4. Silberstein E, Worsley DF, Alavi A, Elgazzar A. The clinical significance of the very low probability (PIOPED) lung scan pattern [Abstract]. *J Nucl Med* 1995;36:113P.
5. Stein PD, Relyea B, Gottschalk A. Evaluation of the positive predictive value of specific criteria used for the assessment of low-probability ventilation/perfusion lung scans. *J Nucl Med* 1996;37:577–581.
6. Stein PD, Gottschalk A, Henry JW, Shivkumar K. Stratification of patients according to prior cardiopulmonary disease and probability assessment based upon the number of mismatched segmental equivalent perfusion defects: approaches to strengthen the diagnostic value of ventilation/perfusion lung scans in acute pulmonary embolism. *Chest* 1993;104:1461–1467.
7. Stein PD, Henry JW, Gottschalk A. Mismatched vascular defects: an easy alternative to mismatched segmental equivalent defects for the interpretation of ventilation/perfusion lung scans in pulmonary embolism. *Chest* 1993;104:1468–1472.

Diagnostic Value of the Gallium-67 Pulmonary Leak Index in Pulmonary Edema

Pieter G.H.M. Raijmakers, A.B. Johan Groeneveld, G.J. Jaap Teule and Lambertus G. Thijs
Medical Intensive Care Unit, Departments of Nuclear Medicine, and Internal Medicine, Free University Hospital, Amsterdam, The Netherlands

We studied the value of a noninvasive, bedside, dual-radionuclide method (^{67}Ga-circulating transferrin and ^{99m}Tc-red blood cells) to measure pulmonary microvascular permeability in efforts to discriminate between pulmonary edema due to adult respiratory distress syndrome (ARDS) and hydrostatic pulmonary edema (HPE). **Methods:** Patients had respiratory insufficiency and bilateral alveolar pulmonary edema on chest radiographs. All patients, except one, were mechanically ventilated. Patients were divided into groups according to various sets of etiologic, hemodynamic and ventilatory factors. Group 1 (n = 8) had risk factors for HPE only. Group 2 (n = 5) had risk factors for both ARDS and HPE, such as a pulmonary capillary wedge pressure (PCWP) above 18 torr. Group 3 (n = 13) had risk factors for ARDS only and a PCWP below 18 torr. Patients were also classified on the basis of a lung injury score, using radiographic and ventilatory variables. Group 4 (n = 12) had a score below 2.5 and Group 5 (n = 14) above 2.5, arbitrarily defined as ARDS. Any radioactivity measurements over the lungs and in blood within 72 hr after admission were used to calculate the 1 hr pulmonary leak index as a measure of microvascular permeability (upper limit of normal 14.1 $\times$ $10^{-3} \cdot min^{-1}$). **Results:** The PLI ($\times 10^{-3} \cdot min^{-1}$) was median 10.2 (range 4.4–16.2) in Group 1, 26.8 (14.2–31.9) in Group 2 and 32.3 (23.0–52.4) in Group 3 ($p < 0.001$). It was 13.3 (4.4–39.9) in Group 4 and 31.1 (14.2–52.4) in Group 5 ($p < 0.01$). Using the various definitions, the sensitivity of a supranormal pulmonary leak index for ARDS was 100% and the specificity varied between 46% and 75%. In receiver operating characteristic curves, the pulmonary leak index performed best when ARDS and HPE were defined on the basis of risk factors only, and performed better than hemodynamic and equally well as ventilatory variables in discriminating between edema types, if definitions of the latter were mainly based on hemodynamic and ventilatory variables, respectively. **Conclusion:** The ^{67}Ga pulmonary leak index is a useful tool to differentiate ARDS from HPE.

Key Words: adult respiratory distress syndrome; hydrostatic pulmonary edema; protein leak; gallium-67; pulmonary leak index

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Pulmonary edema of adult respiratory distress syndrome (ARDS) supposedly results from increased permeability of the pulmonary microvasculature. ARDS is sometimes hard to differentiate from hydrostatic pulmonary edema (HPE), which is presumably caused by a high microvascular hydrostatic pressure. The diagnosis of pulmonary edema is based on the chest radiograph, even though the acute appearance of bilateral, fluffy alveolar consolidations may be caused by other factors than edema (*1–3*). Although the radiographic abnormalities may correlate somewhat with extravascular lung water and may have specific features for either type of edema, the assessment of extravascular lung water is nonspecific and the radiologic differentiation among edema types is hard, necessitating adjunct diagnostic criteria (*1–9*). Various combinations of etiologic, hemodynamic and ventilatory factors are used to help differentiating ARDS from HPE, in the absence of a standard (*1–4,6–20*). For instance, a pulmonary capillary wedge pressure (PCWP) below 15–18 torr is commonly used as a criterion for ARDS (*6–11,13–16,18–20*).

The diagnosis can also be based on the presumed difference in pathophysiology: increased protein permeability for ARDS and normal permeability for HPE. The assessment of protein contents in bronchoalveolar lavage fluids, however, may be impractical and may lack sufficient sensitivity and specificity to be clinically useful in diagnosing permeability edema associated with ARDS (*1,7*). Other methods developed to detect increased microvascular permeability noninvasively utilize intravenously injected radiolabeled proteins and radioactivity measurements over the lung and in blood over time, yielding the pulmonary leak index or analogous indices as measures of the pulmonary transvascular protein transport (*2,3,5,9–18,21–25*). The leak index, using ^{113m}In-transferrin or ^{99m}Tc-albumin may be elevated during ARDS and not during HPE but the diagnostic value is still unclear, since some patients with ARDS may have a normal pulmonary leak index, while some patients with HPE and a PCWP above 30 torr may have an elevated pulmonary leak index, possibly as a consequence of increased protein transport, i.e., solvent drag, induced by high microvascular fluid filtration pressures (*2,9–12,14,15,18,24*). Many of these methods may have methodologic drawbacks and limited clinical applicability at the bedside (*2,9–16,18,21–23*). For instance, measuring the kinetics of the intravenously injected positron emitter ^{68}Ga, binding to circulating transferrin, may be able to discriminate increased permeability from hydrostatic edema of the lungs, but PET is not widely available, cannot be applied at the bedside and the method, like others, does not incorporate an intravascular tracer to correct for potential changes in pulmonary blood volume (*5,9–13,16*). We therefore use a dual radionuclide method and a sensitive, mobile probe system to allow for bedside measurements of the kinetics of the commonly available permeable tracer, ^{67}Ga, supposed to bind

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For correspondence or reprints contact: A.B.J. Groeneveld, MD, PhD, Medical Intensive Care Unit, Free University Hospital, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands.

TABLE 1
Patient Characteristics

	Group 1 (n = 8)	Group 2 (n = 5)	Group 3 (n = 13)
Age (yr)	68 (50–79)†	53 (32–65)	46 (21–78)
Sex	8 men	3 men/2 women	7 men/6 women
Underlying disease*			
Pulmonary sepsis		3	2
Extrapulmonary sepsis		2	6
Near-drowning			4
Hemorrhagic shock/resuscitation		1	1
Postcardiopulmonary resuscitation	2		4
Remote myocardial infarction	6		
Recent myocardial infarction	5	1	
History of coronary revascularization	2		
Hypertension	1		
ICU mortality, number (%)	3 (37%)	2 (40%)	5 (38%)

*Patients may have more than one underlying disease. †$p < 0.05$, Kruskal-Wallis analysis of variance.
Median and range or number of patients, where appropriate.

to transferrin, and an intravascular tracer, ^{99m}Tc-labeled red blood cells (*17,25*). Although transvascular protein transport in the lung has been suggested to indicate permeability (*2,3,5,9–18,21–25*), independently of microvascular pressures and exchange surface area, it is unclear whether this also applies for gallium, since binding to circulating transferrin may be less avid than for indium (*26*). Hence, the ^{67}Ga transferrin pulmonary leak index might be more sensitive but less specific for permeability edema than the ^{113m}In pulmonary leak index (PLI).

To study the value of the ^{67}Ga PLI in assessing pulmonary microvascular permeability and thereby in differentiating between ARDS and HPE, arbitrarily defined according to various sets of clinical criteria, the pulmonary leak index was measured, concomitantly with hemodynamic and ventilatory variables, in patients with radiographic pulmonary edema and respiratory insufficiency.

MATERIALS AND METHODS

Patients

The study was approved by the local ethical committee and informed consent was obtained from the closest relative in each patient. Consecutive patients were studied within 72 hr of admission to the medical intensive care unit, because of respiratory insufficiency with four quadrant alveolar edema on chest radiographs. All patients, except for one Group 1 patient, were intubated and mechanically ventilated with an O_2/air mixture. A catheter was inserted into the radial or femoral artery for monitoring mean arterial blood pressure and for blood sampling. A balloon-tipped pulmonary artery catheter was inserted, except for three Group 1 patients. These latter had a catheter in the jugular or subclavian vein to monitor central venous pressure. Patients were divided into groups, according to known risk factors for HPE, ARDS or both, and the PCWP (Table 1). Group 1 patients (n = 8) were considered to have risk factors for HPE only. They had acute left heart failure as defined by (*4,6,7,9,11,16*): evidence for coronary artery disease and impaired left ventricular function, such as a history of angina, or a remote or recent myocardial infarction diagnosed by electrocardiography and typical enzyme elevations, and poor left ventricular function on echocardiography or an elevated PCWP above 18 torr, in the absence of risk factors for ARDS. Recognized ARDS risk factors (*6–11,13,14,16,18–20*) were present in 18 patients and included sepsis, near-drowning, hemorrhagic shock and resuscitation, while 13 patients had a PCWP <18 torr (Group 3), and 5 patients (Group 2) had sepsis and a PCWP >18 torr. Thus Group 2 had risk factors for HPE and ARDS. Patients were also classified according to the lung injury score, ranging between 0 and 4 (*8*). Group 4 (n = 12) and Group 5 (n = 14) had a score below and above 2.5, respectively, the latter arbitrarily defined as ARDS. The scoring system incorporates radiographic alveolar edema and ventilatory variables such as the ratio of the arterial PO_2 to inspiratory O_2 fraction (P_aO_2/F_iO_2), the level of positive end-expiratory pressure (PEEP, cm H_2O) and the static compliance of the respiratory system. Of 12 Group 4 patients, 8 were from Group 1, 1 from Group 2 and 3 from Group 3. Of the 14 Group 5 patients, 10 were from Group 3 and 4 from Group 2.

To evaluate relative neutrophil and plasma protein binding of ^{67}Ga in vitro, blood was obtained in seven critically ill patients. Tracer doses of ^{67}Ga were added to standard aliquots, placed in a water bath at 37°C. After 30 min of incubation, 0.5 ml samples were obtained and centrifuged. Median 2.1 (range 1.0–3.9%) of total ^{67}Ga radioactivity was in the cell compartment, while 99.1 (95.6–99.9%) of plasma radioactivity was precipitable with ethanol 100%, suggesting extensive protein binding. After adding ^{67}Ga and 30 min incubation at 37°C, whole blood was separated into cell compartments and plasma with use of percoll and centrifuged (n = 3). Of total ^{67}Ga radioactivity, 93.0 (82.9%–95.5%) was in plasma, 3.0 (2.5%–3.7%) in the lymphocyte, 0.9 (0.3%–2.3%) in the neutrophil and 2.1 (1.1%–2.5%) in the red cell compartment, indicating no preferential neutrophil binding of ^{67}Ga.

Study Protocol

Autologous red blood cells were labeled with ^{99m}Tc (300 μCi/11 MBq, physical half-life 6 hr), using a modified in vitro method (*17*). Ten minutes after injection, transferrin was labeled in vivo following intravenous ^{67}Ga-citrate (100 μCi/4 MBq, physical half-life 78 hr). Patients were in the supine position and two probes, each consisting of a sodium-iodine crystal (1.5 · 1.5 in.) fitted with a 2.025 cm thick lead collimator (inner diameter 4.45 cm), extending 7.5 cm in front of the crystal, were positioned over the right and left lung apices. Each probe was connected with a separate Accuspec/NaI Plus Board in a PC. Starting at the time of injection of ^{67}Ga, radioactivity was detected for 53 sec per min, during one hour. The entire spectrum of photon energies was stored on floppy disk. During processing, three peaks were used: the 140 keV peak of ^{99m}Tc and the 184 and 300 keV peaks of ^{67}Ga, with windows of 20% centered around each peak. ^{67}Ga count rates were corrected for background radioactivity, spillover of ^{67}Ga into the

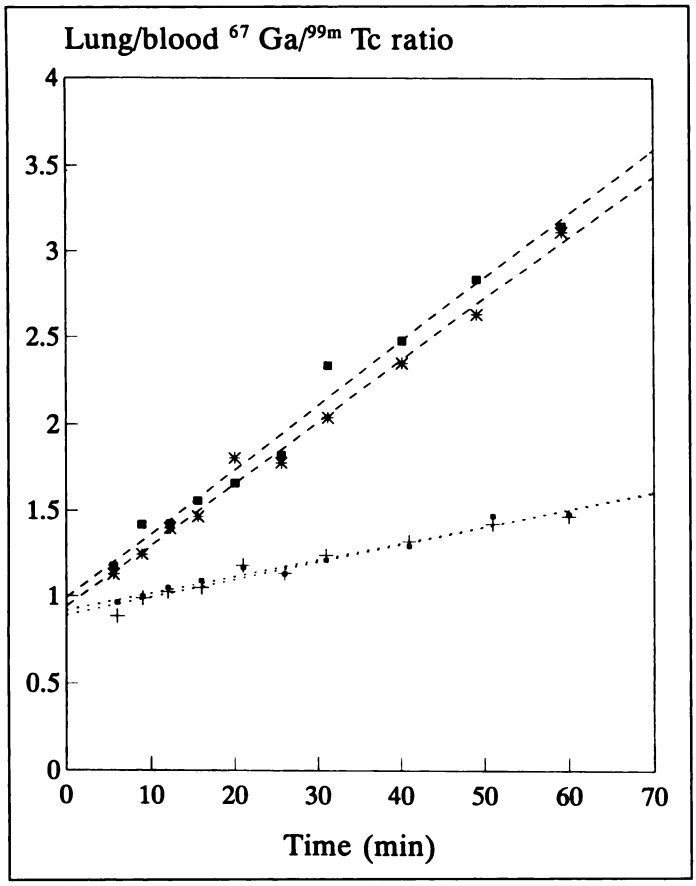

FIGURE 1. Representative examples of the pulmonary leak index, derived from the radioactivity ratio of ^{67}Ga and ^{99m}Tc in lung versus blood as a function of time. The upper dashed lines are values for each lung in a Group 3 patient (mean pulmonary leak index $37.4 \times 10^{-3} \cdot min^{-1}$, r = 0.99) and the lower two interrupted lines are values for each lung in a Group 1 patient (mean pulmonary leak index $11.0 \times 10^{-3} \cdot min^{-1}$, r = 0.98).

^{99m}Tc window and physical half-life, and expressed as counts per minute per lung field. The spillover fraction was repeatedly determined in vitro, and varied from 0.19 to 0.40 during the study. At 5, 8, 11, 15, 20, 25, 30, 40, 50 and 60 min after intravenous ^{67}Ga, arterial blood samples (≈2 ml) were drawn and weighed. Radioactivity was measured by a well-counter. Four peaks were used: 140 keV (^{99m}Tc) and 93, 184 and 300 keV (^{67}Ga), with windows of 20% around each peak. After correction for background, spillover of radioactivity and physical half-life, results were expressed as $cpm \cdot g^{-1}$. For each blood sample, a time-matched cpm over each lung was taken. A radioactivity ratio was calculated $(^{67}Ga_{lung}/^{99m}Tc_{lung})/(^{67}Ga_{blood}/^{99m}Tc_{blood})$, and plotted against time (Fig. 1). The PLI was calculated by linear regression, from the slope of increase of the radioactivity ratio divided by the intercept, representing physical factors in radioactivity detection (*2,14,17,18,21–24*). By taking pulmonary blood volume and thus presumably exchange surface area into account, the radioactivity ratio represents the ratio of extra- to intravascular ^{67}Ga radioactivity. The PLI then represents the transport rate of ^{67}Ga from the intra- to the extravascular space of the lungs. Twelve patients scheduled for aortic surgery served as controls (*25*): the ^{67}Ga PLI was 10.1 (6.6–13.0) and the upper limit of normal (mean + 2× s.d.) $14.1 \times 10^{-3} \cdot min^{-1}$. The pulmonary leak index's and linear correlation coefficients (r), calculated to evaluate the goodness of fit of the regression lines, were averaged for both lungs. The between-lung deviation from the mean pulmonary leak index (%) and its coefficient of variation (%) were calculated, as a measure of reproducibility of the technique. The latter is 14% for control lungs (*25*). The ^{99m}Tc radioactivity at t = 60 min was calculated in lungs and blood and expressed as percentage of baseline. Mean values for lungs were divided by radioactivity changes in blood to evaluate the pulmonary blood volume changes during data acquisition.

Hemodynamic and ventilatory variables and blood samples were obtained at the time of the pulmonary leak index. Concentrations of total protein (biuret method) and albumin (bromocresol method) were measured. The plasma protein colloid osmotic pressure (P_{cod}) was calculated using a nomogram from total protein and albumin concentrations (*27*). The mean pulmonary arterial pressure (MPAP) and PCWP (torr) were measured at end-expiration with patients in the supine position, and measured again after calibration and zeroing to atmospheric pressure at the mid-chest level. The pulmonary microvascular hydrostatic pressure (P_{mv}) was calculated from $P_{mv} = ((MPAP - PCWP) \times 0.4) + PCWP$ (*4*). The difference between P_{mv} and P_{cod} is the estimated net microvascular pressure, governing fluid filtration at a given permeability (*4*). The cardiac index (CI, $l \cdot min^{-1} \cdot m^{-2}$) was measured using the thermodilution technique and a computer taking the average of three injections of 10 ml of 5% dextrose at room temperature at random during the respiratory cycle, because the CI is usually low in the presence of risk factors for HPE and high in case of ARDS, and is a major determinant of the exchange surface area in the lungs. Arterial blood was taken in heparinized syringes for measurement of PO_2. The F_iO_2, PEEP (cm H_2O), tidal volume and plateau inspiratory pressure were taken from the ventilator. The static respiratory compliance was calculated from tidal volume/(plateau pressure-PEEP), $ml \cdot cm\ H_2O^{-1}$ (*8*). In one spontaneously breathing Group 1 patient receiving 3 liter of 100% O_2 per face mask, the F_iO_2 was estimated as 0.4. Patients were followed until death or discharge from the intensive care unit to record the mortality rate.

Statistical Analysis

We studied correlations to judge the influence of hemodynamic factors on the pulmonary leak index. In the absence of a standard for ARDS, we used several sets of clinical criteria to divide patients into two groups of edema types, to evaluate the diagnostic performance of an elevated pulmonary leak index for ARDS. For definition 1, based on etiologic factors only, Group 1 patients were considered to have HPE, and Group 2 + 3 patients to have ARDS. For definition 2, based on etiology and hemodynamics, Group 1 + 2 patients were considered to have HPE and Group 3 to have ARDS. For definition 3, based on the lung injury score, Group 5 patients were considered to have ARDS. To test for differences, the Kruskal-Wallis analysis of variance and the Wilcoxon ranksum test were used. For each definition, the diagnostic value of the pulmonary leak index for ARDS was calculated in terms of sensitivity (fraction of ARDS patients with elevated pulmonary leak index), specificity (fraction of HPE patients with normal pulmonary leak index), likelihood ratio (sensitivity/[1-specificity]), accuracy, positive predictive value (fraction of patients with ARDS among patients with elevated pulmonary leak index) and negative predictive value (fraction of patients without ARDS among patients with normal pulmonary leak index), assuming a pulmonary leak index $>14.1 \times 10^{-3} \cdot min^{-1}$ to be elevated. We also constructed receiver operating characteristic curves by plotting sensitivity versus 1-specificity (*28*), using a statistical program yielding the significance of the area under the curve. The closer the latter to 1, the greater the discriminating power of the test (*28*). Using definitions 2 and 3, areas under the curve were also calculated for hemodynamic and ventilatory variables, respectively, and compared to that of the pulmonary leak index. Data were expressed as median and range and a $p < 0.05$ was considered statistically significant.

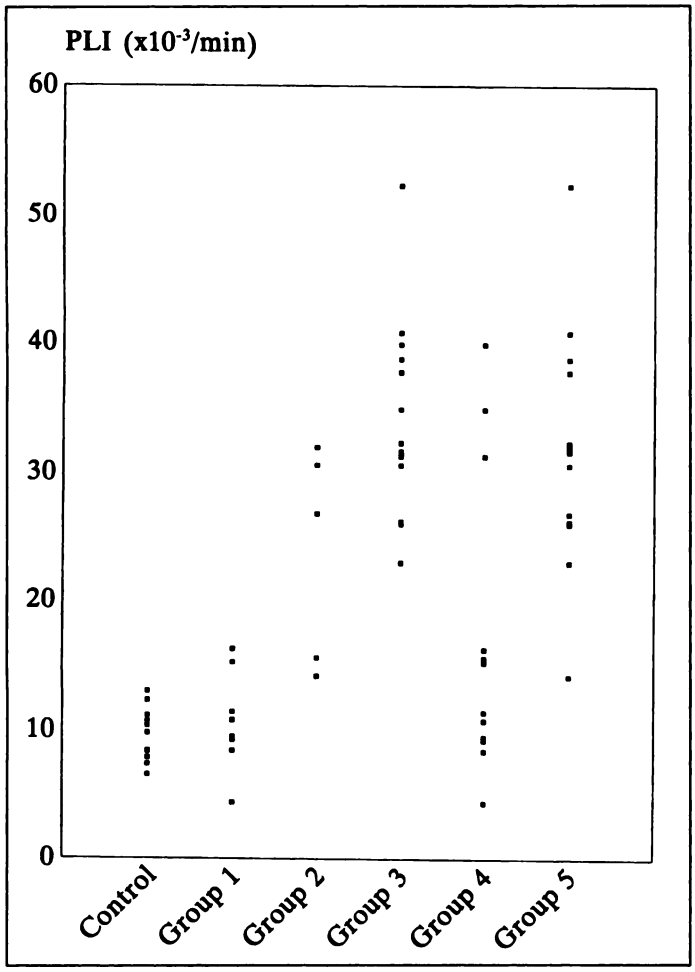

FIGURE 2. Pulmonary leak index in patients without pulmonary edema (control) and patients with pulmonary edema. Group 1: patient with a risk factor for hydrostatic pulmonary edema (HPE) only. Group 2: patients with both adult respiratory distress syndrome (ARDS) and HPE risk factors and a pulmonary capillary wedge pressure (PCWP) >18 torr. Group 3: patients with an ARDS risk factor and a PCWP <18 torr. Group 4: patients with a lung injury score less than 2.5 and Group 5 greater than 2.5.

RESULTS

Patients are grouped according to the etiology of pulmonary edema and the PCWP (Table 1). The patients with a HPE risk factor (Group 1) were somewhat older than those with ARDS, with or without HPE risk factors (Groups 2 and 3, respectively). The mortality rate was independent of etiology.

Pulmonary Leak Index

Figure 1 shows representative examples of PLI calculations. As shown in Figure 2, the pulmonary leak index differed among Groups 1 to 3 ($p < 0.001$) and between Groups 4 and 5 ($p < 0.01$). It averaged 10.2 (4.4–16.2) $\times 10^{-3} \cdot min^{-1}$ in Group 1 (ns versus control) and 31.5 (14.2–52.4) in Group 2 + 3 ($p < 0.005$ versus Group 1), above the upper limit of normal in 2 of 8 Group 1 and in 18 of 18 patients in the latter groups. The pulmonary leak index averaged 14.2 (4.4–31.95) in Groups 1 + 2 and 32.2 (23.0–52.4) in Group 3 ($p < 0.005$), above the upper limit of normal in 7 of 13 of the former and 13 of 13 of the latter patients. No overlaps between Groups 1 and 3 were evident. The pulmonary leak index averaged 13.3 (4.4–39.9) in Group 4 and 31.1 (14.2–52.4) in Group 5 ($p < 0.01$), above the upper limit in 5 of 12 Group 4 and 14 of 14 of Group 5 patients. There was no difference in pulmonary leak index between surviving and nonsurviving patients.

The r for the pulmonary leak index was 0.99 (0.95–0.99, n = 26, $p < 0.001$ for each, ns between groups). The difference in pulmonary leak index between the lungs was 8% (3–28) for Group 1 (coefficient of variation 7.7%), 17% (7–37) for Group 2 (coefficient of variation 13.5%) and 9% (0–32) for Group 3 (coefficient of variation 7.8%) and groups did not differ, so that the reproducibility of the technique was independent of etiology of pulmonary edema. At t = 60 min, 94.6 (86.9%–99.9%) of baseline ^{99m}Tc radioactivity had remained in blood (n = 26, ns between groups). The lung/blood ^{99m}Tc radioactivity change at t = 60 min versus baseline was 99.5 (84.9%–110.7%) (n = 26, ns from 100%, ns between groups).

Hemodynamic and Ventilatory Variables

Table 2 shows that, allowing for differences among groups in the PCWP, the P_{mv} was lower in Group 3 than in Groups 1 and 2. This difference, however, was offset by a lower P_{cod} in Group 3, so that the microvascular filtration pressure was similar among groups. There was no relation of the pulmonary leak index to the microvascular filtration pressure or CI within groups and in pooled data. Of note, 3 of 8 Group 1 patients had a PCWP below 18 torr. Following classification according to the lung injury score (Table 3), the ventilatory abnormalities of Group 5 were more severe than of Group 4.

Sensitivity and Specificity of the Pulmonary Leak Index for Clinically Defined ARDS

Using definition 1 to discriminate among edema types (Group 1 versus 2 + 3), based on risk factors only, a supranormal pulmonary leak index had 100% sensitivity and 75% specificity for ARDS, with a likelihood ratio of 4.0; a positive predictive value of 90%; and a negative predictive value of 100%. A total of 92% of the patients were correctly diagnosed. Figure 3A shows the receiver operating characteristic curve for ARDS according to definition 1: the area under the curve of the pulmonary leak index was 0.98 ($p < 0.005$). Using definition 2 for edema types, based on etiology and PCWP and Group 1 + 2 versus Group 3, an elevated pulmonary leak index had 100% sensitivity and 46% specificity

TABLE 2
Hemodynamic Variables of Patients with Pulmonary Edema, Grouped According to Etiology and PCWP

	Group 1 (n = 8)	Group 2 (n = 5)	Group 3 (n = 13)	KW p
Pulmonary capillary wedge pressure (torr)	16 (12–34)	20 (19–20)	13 (6–17)	0.005
Mean pulmonary artery pressure (torr)	27 (25–55)	29 (25–36)	27 (14–33)	ns
Microvascular hydrostatic pressure (torr)	21.4 (18.0–42.4)	23.0 (21.4–26.8)	17.8 (11.6–22.2)	0.01
Plasma colloid osmotic pressure (torr)	18.4 (14.8–24.2)	13.7 (11.7–22.4)	12.6 (10.5–18.4)	0.005
Hydrostatic-colloid osmotic pressure difference (torr)	2.2 (1.7–26.1)	11.3 (0.4–12.3)	4.5 (−1.4–10.8)	ns
Cardiac index ($l \cdot min^{-1} \cdot m^{-2}$)	2.7 (1.7–3.3)	4.5 (3.7–8.4)	4.5 (2.9–6.5)	0.005

KW = Kruskal-Wallis analysis of variance.

TABLE 3
Ventilatory Variables of Patients with Pulmonary Edema, Grouped According to the Lung Injury Score

	Group 4 (n = 12)	Group 5 (n = 14)	p
Inspiratory O_2 fraction	0.43 (0.34–0.79)	0.71 (0.40–1.0)	0.005
Arterial PO_2 (torr)	78 (57–117)	77 (50–130)	ns
Arterial PO_2/inspiratory O_2 fraction	174 (103–260)	114 (50–233)	0.01
Positive end-expiratory pressure (cm H_2O)	5 (0–8)	11.5 (5–20)	0.001
Tidal volume (ml)	660 (540–880)	615 (420–810)	ns
Static respiratory compliance (ml · cm H_2O^{-1})	49.1 (25.2–67.7)	29.3 (18.1–35.2)	0.01
Lung injury score	2.25 (1.75–2.5)	3.25 (2.75–3.75)	—

for ARDS, with a likelihood ratio of 1.9; a positive predictive value of 65%; and a negative predictive value of 100%, so that 73% of patients were diagnosed correctly. In the receiver operating characteristic curve of Figure 3B for ARDS according to definition 2, the area under the curve was 0.93 for pulmonary leak index ($p < 0.005$), 0.89 for the PCWP ($p < 0.005$), 0.84 for the P_{cod} ($p < 0.005$) and 0.68 for the CI (ns, $p < 0.01$ versus area under the curve for pulmonary leak index), demonstrating greater power of the pulmonary leak index than of hemodynamic variables in diagnosing ARDS. After classification of edema types according to definition 3 (Group 5 versus 4), an elevated pulmonary leak index had 100% sensitivity and 50% specificity for ARDS, with a likelihood ratio of 2.0, a positive predictive value of 70%, a negative predictive value of 100%, so that 77% of patients were diagnosed correctly. In the receiver operating characteristic curve for ARDS defined according to the lung injury score (Fig. 3C), the area under the curve for the pulmonary leak index was 0.81, for the PEEP 0.94, for the P_aO_2/F_iO_2 0.81 and for the compliance 0.81 (all $p < 0.005$, without significant differences). This demonstrates equal power for the PLI as for ventilatory variables in discriminating ARDS from HPE.

DISCUSSION

Our data suggest that a supranormal ^{67}Ga pulmonary leak index is a relatively sensitive and specific marker for increased permeability pulmonary edema associated with ARDS. The pulmonary leak index does not depend on microvascular filtration pressure and exchange surface area in the lungs. The dependence of the pulmonary leak index on permeability may form the basis of its discriminative power between ARDS and HPE, presumably associated with increased and normal permeability, respectively.

Various sets of clinical, hemodynamic and ventilatory variables have been used to define ARDS, but their diagnostic value is uncertain, partly because of lack of a gold standard (*1–4,6–16,18–20*). Therefore, we used several clinical definitions of edema types to evaluate the diagnostic performance of the pulmonary leak index. Using definition 1, based on etiologic risk factors only, the specificity for ARDS and the area under the ROC curve of the pulmonary leak index (Fig. 3A) were higher than when other definitions were used. We cannot judge, however, if the assessment of risk factors only represents the "best" clinical gold standard for judging the type of edema. A PCWP below 15-to-18 torr has been often used to help discriminating ARDS from HPE (*6–10,13–16,18–20*). Invasive catheterization, however, is needed to obtain the PCWP, and a normal PCWP does not exclude HPE if the PCWP is elevated only transiently following initial treatment (*6*), as may have occurred prior to pulmonary leak index measurements in three of our Group 1 patients. Conversely, a high PCWP does not exclude permeability edema aggravated by pressure factors (*4,6*). The PCWP may thus be a poor measure to discriminate among edema types. This may explain the relatively poor diagnostic value of the PCWP and other hemodynamic factors governing pulmonary microvascular fluid filtration, for either type of edema, as compared to the pulmonary leak index (Fig. 3B).

For the ventilatory criteria, an arterial PO_2 to inspiratory O_2 fraction ratio below 250-to-150 has been used to help discriminating ARDS from HPE, even though the severity of hypoxemia may depend on treatment, including mechanical ventilation with PEEP, rather than on the etiology of pulmonary edema (*7,8,12–14,16,18–20*). Similarly, a high lung injury score indicating severe radiographic and ventilatory abnormalities, has also been suggested to help in diagnosing ARDS (*8*). The area under the curve for the pulmonary leak index was significant, if patients were divided into ARDS and HPE groups on the basis of the lung injury score, i.e., the severity of ventilatory abnormalities (Fig. 3C). The fact that the pulmonary leak index area under the curve was somewhat lower than that of PEEP and similar to that for other ventilatory variables, indicates that the pulmonary leak index is not superior to ventilatory variables in diagnosing ARDS. This can be explained by the fact that the lung injury score incorporates all of these ventilatory variables. The data nevertheless illustrate that the pulmonary leak index has diagnostic value if severe ventilatory abnormalities are used to define ARDS.

Taken together, increased permeability may be pivotal in the pathogenesis of clinical ARDS and its ventilatory sequelae. Irrespective of the clinical definition of edema types, the pulmonary leak index may be a useful tool to differentiate ARDS from HPE, since a normal pulmonary leak index excludes ARDS and an elevated pulmonary leak index has a positive predictive value for ARDS of about 80%. These figures may also be higher than those reported in the literature for the clinical evaluation plus the PCWP (*6*) and for the chest radiograph (*1,2*), using various gold standards. Conversely, an elevated pulmonary leak index itself may serve as a gold standard for ARDS. If this is true, the clinical utility of the ^{67}Ga pulmonary leak index can also illustrated as follows. Instead of the upper limit of pulmonary leak index values in normals, the upper limit in Group 1 patients with risk factors for HPE only, i.e., $16.2 \times 10^{-3} \cdot min^{-1}$, could be used to define an elevated pulmonary leak index, since there is no overlap between patients with risk factors for HPE (Group 1) and ARDS (Group 3) only. The pulmonary leak index of Group 2 patients fell into the range of Group 1 patients in 2, with a pulmonary leak index of 14.2 and $15.6 \times 10^{-3} \cdot min^{-1}$, respectively, and in the range of Group 3 in 3 patients, with a pulmonary leak index varying from 26.8 to $31.9 \times 10^{-3} \cdot min^{-1}$, so that the former may have had HPE and the latter ARDS, irrespective of an elevated PCWP in these patients. The ^{67}Ga pulmonary leak index may

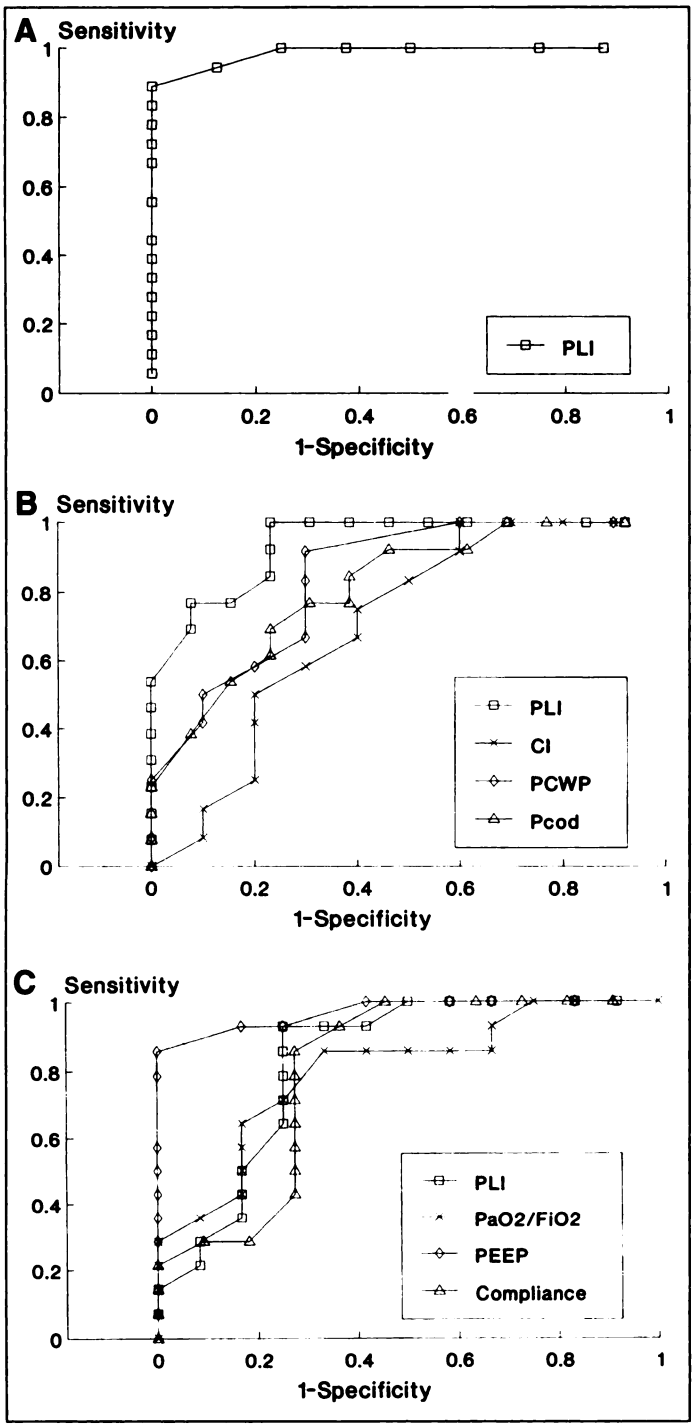

FIGURE 3. Receiver operating characteristic curve of the pulmonary leak index for pulmonary edema patients divided into those with ARDS (Group 2 + 3) and HPE (Group 1) risk factors (A). Receiver operating characteristic curve of the pulmonary leak index, the pulmonary capillary wedge pressure (PCWP), cardiac index (CI), and plasma colloid osmotic pressure (P_{cod}), for pulmonary edema patients divided into those with ARDS (Group 3) and HPE risk factors (Group 1 + 2) (B). Receiver operating characteristic curve of the pulmonary leak index, of the arterial PO_2/inspiratory O_2 fraction (P_aO_2/F_iO_2), the positive end-expiratory pressure (PEEP) and the static respiratory compliance, for pulmonary edema patients divided into those with a lung injury score above 2.5 (Group 5, ARDS) and below 2.5 (Group 4) (C).

help the clinician to evaluate the predominant mechanism of pulmonary edema in unclear cases, particularly if the PCWP does not match with the edema type suspected from risk factors. This, in turn, might contribute to improved patient management and, perhaps, outcome, since the treatment and prognosis of the edema types differ considerably.

Previous experimental studies have shown that radionuclide labeled protein transport across the pulmonary microvasculature, as estimated by the pulmonary leak index or analogous indices, is a sensitive and specific tool for judging the permeability defect associated with endotoxin, oleic acid or thiourea, compounds that directly injure pulmonary vessels, because the PLI may be independent of pressure factors and may increase even before a fall in PO_2 and rise in extravascular lung water during microvascular injury (*5,10,21–24*). The latter may be explained by the pulmonary safety factors, such as increased lymph flow, preventing development of alveolar edema during increased microvascular permeability. Nevertheless, the PLI, either assessed using ^{113m}In transferrin or ^{99m}Tc-albumin may be normal during clinical ARDS thereby challenging the diagnostic value of the method in patients (*2,9,10,12,14,18*). Partly because of differences in methods, absolute values for the pulmonary leak index or similar indices are hard to compare among studies. The ^{67}Ga pulmonary leak index may be similar to the ^{68}Ga pulmonary transcapillary escape rate, measured by positron emission tomography, but may be several fold higher than the ^{113m}In transferrin PLI (*2,5,13,14,16,18*). This difference may relate to less firm binding of ^{67}Ga than of In to circulating transferrin, so that part of the ^{67}Ga transport may be accomplished by transport of small molecular unbound radionuclide, in spite of the apparently high in vitro protein binding. The transport, however, would be pressure dependent, so that the normal PLI during HPE could argue against a major contribution by unbound ^{67}Ga to the pulmonary leak index. Indeed, a mathematical model developed by others, suggests that partly unbound radionuclide may underestimate rather than overestimate the pulmonary leak index, because of rapid equilibration of the unbound fraction between intra- and extravascular spaces, shortly after intravenous injection (*24*). Therefore, the difference among radionuclides, both supposed to bind to transferrin, remains unexplained, unless our previous in vitro observation, that the transmembrane transport of ^{67}Ga in plasma directly relates to the interstitial transferrin concentration by "pulling" intravascular ^{67}Ga from transferrin across the membrane, irrespective of apparent high in vitro protein binding (*26*), is also true in vivo.

The mechanism may contribute to the sensitivity and specificity of the ^{67}Ga pulmonary leak index for ARDS, since transport of unbound ^{67}Ga would be elevated in the presence of an elevated interstitial transferrin concentration induced by increased microvascular permeability, while washout of interstitial transferrin during pressure induced edema would ameliorate transport of unbound radionuclide (*26*). Although the literature suggests that the ^{99m}Tc-albumin leak index may be elevated at very high microvascular pressures during HPE by virtue of solvent drag (*10*), the median pulmonary leak index in our HPE patients was neither lower nor higher than control values. This might be explained if increased solvent drag had been offset by a diminished ^{67}Ga transport associated with washout of transferrin from the pulmonary interstitium during HPE. Conversely, the latter mechanism may explain why the ^{67}Ga pulmonary leak index may be more sensitive and specific than the ^{113m}In pulmonary leak index for clinically defined ARDS, in spite of lower affinity of transferrin for the former (*2,26*), and that the method may detect increased permeability in the lungs of patients at risk for ARDS (*17*), while the ^{113m}In pulmonary leak index may not (*14*). Nevertheless, we cannot exclude that the two supranormal PLI values of 15.2 and 16.2 $\times$ $10^{-3} \cdot min^{-1}$ during HPE were caused by solvent drag and thereby attenuated the specificity of an elevated PLI for ARDS.

Our method may have advantages above other techniques

(*9–13,16*). The radionuclides used are widely available, in contrast to In isotopes and ^{68}Ga used by others for permeability measurements (*2,13–16,18,21,22*). The method may, however, share the disadvantage with that based on ^{99m}Tc-albumin, as far as relatively poor protein binding is concerned (*9–12,24*). The use of mobile and sensitive probes allows for repeated bedside measurements with minimal radioactivity doses. The difference between lungs in the PLI can be taken as a measure of reproducibility of the ^{67}Ga pulmonary leak index and the measurement error, i.e., coefficient of variation, is acceptable, at about 10%. Otherwise, the finding that the percentage difference in pulmonary leak index between lungs did not differ among groups may indicate that the lung injury of ARDS is homogeneous or that potential heterogeneity does not exceed measurement error. Our method takes potential changes in pulmonary blood volume during data acquisition into account. Indeed, decreases in pulmonary blood volume during permeability and increases during hydrostatic edema may result in under- and overestimations of the PLI, respectively, as shown in dogs (*21*). Our data indicate that, on the average, pulmonary blood volume hardly changed during these conditions, but use of a blood-pool marker was still considered mandatory to avoid the adverse effect of unexpected or unnoticed blood volume changes on the pulmonary leak index. Indeed, changes in the lung-to-blood ^{99m}Tc radioactivity ratio suggest that pulmonary blood volume may increase or decrease by as much as 15% during data acquisition, provided that the hematocrit in lung and peripheral blood is similar and ^{99m}Tc eluted from red blood cells does not accumulate in the interstitial space. Assuming unchanged hematocrit during data acquisition, the decline in blood ^{99m}Tc radioactivity of about 5% conforms with the ≈3%–5% per hour elution of ^{99m}Tc from red blood cells reported earlier (*23*). Nevertheless, the contribution of the blood-pool marker to the accuracy and diagnostic value of the pulmonary leak index deserves further study.

CONCLUSION

The ^{67}Ga PLI is a useful tool to differentiate clinical ARDS from HPE. On the basis of the pathophysiology and measurement principle involved, the PLI may even serve as a gold standard to diagnose ARDS.

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REFERENCES

1. Aberle DR, Wiener-Kronisch JP, Webb WR, Matthay MA. Hydrostatic versus increased permeability pulmonary edema: diagnosis based on radiographic criteria in critically ill patients. *Radiology* 1988;168:73–79.
2. Rocker GM, Rose DH, Manhire AR, Pearson D, Shale DJ. The radiographic differentiation of pulmonary edema. *Br J Radiol* 1989;62:582–586.
3. Pistolesi M, Miniati M, Milne ENC, Giuntini C. Measurement of extravascular lung water. *Intensive Care World* 1991;8:16–21.
4. Sibbald WJ, Short AK, Warshawski FJ, Cunningham DG, Cheung H. Thermal dye measurements of extravascular lung water in critically ill patients. Intravascular Starling forces and extravascular lung water in the adult respiratory distress syndrome. *Chest* 1985;87:585–592.
5. Schuster DP, Haller J. A quantitative correlation of extravascular lung water accumulation with vascular permeability and hydrostatic pressure measurements: a PET study. *J Crit Care* 1990;5:161–168.
6. Fein AM, Goldberg SK, Walkenstein MD, et al. Is pulmonary artery catheterization necessary for the diagnosis of pulmonary edema? *Am Rev Respir Dis* 1984;129:1006–1009.
7. Holter JF, Weiland JE, Pacht ER, Gadek JE, Davis WB. Protein permeability in the adult respiratory distress syndrome. Loss of size selectivity of the alveolar epithelium. *J Clin Invest* 1986;78:1513–1522.
8. Murray JF, Matthay MA, Luce JM, Flick MR. An expanded definition of the adult respiratory distress syndrome. *Am Rev Respir Dis* 1988;138:720–723.
9. Byrne K, Tatum JL, Henry DA, et al. Increased morbidity with increased pulmonary albumin flux in sepsis-related adult respiratory distress syndrome. *Crit Care Med* 1992;20:28–34.
10. Sugerman HJ, Tatum JL, Burke TS, Strash AM, Glauser FL. Gamma scintigraphic analysis of albumin flux in patients with acute respiratory distress syndrome. *Surgery* 1984;95:674–681.
11. Spicer KM, Reines DH, Frey GD. Diagnosis of adult respiratory distress syndrome with Tc-99 human serum albumin and portable probe. *Crit Care Med* 1986;14:669–676.
12. Mishkin FS, Niden A, Kumar A, Thomas A, Reese IC, Vasinrapee P. Albumin lung/heart ratio change. A simple clinical measure of documenting increased pulmonary endothelial permeability to protein. *JAMA* 1987;257:953–956.
13. Calandrino FS, Anderson DJ, Mintum MA, Schuster DP. Pulmonary vascular permeability during the adult respiratory distress syndrome: a positron emission tomographic study. *Am Rev Respir Dis* 1988;138:421–428.
14. Rocker GM, Pearson D, Stephens M, Shale DJ. An assessment of a double-isotope method for the detection of transferrin accumulation in the lungs of patients with widespread pulmonary infiltrates. *Clin Sci* 1988;75:47–52.
15. Putensen C, Mutz N, Himmer G, et al. Gamma scintigraphic imaging of lung microvascular permeability in adult respiratory distress syndrome. *Crit Care Med* 1990;18:807–812.
16. Kaplan JD, Calandrino FS, Shuster DP. A positron emission tomographic comparison of pulmonary vascular permeability during the adult respiratory distress syndrome and pneumonia. *Am Rev Respir Dis* 1991;143:150–154.
17. Raijmakers PGHM, Groeneveld ABJ, Schneider AJ, et al. Transvascular transport of ^{67}Ga in the lungs after cardiopulmonary bypass surgery. *Chest* 1993;104:1825–1832.
18. Sinclair DG, Braude S, Haslam PL, Evans TW. Pulmonary endothelial permeability in patients with severe lung injury. Clinical correlates and natural history. *Chest* 1994;106:535–539.
19. Sloane PJ, Gee MH, Gottlieb JE, et al. A multicenter registry of patients with acute respiratory distress syndrome. *Am Rev Respir Dis* 1992;146:419–426.
20. Bernard GR, Artigas A, Brigham KL, et al. The American-European consensus conference on ARDS. *Am J Respir Crit Care Med* 1994;149:818–824.
21. Dauber IM, Pluss WT, VanGrondelle A, Trow RS, Weil JV. Specificity and sensitivity of noninvasive measurement of pulmonary vascular protein leak. *J Appl Physiol* 1985;59:564–574.
22. Welsh CH, Dauber IM, Weil JV. Endotoxin increases pulmonary vascular protein permeability in the dog. *J Appl Physiol* 1986;61:1395–1402.
23. Groeneveld ABJ, Den Hollander W, Straub J, Nauta JJP, Thijs LG. Effects of N-acetylcysteine and terbutaline treatment on hemodynamics and regional plasma extravasation in porcine septic shock. *Circ Shock* 1990;30:185–205.
24. Riddle WR, Roselli RJ, Pou NA. Modeling flux of free and protein-bound radioisotopes into the pulmonary interstitium. *J Appl Physiol* 1990;68:2334–2442.
25. Raijmakers PGHM, Groeneveld ABJ, Rauwerda JA, et al. Transient increase in interleukin-8 and pulmonary microvascular permeability following aortic surgery. *Am J Respir Crit Care Med* 1995;151:698–705.
26. Raijmakers PGHM, Groeneveld ABJ, Den Hollander W, Teule GJJ. Transport of ^{67}Ga and ^{111}In across a membrane. Role of plasma binding and concentration gradients. *Nucl Med Commun* 1992;13:349–356.
27. Nitta S, Ohnuki T, Ohkuda K, Nakada T, Staub NC. The corrected protein equation to estimate plasma colloid osmotic pressure and its development on a nomogram. *Tohuku J Exp Med* 1981;135:43–49.
28. Hanley JA, McNeil BJ. The meaning and use of the area under a Receiver Operating Characteristic Curve. *Radiology* 1982;143:29–36.