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Hypoproteinemia as a marker of acute respiratory distress syndrome in critically ill patients with pulmonary edema

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Abstract *Objective:* To assess the value of serum protein levels for differentiating permeability pulmonary edema in the course of acute respiratory distress syndrome (ARDS) from cardiogenic pulmonary edema (CPE). *Design and setting:* Observational cohort study in intensive care units of 720-bed university hospital. *Patients:* Twenty-four consecutive patients with clinical evidence of edema, 11 fulfilling the consensus definition of ARDS, 7 having sepsis, 5 with all ARDS consensus criteria and sepsis but a pulmonary capillary wedge pressure above 18 mmHg (mixed), and 8 with CPE. All patients except for one with CPE were mechanically ventilated. *Measurements and results:* Radionuclide assessments of pulmonary microvascular protein (transferrin) permeability (pulmonary leak index, PLI) were carried out and serum protein levels determined at admission and for ARDS/mixed patients, at recovery, defined by a decrease in positive end-expiratory pressure to 0 cmH_2O. At admission the PLI was higher in ARDS/mixed than in CPE patients. The total protein and transferrin levels were lower in the former. The area under the curve of the receiver operating characteristic for diagnosing ARDS (vs. CPE) was 0.98 for transferrin (cutoff value 1.5 g/l), 0.95 for total protein (cutoff value 59 g/l) and 0.80 for albumin (cutoff value 24 g/l) levels. In various clinical diagnostic groups the transferrin level approached the PLI in diagnostic value. At recovery the PLI had decreased and serum protein levels increased. *Conclusions:* The data suggest that hypoproteinemia is a marker of ARDS. This may partially reflect increased permeability in the lungs, systemically, or both.

Keywords Acute respiratory distress syndrome · Cardiogenic pulmonary edema · Hypoproteinemia · Pulmonary edema · Pulmonary leak index · Pulmonary microvascular protein permeability

Introduction

Classically, the acute respiratory distress syndrome (ARDS) is diagnosed in the presence of a known risk factor, recent onset bilateral pulmonary infiltrates compatible with edema, critical hypoxemia, and the absence of evidence of a hydrostatic cause of edema, such as a pulmonary capillary wedge pressure (PCWP) below 18 mmHg [1, 2]. The diagnosis therefore requires a pulmonary artery catheter, although a high PCWP does not exclude permeability edema. Indeed, ARDS is believed to result from a lung vascular injury and increased endothelial permeability in response to a variety of inflammatory conditions, while hydrostatic pulmonary edema is caused by heart failure (cardiogenic pulmonary edema, CPE) or overhydration. We have shown that a radionuclide method allowing assessment of transferrin permeability in the lungs noninvasively and at the bedside dis-

criminates well between the edema types; permeability (pulmonary leak index, PLI) is increased about threefold in ARDS and normal in CPE [3, 4, 5]. We have noted that in spite of a lower hydrostatic filtration pressure (PCWP) in the lungs in ARDS than in CPE the difference between hydrostatic and plasma colloid osmotic pressure (COP), i.e., the net intravascular filtration pressure, does not differ between edema types. COP calculated from serum protein levels is lower in ARDS than in CPE, but COP calculated from protein levels may be underestimated in the presence of colloid fluid administration and in the absence of direct COP measurements [3].

Nevertheless, the observation suggests that pulmonary edema depends only little on hypoproteinemia in ARDS. The question of whether hypoproteinemia per se discriminates ARDS from CPE, and how it contributes to ARDS remained unanswered, however. Indeed, hypoproteinemia could reflect, among other causes, increased protein permeability either in the lungs, systemically, or both, if it is true that ARDS is the tip of the iceberg of increased protein permeability during inflammatory conditions [6, 7, 8, 9]. It has recently been shown that during sepsis hypoproteinemia predicts the development of ARDS, suggesting that dilution or decreased hepatic syn-

Table 1 Characteristics of the patients: median (range) or number of patients (%), where appropriate. Patients may have more than one condition (*ARDS* acute respiratory distress syndrome, *CPE* cardiogenic pulmonary edema)

	ARDS (*n*=11)	Mixed (*n*=5)	CPE (*n*=8)	*p*[a]
Age	46 (21–78)	53 (32–65)	68 (50–79)	<0.05
Sex: M/F	7/4	3/2	8/0	n.s.
Underlying diseases				
Near drowning	3			
Sepsis following pneumonia	2	3		
Extrapulmonary sepsis	5	2		
Hemorrhagic shock/resuscitation	1	1		
Diabetic ketoacidosis	1			
Malignancy	3	2		
Liver cirrhosis		1		
Post-CPR	3		2	
Remote myocardial infarction			6	
Recent myocardial infarction		1	5	
Prior coronary revascularization			2	
Hypertension			1	
Bacteremia	3	2		
Hemodynamic data				
Pulmonary capillary wedge pressure (mmHg)	12 (6–17)	20 (19–20)	16 (12–34)	<0.005
Central venous pressure (mmHg)	9 (4–14)	14 (7–19)	8.5 (2–12)	n.s.
Respiratory data				
Arterial PO_2/inspiratory O_2 fraction (mmHg)				
Initial	124 (50–198)	86 (64–116)	184 (142–259)	<0.001
Recovery	204 (144–314)[b]	231 (209–253)[c]		
Chest radiography score				
Initial	4.0 (4.0–4.0)	4.0 (3.0–4.0)	4.0 (4.0–4.0)	n.s.
Recovery	2.5 (1.0–4.0)*[b]	2.5 (2.0–3.0)*[c]		
Mechanical ventilation				
Initial	11 (100%)	5 (100%)	7 (87%)	n.s.
Recovery	6 (75%)	1 (50%)		
Static respiratory compliance (ml/cmH_2O)				
Initial	28 (18–31)	32 (25–35)	49 (33–68)	<0.001
Recovery	25 (13–43)[d]	31[e]		
Positive end-expiratory pressure (cmH_2O)				
Initial	11 (1–15)	8 (5–13)	5.5 (0–8)	<0.05
Recovery	0	0		
Lung injury score				
Initial	3.2 (2.5–3.7)	3.0 (2.5–3.3)	2.1 (1.7–2.5)	<0.001
Recovery	1.6 (1.2–2.5)*[b]	1.4 (1.0–1.8)*[c]		
Mortality	4 (36%)	2 (40%)	3 (37%)	n.s.

*p<0.05 versus intitial (ARDS and mixed together)
[a] Kruskal-Wallis test [b] n=8 [c] n=2 [d] n=6 [e] n=1

thesis and a resultant low COP provokes pulmonary edema, or that increased permeability, in the lungs or systemically, results in hypoproteinemia [10]. Indeed, causal relationships are difficult to determine in the absence of permeability measurements in the lungs since normal permeability suggests the former and high permeability the latter.

We therefore studied serum protein levels and pulmonary vascular permeability to proteins in patients with clinical evidence of pulmonary edema.

Patients and methods

Patients

We prospectively studied 24 consecutive patients admitted into the intensive care unit (ICU) because of respiratory insufficiency and with a pulmonary artery catheter in place. Eleven had the consensus definition of ARDS, five the consensus criteria for ARDS except for a PCWP exceeding 18 mmHg, and eight clinically defined CPE. These patients have been described before [3]; we adhered strictly to consensus criteria and analyzed the circulating protein levels for the current study. Table 1 presents patients' characteristics. Seven ARDS patients, five mixed patients, and no CPE patient had sepsis. Nine of ten recovering ARDS and mixed patients survived, while five nonrecovering patients died in the ICU. Six nonrecovering ARDS and mixed patients died at a median of 3.5 days (range 1–7) after admission, thereby precluding repeated measurements. The mixed/CPE patients had evidence of left ventricular failure, and therefore the PCWP was higher than in ARDS patients, while the CVP was not. The study was approved by the hospital ethics committee, and informed consent was obtained from the closest relative of each patient. At admission PCWP and central venous pressure (CVP) were measured via pulmonary artery catheter, at end-expiration, with patients in supine position and at the midchest level, after calibration and zeroing to atmospheric pressure.

The 11 patients with ARDS and needing mechanical ventilation were studied within 72 h of admission. Patients with ARDS met the following consensus definition [1, 2, 3]: presence of a known ARDS risk factor including sepsis, hemorrhagic shock and resuscitation, near-drowning and pneumonia [2], recent bilateral infiltrates on chest radiography compatible with pulmonary edema [3], severe hypoxemia with a ratio between arterial PO_2 and the inspiratory oxygen fraction (FIO_2) less than 200, regardless of positive end-expiratory pressure (PEEP) [4], absence of evidence of left ventricular failure or a PCWP of or less than 18 mmHg, and [5] no alternative explanation for hypoxemia or radiographic findings. A mixed group of patients (n=5) had risk factors and criteria for ARDS except for a transient elevation in PCWP to 18 mmHg or higher at admission.

The 8 CPE patients were studied within 72 h of admission and had acute left ventricular failure, as defined by: evidence of coronary artery disease and impaired left ventricular function, such as history of angina, or a remote or recent myocardial infarction diagnosed by typical electrocardiographic and blood enzyme changes, and poor left ventricular function on echocardiography or an elevated PCWP above 18 mmHg, in the absence of risk factors for ARDS.

Twelve patients, scheduled for elective aortic surgery (aged 65 years, range 48–80) served as controls [4].

Therapeutic protocol

All pulmonary edema patients, except for one CPE patient, were intratracheally intubated and mechanically ventilated with an O_2/air mixture, when indicated on clinical grounds (Evita, Dräger, Lübeck, Germany). Tidal volume and frequency were adjusted aiming at normocapnia and peak inspiratory pressures below 40 cmH_2O, at an inspiration/expiration time ratio of 1:2. During the course of disease incremental PEEP was dosed, aiming at an FIO_2 below 0.60, concomitantly with an arterial blood O_2 saturation above 90%. A catheter was inserted into a peripheral artery for monitoring and blood sampling. Patients were taken care of by attending physicians not involved in the study. Fluid therapy was given when judged necessary by the treating physician, with crystalloids and artifical colloids, but plasma/albumin was not used.

Study protocol

PLI was measured concomitantly with the other study measurements within 72 h of ICU admission in pulmonary edema patients and prior to surgery in aortic surgery patients [3, 4, 5]. In eight ARDS and two mixed patients a second PLI measurement was performed concomitantly with the other measurements in the study within 48 h after the patient had improved clinically when the treating physician judged it appropriate to decrease the PEEP level to zero, a median of 7 (range 3–26) days after ICU admission. Eight of the ten recovering patients were still on the ventilator when the second study was performed. Pulmonary edema patients were followed until discharge from the ICU.

At each PLI measurement the FIO_2, expiratory tidal volume, the peak inspiratory pressure, plateau pressure, and PEEP were taken from the ventilator for calculation of the lung injury score (LIS [2]) in mechanically ventilated patients. The static respiratory compliance was calculated from tidal volume/(plateau pressure–PEEP). At recovery three ARDS and mixed patients breathed spontaneously, and two of them had been extubated. In these patients the FIO_2 was determined at 0.45 and 0.5 in extubated patients receiving 4 and 5 l of supplemental 100% O_2 per face mask, respectively, and as 0.40 in the patient receiving 40% O_2 via a nebulizer and the intratracheal tube. One CPE patient was on 3 l of 100% O_2 per face mask, so that the estimated FIO_2 was 40%. Arterial blood was sampled in heparinized syringes for measurement of PO_2 (Corning 178/288, Corning Medical and Scientific, Medfield, Mass., USA). This allowed calculation of the arterial PO_2/FIO_2. Chest radiography was performed on admission and on the day on which the PLI measurement was repeated. The chest radiograph was scored by one of the investigators, blinded to the PLI results, as follows: 1 alveolar edema in one quadrant, 2 in two, 3 in three, and 4 in four. With help of the above variables the LIS was calculated according to a previously described scoring method, whereby 0 is normal and 4 represents maximal injury [2].

The PLI was measured according to a previously described dual-radionuclide method [3, 4, 5]. In brief, autologous red blood cells were labeled with ^{99m}Tc (11 MBq; physical half-life 6 h). Ten minutes after injection of the labeled red blood cells transferrin was labeled in vivo following intravenous injection of ^{67}Ga-citrate (4 MBq; physical half-life 78 h). Ten 2-ml blood samples were drawn at fixed time points, up to 60 min after injection. Starting at the time of intravenous injection of ^{67}Ga the radioactivity was detected in 1-min frames for 1 h using two mobile probes. One probe was placed over the left and one over the right lung upper zone, with patients lying still in supine position. For each blood sample a time-matched count rate over the lung was taken. A lung/blood ratio was calculated – $(^{67}Ga_{lung}/^{99m}Tc_{lung})/(^{67}Ga_{blood}/^{99m}Tc_{blood})$ – and plotted against time. The PLI was calculated using linear regression analysis from the slope of increase of the radioactivity ratio divided by the intercept [3, 4, 5]. Values from the two lungs were averaged. The PLI represents the transvascular transport rate of ^{67}Ga-labeled transferrin, corrected for pulmonary blood volume and therefore exchange surface area. We measured total protein (biuret method), albumin (bromocresol method), and transferrin (nephelometry) levels, concomitantly with each PLI and LIS de-

Table 2 Circulating proteins and pulmonary leak index for proteins: median (range) (*ARDS* acute respiratory distress syndrome, *CPE* cardiogenic pulmonary edema)

	ARDS		Mixed		CPE (n=12)	p[a]
	Initial (n=11)	Recovery (n=8)	Initial (n=5)	Recovery (n=2)		
Transferrin (g/l)	1.0 (0.5–1.5)	1.3 (0.7–1.6)	1.2 (0.9–1.4)	1.8 (1.5–2.0)	2.1 (1.5–2.7)	<0.001
Transferrin (% of total protein)	2.1 (1.2–2.9)	2.2 (1.4–3.2)	2.5 (1.8–2.6)	2.9 (2.9)	3.3 (2.5–4.6)	<0.001
Total protein (g/l)	49 (41–59)	53 (49–73)*	52 (46–78)	53 (53)*	63 (51–69)	<0.01
Albumin (g/l)	25 (17–34)	23 (19–31)	26 (19–34)	24 (21–28)	30 (25–43)	n.s.
Albumin (% of total protein)	55 (34–61)	42 (33–63)	59 (29–63)	53 (53)	51 (40–66)	n.s.
Pulmonary leak index ($\times 10^{-3}$/min)	32.3 (23.0–54.4)	15.0 (6.6–25.9)*	26.8 (14.2–31.9)	10.8 (5.6–16.1)*	10.1 (4.4–16.2)	<0.001

*p<0.05 versus initial (ARDS and mixed together)
[a] Kruskal-Wallis test

termination. Normal total protein levels are 60–80 g/l, normal albumin levels 34–50 g/l, and normal transferrin levels 1.85–3.36 g/l.

Statistical analysis

To test for changes in variables in groups the non-parametric Wilcoxon signed-rank test and for differences between groups the Wilcoxon rank sum test were used. For comparison of more than two groups the Kruskal-Wallis test was used. Receiver operating characteristic (ROC) curves were calculated, plotting sensitivity to 1–specificity as a measure of diagnostic performance for ARDS in various clinical diagnostic groups. The greater the area under the curve (AUC) approaching 1, the greater the diagnostic performance. Optimum cutoff values (Medcalc v4 software), specificity and sensitivity, and positive and negative predictive values were calculated for various clinical diagnostic groups. Spearman's rank correlation coefficient was used to express relationships. A level of p<0.05 was considered statistically significant. Continuous data are expressed as median and range.

Results

Protein levels

Protein levels were lower in ARDS and mixed patients than in CPE patients, concomitantly with higher PLI in the former (Table 2, Fig. 1). PLI and transferrin, albumin, and total protein levels did not differ between ARDS patients with near-drowning (n=3) and other causes of ARDS (n=8), for example, for transferrin, 1.2 (1.1–1.5) and 0.9 (0.6–1.5) g/l, respectively. In the near-drowning patients the transferrin level had increased to 1.6 (1.1–1.6) g/l at recovery. Indeed, the protein levels increased at recovery, concomitantly with a fall in the elevated PLI in ARDS and mixed patients. There was a tendency for an increase in transferrin levels also (Fig. 1, p=0.08). After pooling data from all groups the transferrin levels were inversely correlated to the PLI (Spearman's r=–0.73, p<0.001) but not to the filling pressures. There was no significant correlation between protein levels, on the one hand, and LIS and PLI, on the other, in ARDS/mixed patients. In the 12 aortic surgery patients the total protein, albumin, and transferrin concentrations were 65 g/l (59–75), 35 g/l (29–38), and 2.7 g/l (1.8–2.9), respectively, and the transferrin fraction of total protein was 4.1% (2.7–4.5%). The upper limit of normal PLI (mean +2 SD) in these patients was 14.1 (median 10.1×10^{-3}/min, range 6.6–13.0). The CPE patients did not differ in PLI or protein levels from these controls, except for a slightly lower transferrin level (p<0.01).

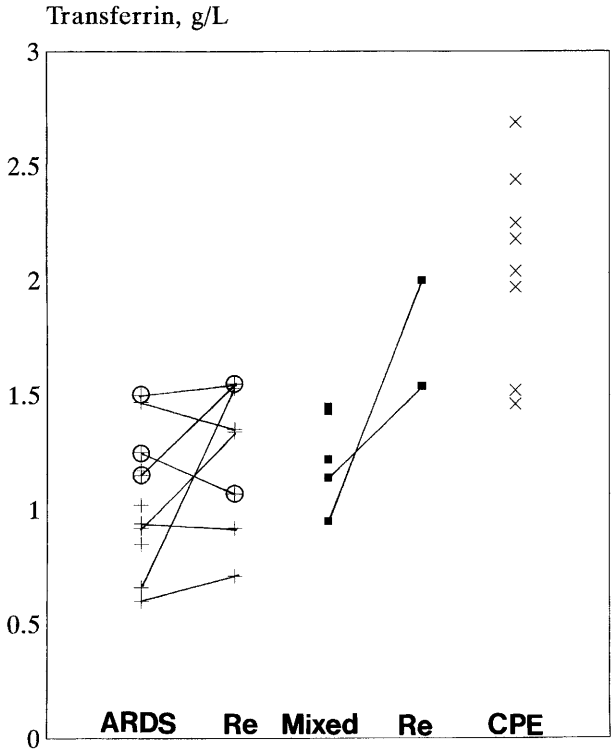

Fig. 1 Transferrin levels in acute respiratory distress syndrome (*ARDS*) and recovery, in patients with a mixed origin of pulmonary edema and recovery (*Re*), and in patients with cardiogenic pulmonary edema (*CPE*). ⊕ Near drowning

Table 3 Diagnostic value of protein markers for ARDS (*ARDS* acute respiratory distress syndrome, *mixed* mixed origin of pulmonary edema, *CPE* cardiogenic pulmonary edema, *AUC* =area under the receiver operating characteristic curve, *PLI* pulmonary leak index of transferrin, PPV positive predictive value, NPV negative predictive value)

	AUC (%)	Cutoff (%)	Specificity (%)	Sensitivity (%)	PPV (%)	NPV (%)
ARDS vs. CPE						
Transferrin (g/l)	0.98***	1.5	87	100	92	100
Total protein (g/l)	0.95***	59	75	100	85	100
Albumin (g/l)	0.80*	24	100	45	100	57
PLI ($\times 10^{-3}$/min)	1***	16.3	100	100	100	100
ARDS vs. mixed+CPE						
Transferrin (g/l)	0.86**	1.25	76	81	75	83
Total protein (g/l)	0.78*	59	53	100	65	100
Albumin (g/l)	0.71	26	69	63	64	69
PLI ($\times 10^{-3}$/min)	0.87**	16.3	76	100	79	100
ARDS+mixed vs. CPE						
Transferrin (g/l)	0.98***	1.5	100	87	100	80
Total protein (g/l)	0.90**	56	87	81	93	70
Albumin (g/l)	0.77*	24	100	44	100	47
PLI ($\times 10^{-3}$/min)	0.98***	16.3	100	87	100	80

*$p<0.05$, **$p<0.005$, ***$p<0.001$

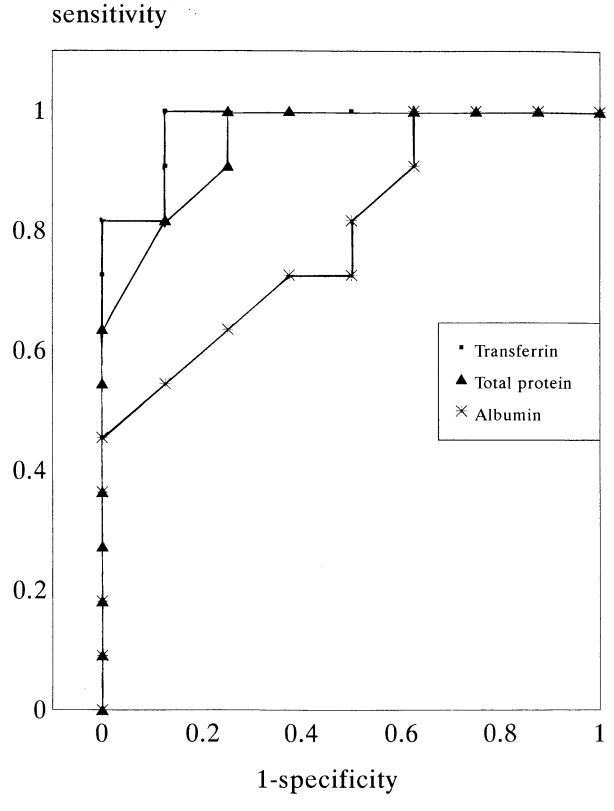

Fig. 2 Receiver operating characteristic curve for circulating transferrin, total protein, and transferrin levels for discriminating acute respiratory distress syndrome from cardiogenic pulmonaryedema. The area under the curve was 0.98 for transferrin ($p<0.001$), 0.95 for total protein ($p<0.001$) and 0.80 for albumin ($p<0.05$)

Diagnostic value

Table 3 summarizes the diagnostic performance of the protein blood concentrations (vs. PLI) in various combinations of clinical diagnostic groups. Sepsis had a 75% sensitivity for ARDS plus mixed vs. CPE and a 100% specificity, at a positive predictive value of 100% and a negative predictive value of 75%, and PLI and transferrin levels therefore had higher diagnostic values. Figure 2. shows that the AUC of the ROC curve for diagnosing ARDS (vs. CPE) was 0.98 ($p<0.001$) for transferrin, 0.95 ($p<0.001$) for total protein, and 0.80 ($p<0.05$) for albumin levels. For PLI the AUC was 1. The diagnostic value of transferrin concentrations approached that of the transferrin PLI (Table 3).

Discussion

Our data suggest that serum protein levels can help to establish the cause of pulmonary edema, since hypoproteinemia/hypotransferrinemia is a marker of increased permeability edema and ARDS. Moreover, protein levels may help to monitor the course of the syndrome. Low total protein and particularly transferrin levels performed almost as well as a diagnostic tool as a supranormal transferrin PLI, which by documenting increased permeability insensitive to fluid overload may be the gold standard for diagnosing and monitoring ARDS [3, 4, 5].

The consensus definition of ARDS, which includes clinical evidence of permeability as opposed to hydrostatic edema, may be imperfect and should be improved

if the aim is indeed to identify the former at the bedside [1, 2]. Indeed, the specificity of the consensus definition for increased permeability edema may be less than that of an elevated PLI or low protein/transferrin levels in the blood, while correct classification may be important for proper therapy and prognosis assessment [1, 2]. For instance, elevated PCWP does not exclude increased permeability edema, as our data and those of others [11] indicate, although excluding ARDS on the basis of the consensus definition. Since the mixed group consisted of patients with increased PLI and PCWP, cardiogenic factors may have been superimposed on increased permeability. To evaluate the diagnostic performance of the protein levels (vs. PLI [3]) we compared various diagnostic groups after combining the mixed group, consisting of patients with a transiently elevated PCWP and risk factors for ARDS, with the "pure" ARDS or with the CPE group. The diagnostic performance of the protein/transferrin levels paralleled that of the transferrin PLI, and was higher when the mixed group was combined with the ARDS than when combined with the CPE group. Hypoproteinemia and hypotransferrinemia may thus help to recognize increased permeability among patients with risk factors for both ARDS and CPE. Nevertheless, the PLI and transferrin levels were of value for differentiating "pure" ARDS from the CPE and mixed groups, since the increase in PLI and fall in protein levels in the blood was greater in "pure" ARDS than in mixed patients. Protein/transferrin levels could thus be helpful in difficult to classify cases when, for instance, clinical ARDS is accompanied by a (transient) elevation in PCWP, or myocardial infarction is associated with pulmonary edema even at a PCWP below 18 mmHg, where low protein levels would support increased permeability/ARDS and normal levels CPE, whereas the consensus definition would suggest CPE and ARDS, respectively.

The consensus definition may inadvertently include pulmonary edema patients as ARDS, having a PCWP in the upper normal range at a normal permeability and heart function, for instance, in the course of overzealous fluid resuscitation and a fall in protein levels in the blood [12]. Our mixed and CPE groups did not include such patients, and we did not separately include them. Although resuscitation with fluids may have contributed to hypoproteinemia, the absence of a high PCWP argues against overhydration in the ARDS group. Hypoproteinemia and hypotransferrinemia did not parallel an elevated PCWP in the groups but marked an elevated transferrin PLI, suggesting that the protein levels were relatively independent of the fluid status in our patients, although the CVP did not differ among groups. Hence, excluding severe hypoproteinemia and hypotransferrinemia may help to prevent misclassification of patients as having ARDS when overhydration dilutes protein levels and permeability in fact is normal. Finally, hypoproteinemia/hypotransferrinemia could be helpful in diagnosing ARDS in the absence of a pulmonary artery catheter but does not exclude a contribution by heart failure or overhydration to pulmonary edema. Further research need to be carried out into the value of circulating protein measurements in patient management.

Some prior studies have reported that hypoproteinemia contributes to a high PCWP-COP gradient predictive of pulmonary edema in critically ill patients, and that (fractional) protein levels in blood, including those of albumin and transferrin, are subnormal in patients with ARDS vs. those with cardiogenic edema and contribute to a high pulmonary edema fluid to serum concentration ratio indicative of permeability edema and ARDS [10, 11, 17]. However, the diagnostic value of hypoproteinemia per se has never been evaluated before. The reason for a better discrimination of total protein and transferrin than of albumin levels between edema types and in reflecting the course of ARDS remains obscure. This discrepancy may relate to the differing regulation of nonalbumin proteins than of albumin in the blood, since hypoalbuminemia may be prevented by an, albeit widely varying, increase in albumin synthesis in the liver, even in the critically ill [18]. Moreover, the permeability characteristics of transferrin and of albumin may slightly differ in spite of similar molecular size, and transferrin permeability may therefore be higher and extravascular distribution volume lower than for albumin [19]. Increased permeability may thus explain in part the fall in fractional transferrin serum concentration in ARDS, as reported previously [15, 17], and the superior diagnostic value of transferrin. The data may also indicate increased permeability for globulins in ARDS, as supported by the literature [11, 14]. Otherwise, the increase in free iron when circulating transferrin is low may contribute to oxidative lung vascular injury [15, 16, 17].

Our results suggest that hypoproteinemia is the result of increased permeability rather than that decreased COP at normal permeability contributes to edema. However, the precise cause of hypoproteinemia remains conjectural and may include extrapulmonary endothelial dysfunction and increased permeability, in the course of sepsis, for instance [9]. During septic shock in pigs, albumin levels and plasma COP decline, while albumin permeability, assessed with help of an analogous radionuclide technique as used in the current study, is increased, more in abdominal organs than in the lungs [7]. Many ARDS and mixed patients had sepsis, and no CPE patient had sepsis. However, the near-drowning ARDS patients had similar protein and transferrin levels as the sepsis ARDS patients, and the sensitivity and diagnostic value of circulating transferrin levels was higher than that of sepsis. Animal studies have suggested that aspiration-induced lung vascular injury results in a general increase in protein permeability both in lungs and systemically [6]. Extrapulmo-

nary leakage of proteins may occur in ARDS patients with trauma [8]. We have also shown that following aortic surgery in humans, both leg and pulmonary permeability to proteins is increased [20]. We thus suggest that ARDS is associated with increased protein permeability and hypoproteinemia, even in the absence of sepsis.

We nevertheless cannot exclude hypoproteinemia contributing in part, together with increased permeability, to a higher LIS and perhaps more severe edema in ARDS than in CPE. During hypoproteinemia and a low plasma COP, the PCWP necessary to evoke edema in the lungs is lowered, according to Guyton's theory, at least in experimental animals with normal permeability when safety factors to prevent edema, including a fall in interstitial protein levels and COP and a rise in lymph flow, are exhausted [12, 21, 22]. Hypoproteinemic pulmonary edema may be treated successfully by elevating the protein levels in the blood, when pulmonary permeability is normal [12]. Safety mechanisms may explain the lack of predictive value for pulmonary edema of the PCWP to COP gradient in patients, reported by others, however [23]. Edema safety factors may also partly explain why colloid fluids for resuscitation from hypovolemia are not proven to be safer, i.e., result less often in pulmonary edema, than crystalloid fluids, although the former maintain or augment and the latter decrease protein levels and COP [9, 20, 24, 25]. However, some animal experiments suggest that when permeability is mildly increased, colloid infusion decreases edema formation compared to crystalloid infusion, at a given PCWP, when safety mechanisms are exhausted [24, 26, 27]. Severely increased permeability, however, may explain a lack of difference between fluids, when fluid filtration is less dependent than normal on protein levels and COP [24]. In our ARDS patients with severely increased permeability hypoproteinemia/hypotransferrinemia may thus have contributed little to the pulmonary edema. Nevertheless, further study is needed to address whether correction of hypoproteinemia in patients with or at risk of ARDS and mildly increased microvascular permeability in the lungs decreases the chance for edema formation at a given PCWP [14, 28].

In conclusion, our results suggest that hypoproteinemia/hypotransferrinemia is a marker of ARDS.

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