ± 0.77	0.006
	t=90	1.44 ± 0.78	2.13 ± 0.89	0.007
	Δ	0.06 ± 0.31	0.02 ± 0.41	0.71
PLI, $x10^{-3}•min^{-1}$	t=0	32.0 (15.4;59.0)	29.0 (16.3;48.0)	0.80
	t=90	35.5 (17.5;69.5)	27.0 (23.0;49.8)	0.52
	Δ	0.5 (-3.4;12.3)	2.0 (-1.5;10.0)	0.79
EVLW, $mL•kg^{-1}$	t=0	7.7 (6.2;10.7)	7.1 (3.4;8.7)	0.08
	t=90	6.8 (5.6;9.3)	8.1 (4.9;10.9)	0.79
	Δ	-0.6 (-1.5;-0.1)	1.4 (1.0;2.0)	-

Mean ± SD or median (interquartile range), when appropriate. EVLW=extravascular lung water; LIS=lung injury score; P_aO_2=pressure of arterial oxygen/F_iO_2=fraction of inspired oxygen; PEEP=positive end-expiratory pressure; PLI=pulmonary leak index. Δ's are the difference between t=90 and t=0 min. NS=not significant.

Correlations

The baseline CI directly correlated to ΔEVLW (Figure 1A) and inversely correlated to ΔCI (r^2=0.17, P=0.001). In contrast, ΔCI did not correlate to ΔEVLW during fluid loading. The baseline PBVI and ΔPBVI directly correlated to ΔEVLW (r^2=0.15, P=0.001 and r^2=0.16, P=0.001, respectively). The baseline CI correlated to the PBVI (r^2=0.23, P<0.001). The $\Delta P_aO_2/F_iO_2$ ratio was positive in patients with a ΔEVLW <10%, but negative in patients with a ΔEVLW ≥10% (P=0.003, Table 2B), and inversely correlated to ΔEVLW (r^2=0.13, P=0.004). The PCWP correlated to the CVP (r^2=0.82 at t=0, P<0.001 and r^2=0.69 at t=90 min, P=0.006).

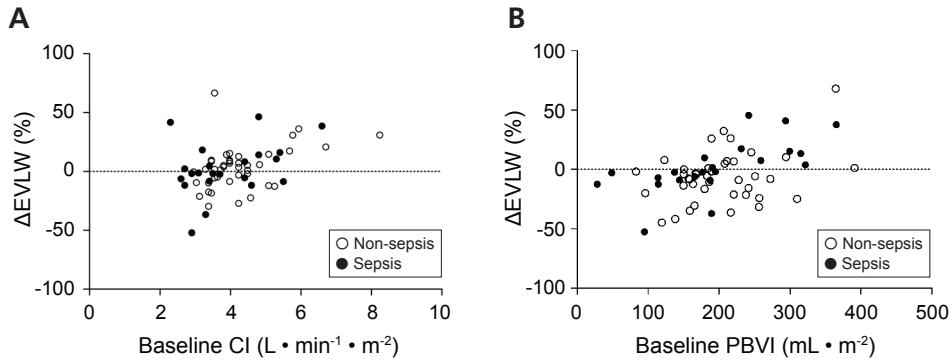

Figure 1 A) Correlation between baseline cardiac index and ΔEVLW (r^2=0.17, P=0.001). Empty circles (o) represent non-septic patients and closed circles (•) represent septic patients. B) Correlation between baseline pulmonary blood volume index and ΔEVLW (r^2=0.15, P=0.001). Empty circles (o) represent non-septic patients and closed circles (•) represent septic patients. EVLW=extravascular lung water.

Regression analysis

Tabel 3 shows multiple logistic regression models of baseline values (Model A) and delta values (Model B). A high CI, PBVI and LIS at baseline individually contributed to prediction of EVLW increase during fluid loading, independent of the presence of sepsis, the PLI, CVP, COP, and the type and volume of fluid loaded. A high baseline EVLW protected against EVLW increase (Table 3, Model A). An increase in CI, PBVI and P_aO_2/F_iO_2 ratio during fluid loading was independently associated with stable or decreasing EVLW, whereas an increase in GEDVI was associated with an increase in EVLW during fluid loading (Table 3, Model B).

Predictive values

Receiver operating curves for a ΔEVLW ≥10% are given in Figure 2. The baseline CI had an AUC of 0.83 (P<0.001), whereas baseline PBVI had an AUC of 0.83 (P<0.001) (Figure 2A). The AUC of ΔCI, ΔPBVI and $\Delta P_aO_2/F_iO_2$ ratio for a ΔEVLW ≥10% was 0.68 (P=0.05), 0.83 (P<0.001) and 0.76 (P=0.004), respectively (Figure 2B). The optimal cut-off values, together with predictive values of these variables are given in Table 4. Comparable predictive values were found in septic and non-septic patients separately (Table 5). Figure 2C shows the receiver operating curves of the regression models given in Table 3. The AUC of the regression model for baseline values was 0.97 (P<0.001), yielding a 92% sensitivity and 96% specificity; the AUC of the regression model for delta values was 0.93 (P<0.001), yielding a 92% sensitivity and 100% specificity.

Table 3 – Multiple logistic regression model of study variables predicting ΔEVLW ≥10%

Variable	Odds ratio	95% Confidence Interval	P-value
Model A – Baseline values			
Cardiac index, $L \bullet min^{-1} \bullet m^{-2}$	5.2	1.2 - 23.4	0.030
Pulmonary blood volume index, $mL \bullet m^{-2}$	1.05	1.01 - 1.09	0.015
Lung injury score	31.3	1.4 - 690.0	0.029
Extravascular lung water, $mL \bullet kg^{-1}$	0.40	0.17 - 0.91	0.030
Model B – Delta values			
Δ Cardiac index, %	0.88	0.80 - 0.97	0.012
Δ Pulmonary blood volume index, %	0.86	0.78 - 0.95	0.006
Δ Global end-diastolic volume index, %	1.02	1.004 - 1.04	0.022
Δ P_aO_2/F_iO_2 ratio	0.94	0.89 - 0.99	0.021

Odds ratios refer to odds ratios for ΔEVLW ≥10% per unit increment of the variable.

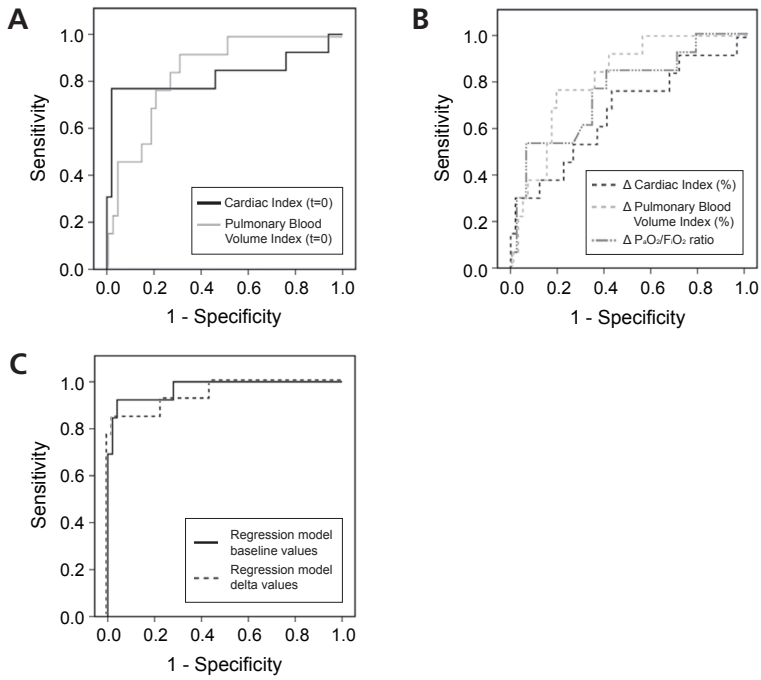

Figure 2 A) Receiver operating curves of baseline cardiac index (CI), baseline pulmonary blood volume (PBVI). The area under the curve is 0.83 (P<0.001) for baseline CI and 0.83 (P<0.001) for baseline PBVI. B) Receiver operating curves of the ΔCI, ΔPBVI and $\Delta P_aO_2/F_iO_2$ ratio for a ΔEVLW ≥10%. The area under the curve is 0.68 (P=0.05) for ΔCI, 0.83 (P<0.001) for ΔPBVI, and 0.76 (P=0.004) for $\Delta P_aO_2/F_iO_2$ ratio. C) Receiver operating curves of the regression model of baseline values and the regression model of delta values for a ΔEVLW ≥10% (Table 3). The area under the curve is 0.97 (P<0.001) for the regression model of baseline values, and 0.93 (P<0.001) for the regression model of delta values. EVLW=extravascular lung water.

Table 4 - Predictive values of baseline and delta values for an increase in EVLW ≥10%

	Sens/Spec (%)	PPV/NPV (%)	LR pos/neg
Baseline values			
CI >4.8 L•min^{-1}•m^{-2}	77/98	91/94	38.5/0.01
PBVI >198 mL•m^{-2}	92/68	43/97	2.9/0.11
Delta values			
Δ CI <12.2%	69/59	31/88	1.7/0.53
Δ PBVI <1.5%	77/82	53/93	4.3/0.28
Δ P_aO_2/F_iO_2 <2.1	77/66	37/92	3.2/0.35

CI=cardiac index; PBVI=pulmonary blood volume index; PPV=positive predictive value; NPV=negative predictive value; Sens=sensitivity; Spec=Specificity; LR=likelihood ratio.

Table 5 - Predictive values in septic and non-septic patients for an increase in EVLW ≥10%

	Sepsis			Non-sepsis		
	AUC	Cut-off	Sens/Spec (%)	AUC	Cut-off	Sens/Spec (%)
Baseline values						
CI, L•min^{-1}•m^{-2}	0.73 (P=0.08)	>4.7	71/93	0.89 (P=0.003)	>5.0	83/100
PBVI, mL•m^{-2}	0.88 (P=0.005)	>209	86/87	0.80 (P=0.02)	>213	83/66
Delta values						
Δ CI, %	0.65 (P=0.263)	<14.1	71/71	0.77 (P=0.04)	<11.1	83/56
Δ PBVI, %	0.88 (P=0.005)	<7.3	86/79	0.82 (P=0.01)	<2.1	83/79
Δ P_aO_2/F_iO_2	0.78 (P=0.040)	<10.5	100/64	0.74 (P=0.07)	<-28.8	67/94

AUC = area under the curve; Sens = sensitivity; Spec = specificity; CI= cardiac index; PBVI = Pulmonary blood volume index.

DISCUSSION

The main finding of this study is that a plateau of CI and PBVI, rather than permeability and pressures, predicts EVLW increase during fluid loading in presumed hypovolemic, critically ill patients, independently of the presence of sepsis, and the volume and type of loading fluid.

Patients with a relatively high baseline CI had a relatively low ΔCI and a high ΔEVLW, suggesting that these patients were on the plateau of their cardiac function curve and developed pulmonary edema upon fluid loading. Indeed, high predictive values were found for baseline CI. Although a relatively low baseline CI suggests recruitable CI, a highly variable ΔCI was found in the group of patients without an EVLW increase, likely reflecting different causes for the low baseline CI, i.e. causes sensitive to fluid loading, e.g. preload responsiveness, and causes relatively insensitive to fluid loading, e.g. impaired myocardial contractility or increased afterload. Although a lack of recruitable

CI may not necessarily be associated with an EVLW increase, a recruitable CI may exclude an EVLW increase and may thereby render continuation of fluid loading safe. This is reflected by the finding that the ΔCI had a moderate to high sensitivity and negative predictive value, but a low specificity and positive predictive value for an increase in EVLW (Table 4).

Besides CI, both baseline PBVI and ΔPBVI were associated with an EVLW increase. As suggested before [21,22], pulmonary vascular filling closely related to fluid extravasation. A low baseline PBVI may indicate reserve capacity of the vascular bed, allowing fluid loading, whereas absence of such reserve capacity (high PBVI) may preclude fluid loading. Because ΔPBVI relates to ΔEVLW, ΔPBVI may be used to monitor fluid loading. Combining baseline PBVI and CI in a multiple logistic regression model even enhanced predictive values for a ΔEVLW ≥10%. The observation that PBVI relates to CI at baseline suggests that a plateau in cardiac function is associated with a plateau of pulmonary vascular filling and that fluid loading in this plateau leads to pulmonary congestion, fluid extravasation and edema formation, in line with existing literature [23]. In a previous study, the discriminatory value of EVLW over blood volume ratios was evaluated, but it remained unclear whether cardiac or pulmonary blood volumes were most suitable to normalize EVLW [24]. The current study suggests that normalisation by PBVI is more in line with prediction of EVLW and underlying physiology.

A plateau in pulmonary vascular filling suggests maximal recruitment of the pulmonary vasculature. According to the Starling equation fluid extravasation is not only determined by pressures and permeability, but also by surface area, explaining the finding that pulmonary congestion affects fluid extravasation independent of pressures and permeability, and apparently this effect is greater than that of permeability and pressures [22]. Indeed, derecruitment of injured areas is a mechanism to protect against edema in animal experiments [25], whereas increased perfusion of damaged areas may promote edema formation, which is further enhanced by impaired lymphatic drainage [26]. Our findings that baseline LIS contributes to prediction of EVLW increase, and that combining LIS and PBVI in a regression model (Table 3, Model A) increases predictive values for an increase in EVLW support the concept that increased perfusion of injured areas is an important determinant of pulmonary edema Yet, pulmonary edema is not augmented per se by an increase in cardiac output perfusing normal or injured lungs, as was demonstrated before in the experimental setting [27]. The fall in P_aO_2/F_iO_2 ratio associated with an increase in EVLW underscores the clinical relevance of the effect of edema on pulmonary gas exchange and oxygenation and the possibility of using the ratio to prevent fluid overloading in the absence of transpulmonary dilution-EVLW measurements.

The occurrence of sepsis and the baseline EVLW were higher in patients with a ΔEVLW ≥10%, but these interrelations did not confound the predictive value of baseline CI and PBVI for fluid-loading-induced pulmonary edema formation for the following reasons. First, in multiple logistic

regression analysis, CI and PBVI predicted a ΔEVLW ≥10% independent of the presence of sepsis and PLI. Second, the changes in EVLW were comparable for septic and non-septic patients. Third, the predictive values of CI and PBVI for ΔEVLW ≥10% were comparable in septic and non-septic patients.

Patients in this study were presumed to be hypovolemic, which was arbitrarily defined as a systolic arterial pressure <110mmHg without elevated filling pressures (either CVP or PCWP, Methods section). As filling pressures are poor predictors of fluid responsiveness [1], we used changes in filling pressures to monitor fluid loading, which may be independent of airway pressures in mechanically ventilated patients. Yet, 20% of our patients showed an increase in EVLW≥10%, of whom only 38% were fluid responsive, whereas 50% of patients with a ΔEVLW <10% (80%) were fluid responsive. The EVLW groups did not differ in baseline and changes in CVP nor in GEDVI, which is regarded as a better indicator of fluid responsiveness than CVP. Taken together, this again suggests that filling pressure-guided fluid loading poorly predicts (binary defined, preload-dependent) fluid responsiveness and EVLW increase and that the latter are not fully, mutually exclusive.

Our study has some limitations. First, it was originally designed for evaluating the effect of fluid types on edema formation rather than for evaluating mechanisms. In relatively few patients of the study population the PCWP was obtained that may be a direct measure of pulmonary capillary hydrostatic filtration pressure. However, PCWP strongly related to CVP, suggesting that CVP may adequately replace PCWP in these patients without, apparently, severely depressed left ventricular function. Second, in our study a double indicator dilution method was used to obtain transpulmonary hemodynamic variables. At present, the use of single indicator methods is common practice, but the EVLW derived with single thermodilution is interchangeable with that obtained by the reference standard of thermal dye dilution as used in this study [28,29]. Third, since this was a single center study, optimal cut-off values may differ between patient populations. However, our study is a proof of principle study and underscores the value of transpulmonary thermodilution rather than central venous or pulmonary artery catheterisation in guiding fluid loading to prevent pulmonary edema formation, although it was not designed for a formal comparison. Alternatively, dynamic indices and predictors of fluid responsiveness used to optimise fluid loading in patients with permeability-edema and acute respiratory distress syndrome could also be helpful in preventing edema formation, but we did not study these variables since their value is restricted to patients on full mechanical ventilation with relatively large tidal volume, low respiratory frequencies and with normal sinus rhythm.

In conclusion, our study suggests that EVLW increase during fluid loading in the critically ill is predicted by a plateau of cardiac function and pulmonary vascular filling at baseline, rather than by pulmonary vascular permeability and cardiac filling pressures. These observations may help to prevent pulmonary edema formation during fluid loading.

ACKNOWLEDGEMENTS

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Chapter 8
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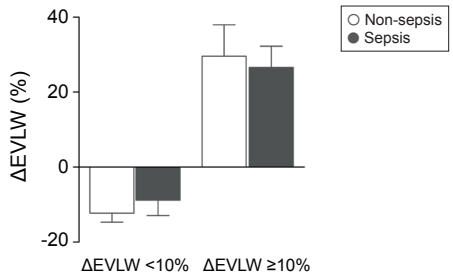
Supplementary Information

SUPPLEMENTARY FIGURE



Supplementary Figure 1 Percentual change in EVLW in patients with a ΔEVLW <10% and in patients with a ΔEVLW ≥10%, separately for septic (white bars) and non-septic patients (black bars). Data represent mean ± SEM. EVLW=extravascular lung water.

CORRESPONDENCE

RESPONSE 1 - Importance of events per independent variable in logistic regression analysis

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Critical Care Medicine 2012;40:1392

To the Editor: I read with great interest the article by Aman et al. [1], aiming to identify predictors for pulmonary edema development during fluid loading in the presumably hypovolemic critically ill patients. I have some remarks regarding this study. Sixty-three supposed hypovolemic patients were included; 50 (79%) had a change of extravascular lung water (ΔEVLW) < 10%, and 13 patients (21%) showed a ΔEVLW ≥ 10% during fluid loading. The authors performed a multiple logistic regression analysis to analyze the development of pulmonary edema with ΔEVLW as the dependent variable. The number of outcome events is defined in logistic regression by the smaller number of binary outcomes of the dependent variable. In this study, 10 independent variables (model A) were examined for their association with 13 ΔEVLW ≥ 10%. Therefore, the ratio of events per variable (EPV) was too small (13/10 = 1.3). However, in multiple logistic regression analysis, a too small EPV may affect the accuracy and precision of regression coefficients for independent variables, and their associated individual tests of statistical significance [2,3,4]. Under such circumstances, regression models can yield unstable risk estimates and can suggest misleading associations. In analogy of type I errors, the results may erroneously reject the null hypothesis that a variable has no impact on the outcome. In an analogy to type II errors, the analysis may lack power to detect the impact of

important variables. In an analogy to type III error, a variable having a distinctly positive effect on the outcome may be reported as having an important negative effect (or vice versa). Large confidence intervals associated with individual risk estimates as seen in this study (cardiac index, odds ratio 5.2; 95% confidence interval [1.2-23.4], and lung injury score, odds ratio 31.3; 95% confidence interval [1.4-690]) indicate an overfitted model. Consequently, a large number of outcome events is needed if many independent variables are included in the analysis. A useful rule of thumb comes from simulation experiments [4], which suggest that the EPV should be at least 10, and preferably greater. Therefore, the results of multiple logistic regression analysis in this study may not be trustworthy. Moreover, the interpretation offered of the odds ratios from their Table 3, is somewhat misleading. Indeed, the authors mentioned that high cardiac index, pulmonary blood volume index, and lung injury score at baseline individually contributed to prediction of EVLW increase during fluid loading (paragraph "regression analysis" in "results" section). This interpretation is based in the fact that the odds ratios of these independents variables were all above 1 (Table 3, model A). However, for logistic regression, the odds ratio tell us how much the likelihood of the outcome changes with a one-unit change in the independent variable. What does this mean? It means that, for example, for every increase of 1l.min-1.m-2 in cardiac index from any level (low or high), the likelihood of having an elevation of EVLW during fluid loading increases by a factor of 5.2. Finally, it is unclear how high baseline EVLW protects against EVLW increase during fluid loading.

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AUTHORS COMMENT:

With interest we have read the comments of dr. Mallat on our publication [1], in which he expresses his concerns about the multiple regression analysis (MRA) used in our study. To summarize, two concerns were raised: First, the ratio of events per variable (EPV) is too small (1.3 in stead of 10 as recommended). Second, the interpretation of the odds ratio (OR) from the MRA could be misleading. Here we would like to respond to these concerns and argue that the suggested limitations do not affect the conclusions of the study.

In our study, the MRA was performed with 10 independent variables (yielding an EPV of 1.3). However, when the same analysis was performed with the 4 independent variables shown in Table 3 (yielding and EPV of 3.3), the OR did not change, indicating that the final OR in our regression model is hardly affected by the number of independent variables. Furthermore, the quality of the regression model was assessed with the Hosmer & Lemeshow test (Model A: $\chi 2=3.7$, df=8, P=0.89; Model B: $\chi 2=13.5$, df=8, P=0.10). Although we agree with the author that an EPV>10 is preferable, these analyses virtually exclude 'overfitting' of the models provided in Table 3.

We acknowledge that the language used to describe the outcome of the MRA may be too strong. But for several reasons we consider the results of the MRA as provided in Table 3 informative: A) Even though the independent variables were continuous, the interpretation of the OR remains the same: an OR >1 indicates relatively higher odds and thus increased risk, whereas an OR <1 indicates relatively lower odds and thus decreased risk. B) Given the low initial risk of an increase in extravascular lung water (EVLW), the chance that the OR importantly deviates from the relative risk (either a high overestimation in case of an OR >1 or an underestimation in case of an OR <1) is small [2]. C) As the odds ratio indicates changes in odds/likelihood ratio in relation to other variables, it provides mechanistic insights. Therefore a rough estimator like the OR may suffice to prove that CI and PBVI relate to changes in EVLW independent of established factors like pressures and vascular permeability. Taking these considerations into account, we believe that the main conclusion from the MRA that a higher cardiac index and pulmonary blood volume index are associated with a higher risk for EVLW increase, independent of pressures and vascular permeability is justified.

From a general point of view, we want to stress that the main conclusion of our study is based on observations obtained by various statistical methods. Comparison of means, correlation, MRA and analysis of the area-under-the-receiver-operating-curve (AUC) all show similar results, which on the one hand supports the conclusions of the MRA, and on the other hand makes the main conclusion independent of the MRA. Predictive values and clinical implications as provided in the article do not depend on the MRA, but were derived from AUC and sensitivity/specificity calculations.

In conclusion, we acknowledge the drawbacks of the MRA in the current study. At the same time, we argue here that these drawbacks do not importantly hamper interpretation of the MRA, and do not affect the main message of our study.

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RESPONSE 2 - Revised Starling equation predicts pulmonary edema formation during fluid loading in the critically ill with presumed hypovolemia

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Critical Care Medicine 2012;40:2741-2.

We congratulate Aman, Groeneveld and van Nieuw Amerongen on their important contribution showing that cardiac filling pressures and pulmonary vascular permeability have poor predictive value for pulmonary edema, which they state is contrary to predictions based on the Starling equation [1]. We would point out that the Starling equation was substantially revised when researchers at the University of California demonstrated that colloid osmotic forces opposing filtration across continuous capillaries are developed across the endothelial glycocalyx layer [2] and in its new form the revised Starling equation predicts their clinical observations well. The glycocalyx is a fiber matrix of proteoglycans and glycoproteins lining the luminal aspect of capillaries. It contains several types of glycosaminoglycans and is only semi-permeable to albumin, so that filtered fluid within the inter-endothelial clefts is almost albumin-free. The revised Starling equation explains that absorption of interstitial fluid by capillaries with a continuous glycocalyx layer is very limited, and pulmonary edema occurs when transcapillary fluid flux (Jv) exceeds lymphatic flow (QL) [3]. While the hydrostatic pressure difference between capillary and tissue interstitial space (delta P) is less than the oncotic pressure difference between plasma and the subglycocalyx protected regions within the inter-endothelial clefts (delta pi), Jv will be close to zero at any capillary pressure and the patient will not be at risk of edema. Raised interstitial protein concentration, as expected in patients whose pulmonary vascular permeability to gallium transferrin is increased, has no direct effect on Jv. Only at higher capillary pressures and when delta P is higher than the maximised delta pi will Jv become dependent on capillary pressure [4]. Increased QL will limit accumulation of interstitial fluid, but when QL is restricted or reduced, for instance by elevated central venous and thoracic duct pressure, edema will occur. The finding that extravascular lung water increase during fluid loading coincides with a plateau in cardiac function and pulmonary blood volume can therefore be explained by higher pulmonary capillary pressure, raised Jv and restricted QL. It is important to

recall that the reported pulmonary artery occlusion pressure measurement, sometimes also called the pulmonary capillary wedge pressure, is an approximation of the pulmonary venous pressure rather than pulmonary capillary pressure. The revised Starling equation's no absorption rule explains the Amsterdam team's earlier finding that the risk of pulmonary edema is uninfluenced by the colloid oncotic pressure of the resuscitation fluid [5]. We recommend that future discussions on the important topic of fluid therapy should take into account the crucial role of the endothelial glycocalyx layer and the explanatory power of the revised Starling equation.

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AUTHORS COMMENT:

We would like to thank dr. T.M. Woodcock and dr. T.E. Woodcock for their interest in our recent study, and appreciate their valuable suggestions for interpretation of our data. In response to their Letter we would like to make a few remarks. First of all, we did not state that our findings are contrary to the Starling equation, as suggested by the authors. In the Discussion of our publication [1] we proposed that edema development during fluid loading is to be explained by Starling factors which are relatively unknown (like capillary surface area, as component of the K_{fc}), rather than more widely known Starling factors like hydrostatic pressure (ΔP) or oncotic pressure ($\Delta \pi$).

In the context of this discussion we appreciate that the authors draw attention to the Revised Starling Equation. In particular the 'no absorption' rule may shed light on the (patho)physiology of edema development and fluid loading [2], and provide an additional interpretation of our data. Yet, in our opinion the Revised Starling Equation, and especially the glycocalyx-cleft model [3], is still insufficiently developed in context of the inflammatory conditions sepsis and ALI/ARDS. Therefore it cannot explain our observations with certainty. In particular, three issues are at stake here:

1) The effects of sepsis and ALI/ARDS on the glycocalyx are far from established. Although studies have related sepsis with increased circulating levels of glycocalyx proteins [4], there is only indirect evidence that clinical sepsis or ALI/ARDS lead to glycocalyx shedding or impaction, since other origins of these proteins could not be excluded yet.
2) Assuming that sepsis and ALI/ARDS lead to glycocalyx shedding and impaction, this yields important consequences for the glycocalyx-cleft model, since complete glycocalyx shedding implicates absence of glycocalyx (a prerequisite for the glycocalyx-cleft model).
3) The relative contribution of the glycocalyx to endothelial barrier function, and vice versa, the contribution of glycocalyx shedding to endothelial barrier dysfunction is largely unknown. Thus far, the edema formation during severe inflammatory conditions has been predominantly contributed to endothelial activation and gap formation [5]. Important factors in this process involve dissociation of interendothelial junctions (in particular the adherens junction), endothelial cell retraction due to actomyosin contraction and loss of endothelial cell adhesion to the extracellular matrix. We agree with the authors that the glycocalyx is part of the endothelial barrier; its relative contribution besides other endothelial barrier regulating mechanisms remains to be established, however.

Altogether, we consider the Revised Starling Equation a valuable insight in the discussion on edema development and fluid loading. Yet, the issues indicated above warrant caution in the application of these principles during sepsis, and support further research in the field.

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RESPONSE 3 - The role of inflammatory mediators in the association of pulmonary edema with increased cardiac index and pulmonary vascular filling

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Critical Care Medicine 2012;40:3107

To the Editor: A recently reported study established a link between increased and static cardiac index and pulmonary vascular filling after fluid loading and increased extravascular lung water in critically ill patients with lung injury. There was no influence of permeability of the vascular bed to proteins on extravascular lung water. The authors claimed that this may be due to the increased surface area of the pulmonary vascular bed increasing extravasation [1]. Mortality of lung injury has previously been linked to reduced pulmonary fluid clearance [2]. Pulmonary fluid clearance is linked to the function of epithelial sodium and chloride channels as shown for children with meningococcal septicaemia in vivo [3]. Absorption of sodium and chloride from the alveolar space generates the osmotic gradient required for pulmonary fluid clearance. Inflammatory mediators released in patients with infection and tissue trauma including extensive surgery can reduce epithelial sodium and chloride channel function leading to a predisposition to pulmonary edema [4]. The increased cardiac index in patients with more severe lung injury may have been due to increased output of inflammatory mediators causing tachycardia. The increased pulmonary vascular filling may have been due to nitric oxide induced dilatation of pulmonary vascular smooth muscle cells. Nitric oxide and its metabolite peroxynitrite reduce epithelial sodium and chloride channel function by nitrosylation and phosphorylation [4] and cause mitochondrial dysfunction by nitrosylation of mitochondrial proteins. Mitochondiral dysfunction leads to cellular ATP depletion reducing the function of the basolateral ATP dependent sodium pump (sodium potassium ATPase), which drives apical epithelial sodium transport required alveolar fluid clearance. The abnormal cardiovascular parameters the authors found to be predictive of increased extravascular lung water may therefore reflect the action of inflammatory mediators causing pulmonary edema by other mechanisms.

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AUTHORS COMMENT

We thank the author for his comments. In our study we evaluated the predictive values of current cardiopulmonary parameters during fluid loading. From all parameters we distinguished the parameters that, measurable at the bedside, predict pulmonary edema during fluid loading. In addition, we proposed mechanisms that could explain the relation between found parameters and edema development. As dr. Eisenhut indicates in his Letter, other mechanisms will likely occur besides the mechanisms we proposed. The correlation coefficients found in our study (r^2 ranging from 0.15 to 0.17) indicate that development of extravascular lung water indeed partly depends on cardiac index and pulmonary blood volume index. We therefore concur with the conclusion of the Letter, even though the clinical evidence for the mechanisms suggested by the author and the tools to measure them are limited. The absence of a definite explaining mechanism, however, does not limit the relevance of our study for clinical management, as it provides readily measurable parameters that may help to guide fluid loading.