Intensive Care Med (2002) 28:1246–1253
DOI 10.1007/s00134-002-1414-3

ORIGINAL

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Detecting lung injury in patients with pulmonary edema

Received: 2 January 2002
Accepted: 7 June 2002
Published online: 19 July 2002

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Abstract *Objective:* Current entry rules for clinical trials of acute lung injury (ALI) depend on clinical criteria and arterial blood gas measurements. The objective of this study was to determine whether estimates of pulmonary vascular permeability could be used to more accurately identify patients with ALI for this purpose. *Design and setting:* Cross-sectional study in a university hosptial in a large metropolitan city. *Patients and participants:* 21 patients with noncardiogenic pulmonary edema, 7 patients with hydrostatic forms of pulmonary edema, and 10 healthy volunteers. *Interventions:* Positron emission tomographic (PET) imaging with ^{68}Ga-labeled transferrin, or γ-camera scintigraphy (γ-S) with ^{99m}Tc-labeled albumin. All patients were studied within 24 h of onset, and all were selected exclusively on the basis of radiographic, not clinical, criteria. PET estimates of PTCER were used as a "gold standard." *Measurements and results:* Radioactivity data were analyzed to compute the pulmonary transcapillary escape rate (PTCER) and the normalized slope index. PTCER by γ-S was more strongly correlated to $PTCER_{PET}$ than normalized slope index by γ-S. Although $PTCER_{\gamma}$ was significantly correlated with PaO_2/FIO_2, it did not distinguish patients with noncardiogenic pulmonary edema from those with hydrostatic pulmonary edema. *Conclusions:* These data cast doubt on whether the γ-S method can be used as a screening tool in clinical trials of ALI.

Keywords Respiratory distress syndrome, adult · Capillary permeability · Tomography, emission-computed · Radionuclide imaging

Introduction

The detection of acute lung injury (ALI), especially for the purpose of identifying appropriate patients for clinical trials of novel treatments, remains a controversial and important problem [1, 2, 3, 4, 5]. At present the diagnosis of ALI (or the putatively more severe form of the acute respiratory distress syndrome, ARDS) depends entirely on a set of readily obtained but clearly nonspecific clinical criteria, collectively known as the American-European Consensus Conference (AECC) criteria [6]. The value of these criteria has been challenged [2, 3, 4, 5], but in the absence of some evidence-based alternative the AECC criteria continue to be used, almost universally, to establish inclusion criteria for ALI/ARDS clinical trials.

Regardless of which *criteria* are used, all *definitions* of ARDS incorporate the concept of damage to the normal barrier function of the alveolocapillary membrane [5, 6]. The result presumably should be measurable increases in pulmonary vascular "permeability." While changes in barrier integrity can often be inferred clinically (e.g., from hemodynamic measurements, chest radiographic patterns, or protein concentrations in pulmonary edema fluid), quantitative approaches to measuring vascular permeability are almost all based on measuring the

accumulation of radioactively labeled substances (usually proteins) into the lungs [7]. However, different radiolabels, proteins for labeling, instrumentation, and mathematical treatments of the data lead to numerous unique combinations to accomplish the same goal, yet few if any direct comparison studies have been performed, either experimentally or clinically [8, 9, 10, 11].

To initiate such a study we reasoned as follows: There is little controversy that positron emission tomography (PET) imaging is the most accurate means of measuring tissue radioactivity in vivo [12]. Likewise, calculation of the pulmonary transcapillary escape rate (PTCER) from the acquired radioactivity data using a formally derived two-compartment model of the pulmonary vasculature clearly rests on the soundest mathematical base [8]. Accordingly, we assumed that PTCER calculations from PET-derived data would provide a noninvasive "gold standard" against which other methods could be compared.

On the other hand, PET is cumbersome, expensive, and not readily available at all times or at all institutions, while mobile γ-scintigraphy (γ-S) cameras are available at virtually all institutions as they are still the most commonly employed tool used to detect pulmonary emboli, even in critically ill patients who cannot be moved to various alternative imaging facilities. Furthermore, ^{99m}Tc labeling of albumin is simple and straightforward. Thus measuring the rate of pulmonary accumulation of ^{99m}Tc-labeled albumin by γ-S represented to us one particularly attractive possibility for evaluating pulmonary vascular permeability that could theoretically be incorporated into the study design of clinical trials of new treatments for ALI/ARDS.

Finally, previous studies of these and similar techniques have always been conducted in carefully defined patient groups ("ARDS," "heart failure," etc.). However, if these techniques indeed hold any added value, they must help *resolve* confusion in cases where the cause is not already clear from current clinically based approaches. Accordingly, we recruited patients only on the basis of whether their chest radiograph met carefully defined criteria for pulmonary edema, without regard to a putative clinical cause.

The purpose of this study was therefore to first compare calculations of PTCER (as well as alternative mathematical treatments) obtained by γ-S to a "gold standard" of similar calculations obtained by PET imaging and then to apply the best γ-S technique to a diverse group of patients, all of whose chest radiographs met prospectively defined criteria for pulmonary edema due to either ALI, ARDS, or other causes.

Methods

These studies were approved by the Washington University School of Medicine Human Studies Committee, in accord with the 1964 Declaration of Helsinki.

Subjects

We studied 28 patients with acute pulmonary edema and 10 normal subjects (Fig. 1). In retrospect (i.e., after the study was completed) the cause was considered to be noncardiogenic in 21 patients (NCPE; Table 1), and of these all but two met the AECC gas exchange criteria for ALI or ARDS. The cause of pulmonary edema in the remaining 7 patients was presumed to be either cardiogenic or volume overload (hydrostatic pulmonary edema, HPE), based on clinical context and standard clinical criteria. All patients with pulmonary edema were studied by γ-S, and 5 of these were also studied with PET.

Patients were identified by a trained research nurse who reviewed the chest radiographs of all new admissions to the medical and surgical intensive care units. The radiographs were scored according to a previously reported system (see below), and patients and/or their families were approached about study participation only if: (a) the radiograph met criteria for pulmonary edema (see below), (b) the onset of radiographic findings could be verified to be newly developed within the previous 24 h, and (c) PaO_2 was higher than 70 mmHg on FIO_2 lower than 0.7, the dose of vasoactive medications (e.g., dopamine) had not been increased for at least 6 h, and there was no evidence of cardiac arrhythmia. Patients were *not* selected on the basis of clinical cause of pulmonary edema (e.g., NCPE or HPE).

After enrollment clinical and demographic information were abstracted from the patient record. A γ-S study was then obtained. Patients in whom a PET study was also obtained were then moved to the PET facility, usually within 2 h of beginning the γ-S study.

All 10 healthy volunteers were studied with both γ-S and PET.

Chest radiographic evaluation

Each qualifying radiograph met all three of the following criteria [13]: (a) a chest radiographic score higher than 4 (see following), (b) involvement of basilar and perihilar regions bilaterally at a minimum, and (c) at least one region on each side with a score higher than 2. To score the radiograph each lung was divided into apical, perihilar, lateral, and inferior regions. Each region was then evaluated separately on a scale of 0–3: 0=no infiltrate, 1=minimal or barely perceptible infiltrate, 2=moderate interstitial infiltrate but without obscuration of pulmonary vessels, and 3=extensive confluent infiltrate with or without air bronchograms that obscured pulmonary vessels. The highest possible score within a re-

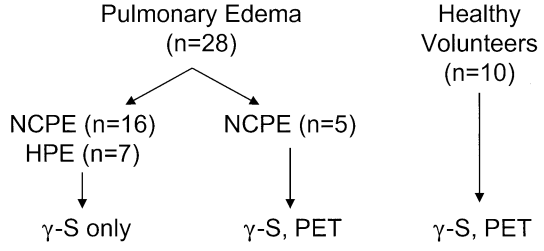


Fig. 1 Distribution of imaging studies among patients with pulmonary edema and healthy volunteers. *NCPE* Noncardiogenic pulmonary edema; *HPE* hydrostatic pulmonary edema; PET positron emission tomography; *γ-S* γ-scintigraphy

Table 1 Clinical and demographic data on patients with pulmonary edema (*P/F* PaO_2/FIO_2 ratio, *Vent* ventilator, CXR chest radiography, *HPE* hydrostatic pulmonary edema, *CHF* congestive heart failure, *CS* cardiogenic shock, *FO* fluid overload, *P* pneumonia, *ARDS* acute respiratory distress syndrome, *NCPE* noncardiogenic pulmonary edema, *Asp* aspiration)

Patient no.	Cause	Diagnosis	Age (years)	Race	Sex	P/F	Vent	CXR score	Outcome
γ-1	HPE	CHF	48	Black	M	–	No	5.5	Alive
γ-2	HPE	CHF	67	Black	F	–	No	8.5	Alive
γ-5	HPE	CS	78	White	M	255	Yes	4.5	Dead
γ-9	HPE	CHF	78	White	M	85	Yes	6	Dead
γ-10	HPE	CHF	70	White	F	–	No	11	Alive
γ-15	HPE	FO	65	Black	M	265	Yes	9	Alive
γ-17	HPE	CHF	38	White	F	87	Yes	6	Alive
γ-3	NCPE	P	81	White	F	119	Yes	10.5	Alive
γ-4	NCPE	FO/ARDS	45	White	F	48	Yes	5.5	Alive
γ-6	NCPE	CHF/sepsis	79	White	M	86	Yes	9	Alive
γ-7	NCPE	ARDS	42	Black	F	65	Yes	12	Alive
γ-8	NCPE	ARDS	62	White	F	213	Yes	8.5	Dead
γ-11	NCPE	P	41	White	M	59	Yes	11.5	Dead
γ-12	NCPE	Sepsis	90	Black	F	–	No	8	Alive
γ-13	NCPE	FO/MTx	65	White	M	–	No	7	Alive
γ-14	NCPE	FO/sepsis	64	Black	M	194	Yes	10	Alive
γ-16	NCPE	Sepsis	80	Black	M	92	Yes	5	Dead
γ-18	NCPE	P	38	Black	M	533	No	9	Alive
γ-19	NCPE	P	63	White	F	120	No	9	Alive
γ-20	NCPE	P	20	Black	F	81	Yes	11	Alive
γ-21	NCPE	Asp	44	White	M	203	Yes	8	Alive
γ-22	NCPE	Trauma	29	Black	M	190	Yes	7.5	Alive
γ-23	NCPE	Asp	43	White	M	123	Yes	7.5	Alive
γ/PET-1	NCPE	P	25	White	F	203	Yes	9	Dead
γ/PET-2	NCPE	Sepsis	50	White	F	107	Yes	10	Dead
γ/PET-3	NCPE	Sepsis	45	Black	M	332	Yes	10	Alive
γ/PET-4	NCPE	Sepsis	59	White	F	232	Yes	9	Alive
γ/PET-5	NCPE	FO/Asp	41	Hispanic	M	168	Yes	12	Alive

gion was used (e.g., the entire region did not have to be involved uniformly to achieve a score of "3." Each lung was scored separately, and the scores for each lung were summed. Then the total scores of each lung were averaged. Thus the final total score could range from 0 to 12.

PET techniques

PET scans were performed using a Siemens/CTI ECAT EXAC HR plus 962 scanner (Siemens/CTI, Knoxville, Tenn.,USA). Time-activity data were obtained after intravenous injection of ^{68}Ga-labeled citrate. Methods for preparation of ^{68}Ga-labeled citrate have been described previously [14]. After performing background and transmission scans (to correct for tissue attenuation during subsequent emission scans) [12, 15] up to 6 mCi ^{68}Ga-labeled citrate was injected intravenously. The ^{68}Ga rapidly dissociates from citrate and avidly binds to endogenous transferrin. Serial emission scans were obtained for 44 min after radionuclide administration.

γ-Scintigraphic techniques

Following the intravenous injection of approx. 25 mCi ^{99m}Tc-labeled human serum albumin, lung and heart imaging was performed in supine patients using a GE Starcam mobile gamma camera with a 25-cm field of view, with a diverging collimator so that both lungs and the cardiac blood pool could be positioned within the field of view. The camera's energy pulse height analyzer was set for a 20% window centered on the 140 keV photopeak of ^{99m}Tc. Image acquisition began when the radiolabeled albumin was injected. Serial digital images were obtained at the rate of one frame/minute for 45 min.

Image analysis

For PET imaging regions of interest (ROIs) for the lung and right ventricular blood pool were defined. The data from each slice from both lungs were averaged so that the final data represents one analysis per patient. For γ-S imaging whole-lung ROIs were drawn on the planar (anterior) images. An ROI was also drawn over the cardiac blood pool.

Computations

Methods for computing PTCER from radiolabeled protein time-activity data have been described previously [8, 14, 16]. The same computational approach was applied to data obtained by PET or γ-S. Also, a normalized slope index (NSI) was calculated by a modification of the methods described by Roselli and Riddle [8]. In the original method ^{51}Cr-labeled erythrocytes were used to account for possible changes in blood volume during the scan period. We chose to eliminate this step (see "Discussion"). Instead, we first calculated the "normalized index" (NI) for each dynamic frame as: $NI=(L_t/L_0)/(H_t/H_0)$ where L_t and H_t are activity measurements in lung and heart ROIs, respectively, at each time t, and L_0 and H_0 are activities in these same regions beginning 2 min after tracer injection (time "zero"). The NSI then was calculated by simple linear regression of NI over time. The same analytic approach was used for both the PET and γ-scintigraphic acquired activity data.

Statistical analysis

All data are presented as mean ±standard deviation. Group means are compared by Student's *t* test for unpaired data. Relationships among variables were analyzed by standard linear regression methods. A *p* value less than 0.05 was considered statistically significant. Sigma-Stat (version 2.03; SPSS) was used to perform these calculations.

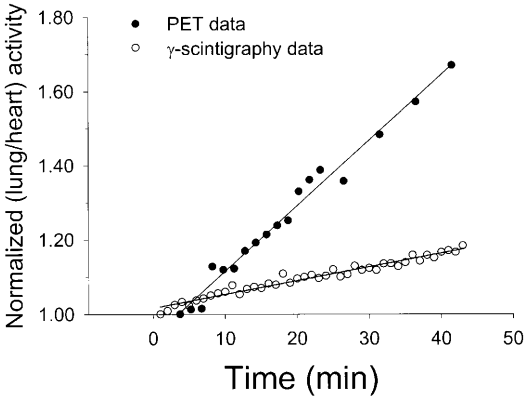


Fig. 2 Examples of time-activity data obtained by positron emission tomography (*PET*; closed symbols) and γ-scintigraphy (*open symbols*), both used to calculate the normalized slope index, as described in the text. Linear regression fits to the data are also shown. The normalized slope index for the PET data was 176 $min^{-1}\times10^{-4}$; for the $_{\gamma}$-S data it was 37 $min^{-1}\times10^{-4}$

Results

Time-activity curves obtained with PET in patients with ALI, used to calculate the PTCER for ^{68}Ga-labeled transferrin, have been shown in a previous report by our group [17]. Figure 2 shows an example of how these same data were analyzed to compute the NSI, alongside an example of similar data used to calculate NSI from γ-S.

For the patients with pulmonary edema, the chest radiography score averaged 8.5±2.1 (pulmonary edema was defined as a minimum score of >4, with a range of values from 0 to 12). The score was statistically higher (p=0.05) in the 21 patients with NCPE (9.0±1.9) than in the 7 patients with non-ALI (7.2±2.3). Both PTCER and NSI calculated from PET data were lower in the healthy volunteers than in patients with NCPE (Fig. 3). The values for PTCER by PET in the healthy volunteers and in the patients with NCPE were similar to those previously reported by our group [17]. Likewise, both PTCER and NSI calculated from the γ-S data were lower in the healthy volunteers than in patients with NCPE (Fig. 4). The values for both NSI by γ-S in the healthy volunteers and in the patients with NCPE were similar to those previously reported by others [11].

PTCER and NSI, when both were obtained by PET, were highly correlated (Fig. 5), although the NSI values systematically underestimated the PTCER calculations.

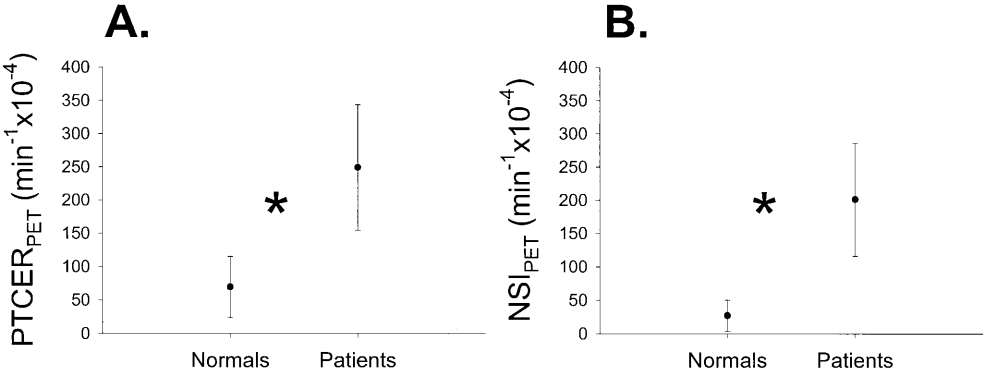


Fig. 3 Mean ±SD for the pulmonary transcapillary escape rate (*PTCER*; **A**) and the normalized slope index (*NSI*; **B**), obtained by positron emission tomographic (*PET*) imaging, for normal volunteers and for patients with pulmonary edema. *p<0.05 10 healthy volunteers vs. 5 patients with noncardiogenic pulmonary edema

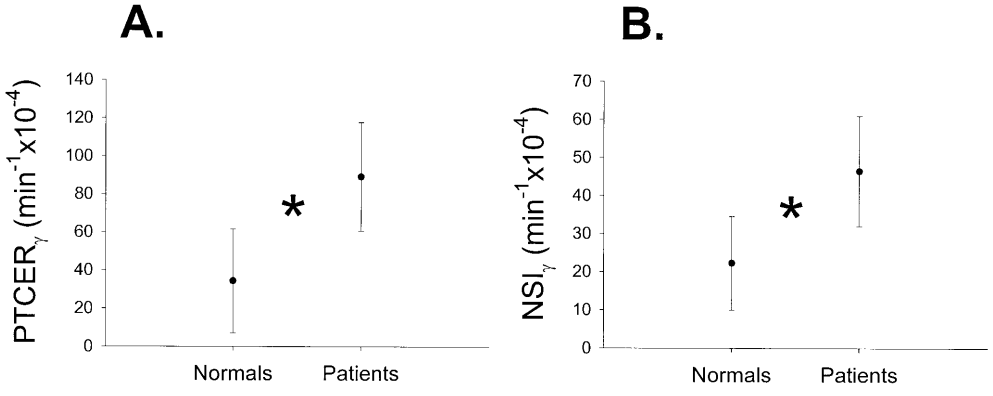


Fig. 4 Mean ±SD for the pulmonary transcapillary escape rate (*PTCER*; **A**) and the normalized slope index (*NSI*; **B**), obtained by γ-scintigraphy ($_{\gamma}$-*S*), for normal volunteers and for patients with pulmonary edema. *p<0.05 10 healthy volunteers vs. 5 patients with noncardiogenic pulmonary edema

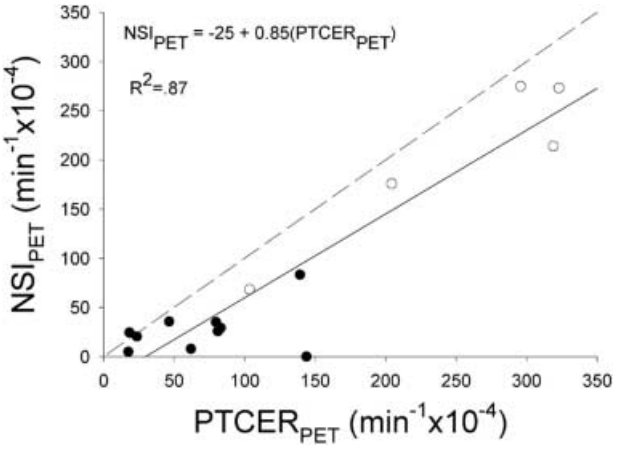


Fig. 5 Correlation plot of the normalized slope index (*NSI*) and the pulmonary transcapillary escape rate (*PTCER*), as calculated from positron emission tomographic (*PET*) data. Also shown is the linear regression fit to the data (*solid line*) and the line of identity (*dashed line*). Data were obtained from 10 healthy volunteers and 5 patients with noncardiogenic pulmonary edema

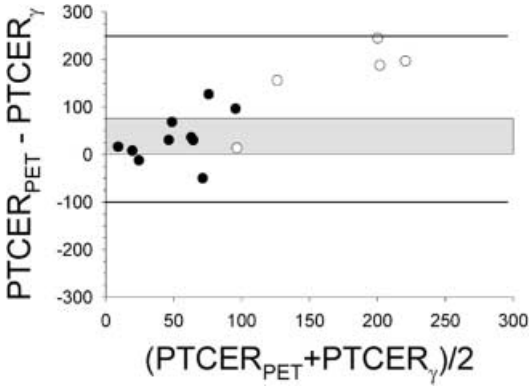


Fig. 6 Bland-Altman plot [30] of the difference between the pulmonary capillary escape rate (*PTCER*) as calculated by positron emission tomography (*PET*) and PTCER calculated from γ-scintigraphy (γ-S) vs. the mean of each set of PTCER values, obtained from 10 healthy volunteers and 5 patients with noncardiogenic pulmonary edema. *Gray bar* Bias in the measurement from complete agreement between the two measurements (i.e., departure from zero); *solid horizontal lines* show ±1 SD from the mean (i.e., the "limits of agreement," according to this form of analysis)

The correlation was equally strong (R^2=0.87) if only the 5 patients with ALI/ARDS were included in the regression analysis. PTCER when calculated from the PET data, and NSI when calculated from the γ-S data, were positively, although poorly correlated (R^2=0.27). The correlation improved significantly when the γ-S data were used to calculate PTCER (R^2=0.44). Even so, the γ-S calculation of PTCER was systematically lower than the PTCER calculation from the PET data (Fig. 6), and the difference increased as PTCER increased.

Both $PTCER_\gamma$ and NSI_γ were correlated significantly with the PaO_2/FIO_2 ratio in the 21 patients with pulmonary edema in whom we were able to obtain an accurate measure of the FIO_2 (20 patients on mechanical ventilation and one patient on room air at the time of the γ-S study; Fig. 7). However, the strength of the correlation with $PTCER_\gamma$ was considerably greater than with NSI_γ. Neither correlation was improved when the chest radiography score was added in a multivariate regression analysis (data not shown). Nevertheless, given the stronger

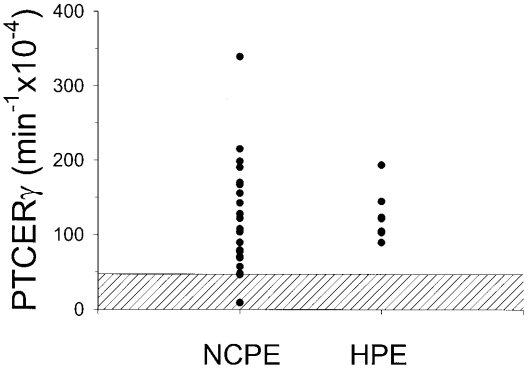
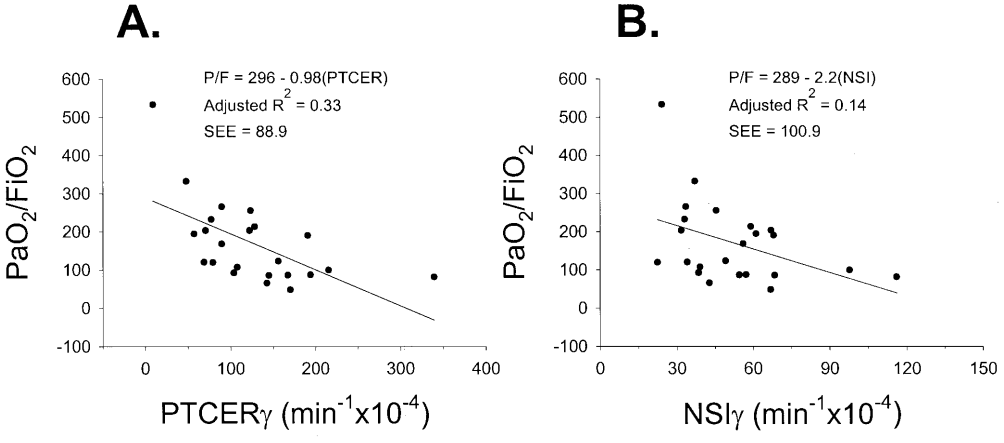


Fig. 8 Distribution of individual values for the pulmonary transcapillary escape rate (*PTCER*) for all patients with pulmonary edema studied by gamma scintigraphy (*n*=28), sorted by putative clinical cause (noncardiogenic pulmonary edema, *NCPE*; hydrostatic pulmonary edema, *HPE*). Means values from the two groups were not statistically different. *Hashed bar* Range of normal values ±1 SD (from data in Fig. 3).

Fig. 7 Correlation plots of the PaO_2/FIO_2 ratio vs. the pulmonary transcapillary escape rate (*PTCER*; **A**) or the normalized slope index (*NSI*; **B**), calculated from data obtained by gamma scintigraphy (γ-S), in 21 patients with pulmonary edema. Also shown are the linear regression fits to the data (*solid lines*)



correlations of $PTCER_{\gamma}$ than NSI_{γ} with both $PTCER_{PET}$ (our "gold standard") and with PaO_2/FIO_2, we chose $PTCER_{\gamma}$ as the principal analytic method to "detect" acute lung injury in all 28 patients with radiographic pulmonary edema. $PTCER_{\gamma}$, however, was *not* significantly different in patients with NCPE than in patients with HPE (Fig. 8), nor was it significantly different between patients requiring or not-requiring mechanical ventilation (data not shown). Finally, $PTCER_{\gamma}$ was not predictive of hospital survival.

Discussion

The significant new findings of this study may be summarized as follows. (a) PTCER and NSI are strongly correlated with one another, and therefore either can potentially serve as a quantitative estimate of the rate of radiolabeled protein accumulation as a marker of lung injury (Fig. 5), (b) $PTCER_{\gamma}$ shows a stronger correlation with $PTCER_{PET}$ (the presumptive "gold standard," see below) and PaO_2/FIO_2 than NSI_{γ} (Fig. 7), (c) $PTCER_{\gamma}$, however, does not reliably distinguish NCPE from non-ALI in unselected patients with pulmonary edema (Fig. 8). On balance, we believe these data indicate that while these methods may be used to quantify the *severity* of lung injury when ALI can be presumed on clinical grounds, they cast doubt on whether they can be used to reliably identify patients with lung injury, for instance to qualify patients for clinical trials.

Choice of instrumentation

It is obvious that any noninvasive attempt to evaluate pulmonary vascular permeability by measuring the time-dependent accumulation of an intravenously administered radiolabeled protein critically depends on the accuracy of the radioactivity measurements themselves in both lung tissue and in the blood pool. In this regard, PET imaging is clearly a superior technology to alternative methods [12, 15]. Additionally, the PET method is the only technique which has been shown to be correlated with estimates of lung damage histopathologically [18].

A potential *disadvantage* of using PET imaging to evaluate pulmonary vascular permeability is that only one radiotracer can be employed at any given time, because all radiation used in producing PET images is monoenergic, making it impossible to separately detect simultaneously administered radiotracers (for instance, to monitor changes in blood volume). Although Dauber et al. [19] found that ignoring vascular volume changes during the scan period eliminated the ability to differentiate hydrostatic and injury forms of pulmonary edema from one another in experimental animals [19], we reported in simulation studies that ignoring such changes should significantly affect estimates of PTCER only in normal, not injured, lung tissue [10]. Importantly, Raijmakers et al. [20], using the double-isotope method, failed to detect any systematic change in intrapulmonary blood volume during a 60-min data acquisition period in patients with ALI.

Our decision to test γ-S against data obtained by PET imaging was more straightforward. Although alternative, even simpler, systems (i.e., probes) have been used in studies of pulmonary vascular permeability during ALI, they are not widely available, poorly standardized, and prone to user variability. Since our focus was on evaluating these measurements as a screening tool for clinical trials, we chose to use mobile γ-S cameras, which are both familiar and widely available.

Choice of tracers

Both radiolabeled albumin and transferrin have been used to evaluate pulmonary vascular permeability [11]. In a previous study in dogs we showed that although the PTCER for transferrin is consistently higher than that for albumin, the two are highly correlated, justifying the use of either [21]. Given the ease of radiolabeling transferrin rather than albumin for PET imaging, we chose to use the former. For the γ-S studies both proteins can be radiolabeled rather easily, and both have been used in numerous studies [11]. However, ^{67}Ga (used to label transferrin for γ-S) cannot be used with *mobile* γ-S cameras because of its relatively high energy. Accordingly, given our choice to employ mobile γ-S cameras, we used ^{99m}Tc labeling of albumin. The γ-S technique can be employed with *two* radiotracers, a protein labeled tracer and a red cell tracer to monitor potential changes in intravascular blood volume [8, 11]. However, once we decided to use ^{99m}Tc to label albumin, we would have had to choose an alternative label for red cells, with issues of complexity and appropriateness for mobile γ-S imaging, making this approach unattractive as a screening tool for clinical trials.

Choice of model

The two most common analytic approaches to the time-activity data are to implement a two-compartment model (vascular + extravascular), or to analyze serial measurements of lung tissue-to-blood activity ratios by linear regression (e.g., as in Fig. 2) [1, 8, 11, 22, 23]. As discussed elsewhere, these two approaches actually share a common mathematical foundation and set of assumptions [8, 9, 10]. In the current study we show for the first time in a clinical setting that the two calculation methods are indeed highly correlated (Fig. 5). Nevertheless, PTC-

ER_{γ} showed a stronger correlation to $PTCER_{PET}$ than did NSI_{γ}, although in absolute terms neither correlation was particularly strong.

Implications

In this study the inability of the $_{\gamma}$-S approach to reliably differentiate apparent cases of hydrostatic edema (based on clinical criteria) from those due to lung injury (Fig. 8) appears to be at odds with previous reports from several groups, including our own (reviewed in [11]). For reasons discussed above, we discount the possibility that the failure to include a blood pool marker is the reason for failure to distinguish the different causes of pulmonary edema. However, even if it were true here, we contend that the need to add the additional complexity of a second radiotracer would essentially eliminate any potential attractiveness of this technique anyway as a means of screening patients for clinical trials in acute lung injury.

A second possibility is that our patients were inadequately or inappropriately characterized as having pulmonary edema due to hydrostatic causes (in general, congestive heart failure or volume overload). We cannot exclude this possibility since we did not have direct hemodynamic information from pulmonary artery catheterization and instead depended upon the clinical context and the treating team's assessment to classify patients this way (as is common practice in any case for deciding appropriateness for entry into clinical trials).

A related possibility is the difference by which patients were recruited to this study compared to previous studies [17, 20, 24, 25, 26]. Although widely quoted as being able to distinguish NCPE from hydrostatic causes of pulmonary edema, the number of patients with "heart failure" or "volume overload" who have been studied with one of these methods is actually relatively small. In the majority of cases we suspect that patients with "heart failure" or "volume overload" were carefully selected, often after sufficient time had elapsed so that the diagnostic classification would be clear. In many cases, we suspect, the clinical status of the patients was already improving at the time of the radionuclide study. It is in such circumstances that the measurement of pulmonary vascular permeability in these patients with clinically apparent HPE may well have been "normal."

In contrast, we selected patients only on the basis of their chest radiography score, the willingness of the patients or their families to participate in this research study, and the availability of the appropriate technical staff. In retrospect, 25% of our patients were classified as having hydrostatic forms of pulmonary edema. All were studied within the first 24 h of hospital admission, consistent with entry criteria to most clinical trials of ALI/ARDS.

It should be noted at this point that the term "permeability" is imprecise, because the two-compartment model upon which it is based implies that protein transport across the endothelium occurs via a purely diffusive mechanism. However, the measurements of flux of radiolabeled protein cannot distinguish diffusive from convective protein transport across the vascular-extravascular barrier. Although transendothelial convective transport may not be significant under normal conditions, it may become considerably more important when hydrostatic pressures are high. Lesser degrees of structural lung injury ("alveolar damage") or capillary stress failure associated with high intrasvascular pressure and mechanical ventilation (which may be rapidly reversible) may allow rapid egress of radiolabeled proteins from the vascular space during the most acute period of pulmonary edema, which translates into high calculated values for PTCER (or NSI). PTCER (or NSI) may then rapidly become "normal" once the hydrostatic pressures are adequately controlled, even in the presence of continued or residual pulmonary edema radiographically. In this regard, it is important to note that in the study with the largest number of hemodynamically well-characterized patients there was considerable overlap of values from patients with HPE and those with clinically apparent ALI [24], especially when the pulmonary artery occlusion pressure was higher than 30 mmHg.

Regardless, these uncertainties unfortunately cast doubt on the ability of the $_{\gamma}$-S technique to be used as a screening tool for entry criteria into clinical trials of new treatments for acute lung injury. In this sense, the results are similar to disappointing attempts by others to use inhalational techniques with radiolabeled tracers to identify patients with ALI [27]. Since we did not make measurements with PET in a comparably large group of patients, it is still possible that measurements with this more sophisticated method can successfully distinguish lung injury patients from those without lung injury. However, PET imaging is an expensive and impractical tool and would also be inappropriate for screening patients for entry into clinical trials involving acute lung injury. For this, more specific, easily obtained, markers of endothelial or epithelial cell damage are still needed [28, 29].

Acknowledgements The authors wish to gratefully acknowledge the contributions of Jim Kozlowski (PET imaging and analysis), Salome Niesenbaum RN and Janet Voorhees RN (patient recruitment), Claire Anderson MD for her review of the chest radiographs, and the staff of the Division of Nuclear Medicine (technical support) to this study. Source of support: NIH HL56627.

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