

# Pulmonary edema after transfusion: How to differentiate transfusion-associated circulatory overload from transfusion-related acute lung injury

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**Objective:** Pulmonary edema is an underrecognized and potentially serious complication of blood transfusion. Distinct mechanisms include adverse immune reactions and circulatory overload. The former is associated with increased pulmonary vascular permeability and is commonly referred to as transfusion-related acute lung injury (TRALI). The latter causes hydrostatic pulmonary edema and is commonly referred to as transfusion-associated circulatory overload (TACO). In this review article we searched the National Library of Medicine PubMed database as well as references of retrieved articles and summarized the methods for differentiating between hydrostatic and permeability pulmonary edema.

**Results:** The clinical and radiologic manifestations of TACO and TRALI are similar. Although echocardiography and B-type natriuretic peptide measurements may aid in the differential diagnosis between hydrostatic and permeability pulmonary edema, invasive techniques such as right heart catheterization

and the sampling of alveolar fluid protein are sometimes necessary. The diagnostic differentiation is especially difficult in critically ill patients will multiple comorbidities so that the cause of edema may only be determined *post hoc* based on the clinical course and response to therapy. Guided by available evidence, we present an algorithm for establishing the pretest probability of TRALI as opposed to TACO. The decision to test donor and recipient blood for immunocompatibility may be made on this basis.

**Conclusions:** The distinction between hydrostatic (TACO) and permeability (TRALI) pulmonary edema after transfusion is difficult, in part because the two conditions may coexist. Knowledge of strengths and limitations of different diagnostic techniques is necessary before initiation of complex TRALI workup. (Crit Care Med 2006; 34[Suppl.]:S109–S113)

**KEY WORDS:** pulmonary edema; transfusion; adult respiratory distress syndrome; congestive heart failure; fluid therapy

**P**ulmonary edema is the abnormal accumulation of extravascular lung water due to an imbalance between fluid filtration and resorption (1–3). Traditionally it has been divided into hydrostatic (cardiogenic) and permeability (noncardiogenic) categories depending on the presumed mechanism (1, 2). When pulmonary edema and resultant hypoxemia occur within 6 hrs of a blood product transfusion, the distinction between hydrostatic edema (transfusion-

associated cardiac overload—TACO) and permeability edema (transfusion-related acute lung injury—TRALI) needs to be made (4). Their differential diagnosis, however, poses a diagnostic challenge (4, 5)

To identify relevant literature we searched the National Library of Medicine PubMed database using the following two search strategies: Search 1: (acute lung injury OR ARDS OR noncardiogenic pulmonary edema OR permeability pulmonary edema AND (hydrostatic pulmonary edema OR congestive heart failure OR cardiogenic pulmonary edema) Field: All Fields, Limits: All Adult: 19+ years, Publication Date from 1965, only items with abstracts, English, Humans. Search 2: (pulmonary edema OR circulatory overload OR acute lung injury) AND transfusion Field: All Fields, Limits: All Adult: 19+ years, Publication Date from 1965, only items with abstracts, English, Humans.

This strategy was supplemented by hand searching of the references and contacting experts in the field.

The objectives of this review article are as follows: 1) to review the incidence and outcome of TACO; 2) to discuss the differential diagnosis between TACO and TRALI.

## Epidemiology and Clinical Characteristics of TACO

TACO appears to be a relatively common yet underrecognized complication of blood transfusion (6). Few studies have defined the incidence of TACO, and estimates vary from <1% in hemovigilance reports to 8% in elderly patients following joint replacement surgery (6, 7). In a retrospective study using a custom-designed electronic surveillance system, we have recently identified TACO in 25 of 1,351 critically ill medical and surgical patients who did not require respiratory support at the onset of transfusion (8). In a subsequent 4-month prospective study on critically ill medical patients, we identified TACO in 16 of 142 patients, suggesting a remarkably high incidence of 11% in this population (9).

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Supported, in part, by grants NBF 2004-05 and K23 HL078743 from the National Blood Foundation and NHLBI.

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DOI: 10.1097/01.CCM.0000214311.56231.23

The clinical presentation of TACO is similar to other causes of hydrostatic pulmonary edema. In addition to dyspnea, tachypnea, and jugular venous distension, elevated systolic blood pressure is usually present (6, 10). Although signs of fluid overload are usually present before, transfusion may precipitate acute hydrostatic pulmonary edema (6). Prompt volume reduction with diuresis usually results in rapid improvement, but mechanical ventilation may be required. A mortality rate of 5–15% has been reported (6). In patients with suspected underlying cardiac dysfunction, slower transfusion rates (1 mL/kg/hr) and diuretic use have been recommended to prevent development of TACO (10).

### Diagnostic Tools to Differentiate Between Hydrostatic and Permeability Pulmonary Edema

Although a history of heart disease, a positive fluid balance, physical exam findings consistent with systemic and/or pulmonary venous hypertension, and the absence of acute lung injury (ALI) risk factors establish a pretest probability in favor of TACO, in many instances the classification of pulmonary edema remains very much in doubt (1, 2, 11). Many of the diagnostic tests in support of TACO are invasive whereas serologic tests for TRALI have yet to be validated against an accepted gold standard.

**Pulmonary Artery Occlusion Pressure.** After the somewhat uncritical acceptance of pulmonary artery pressure monitoring as the definitive test for distinguishing between hydrostatic and permeability pulmonary edema in the 1970s, accuracy, precision, and clinical utility of this technique have come under considerable scrutiny. Not only there is substantial interobserver variability in the interpretation of hemodynamic data, even among intensivists and anesthesiologists (12, 13), but some studies have also suggested that hemodynamic monitoring is associated with increased morbidity and mortality (14).

Although in expert hands the measurement of pulmonary artery occlusion pressure (PAOP) is an excellent surrogate for left atrial pressure, each measurement represents just one snapshot in time and cannot inform about the barrier properties of the pulmonary vasculature. For example, in patients with hydrostatic “flash pulmonary edema,” due to myocardial ischemia, the PAOP may be normal

and misleading unless it is measured during ischemia (11). Alternatively, a significant proportion of patients with ALI may have concomitant cardiac dysfunction and left atrial hypertension (15, 16). Esteban et al. (17) correlated lung pathology findings with clinical ALI criteria as had been established by the European-American ARDS Consensus Conference (AECC) in 1993 (18) and observed that reliance on a dichotomous PAOP threshold contributed to the misclassification of many patients who had concomitant heart and lung disease. Similarly, in a cohort of patients enrolled in the NIH-sponsored Fluids and Catheters Treatment Trial (FACTT), where patients with acute lung injury were randomized to either central venous pressure or pulmonary artery pressure catheters, a significant number of patients thought to have only increased permeability edema were found to have elevated PAOP: The ARDS Network reported in its annual American Thoracic Society presentation (May 2005, San Diego) that >20% of patients enrolled in the pulmonary arterial catheter portion of FACTT have been found to have a PAOP >18 mm Hg at the time the catheter was inserted. The final results of this trial and the final data on this issue will be available in late 2005 or early 2006 as the 1,000-patient trial is almost complete (980 patients enrolled as of August 24, 2005, personal communication from MA Matthay). Since the measurements of PAOP is invasive and lacks sufficient sensitivity and specificity, its use is now considered optional in the diagnosis of ALI (18, 19).

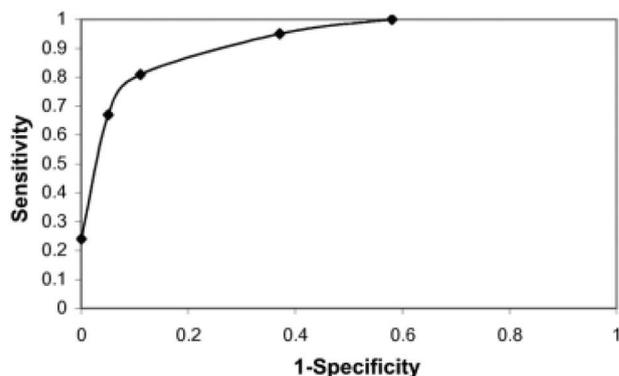
**Pulmonary Edema Fluid Protein Concentration.** The pulmonary edema fluid to plasma protein concentration ratio has been considered a sensitive and specific test of pulmonary vascular barrier integrity (20). A small catheter is inserted blindly into a distal airway, and alveolar fluid is sampled by gentle suction. A ratio of pulmonary edema/plasma protein concentration <.65 identifies a transudative process and suggests hydrostatic pulmonary edema (21). Despite its compelling rationale, the technique has several important drawbacks. It has been largely employed in a research setting and not been validated in a large representative patient population. Its use is restricted to intubated patients, and its feasibility and validity in patients with subacute or chronic forms of pulmonary edema are very much in doubt. The alveolar fluid needs to be sampled as soon as the pa-

tient is intubated as active resorption of edema fluid by alveolar epithelial cells may lead to increase in protein concentration, therefore limiting diagnostic accuracy (3). This technique has been identified to determine the etiology of pulmonary edema in patients undergoing orthotopic liver transplantation, many of whom were presumed to have TRALI (22).

**Chest Radiography.** The general appearance of the chest radiograph does not identify the specific mechanism of edema (23). Radiologist reports are generally not helpful unless they are based on formal measurements of the vascular pedicle width and cardiothoracic ratio (24). In a sample of patients in whom pulmonary vascular pressures were measured with pulmonary artery flotation catheters, a vascular pedicle width >70 mm and cardiothoracic ratio >.55 had a sensitivity of 46% and specificity of 85% for predicting a PAOP increase >18 mm Hg (24).

**Echocardiography.** Although the echocardiographic measurement of left ventricular ejection fraction is a sensitive and specific test of systolic function, a normal value by no means rules out hydrostatic pulmonary edema due to diastolic dysfunction (25). The Doppler mitral annular velocity (E/Ea) is a much more specific index of impaired diastolic filling (26), but its usefulness in distinguishing permeability from hydrostatic pulmonary edema has yet to be determined.

**B-Type Natriuretic Peptide.** B-type natriuretic peptide (BNP) is a cardiac neurohormone specifically secreted from the ventricles in response to volume expansion and pressure overload (27). In patients presenting to an emergency room or urgent care clinic (28, 29), plasma BNP has been shown to be a sensitive and specific indicator of dyspnea from cardiac causes irrespective of the specific nature of cardiac impairment (30). However, a recent study in critically ill patients who were monitored with a pulmonary artery catheter showed no correlation between plasma BNP and PAOP (31, 32). This may reflect the fact that in critically ill patients BNP changes less rapidly than one might surmise from its normally short half-life (33). It may also reflect the high degree of biological variability in BNP concentrations in this population (33, 34). High levels of BNP were observed in patients with ALI even in the absence of left ventricular dysfunction (33, 35). BNP is elevated in cor pulmonale (36, 37),



Posttransfusion-to-pretransfusion BNP ratio	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
0.5	100	42	65	89	70
0.7	100	42	71	92	70
1.0	95	63	73	86	80
1.5	81	89	89	81	87
1.7	67	95	93	72	80
3.0	24	100	100	54	60

Figure 1. The accuracy of B-type natriuretic peptide (BNP) in the diagnosis of transfusion-associated circulatory overload. Reprinted with permission from Ref. 39. PPV, positive predictive value; NPV, negative predictive value.

although the levels are usually lower than those observed in patients with left ventricular dysfunction and generally do not exceed 600 pg/dL (38). In a recently completed prospective study at Mayo Clinic, BNP concentrations <250 pg/mL largely excluded pulmonary venous hypertension as a cause acute pulmonary edema in critically ill patients (R. Rana, personal communication).

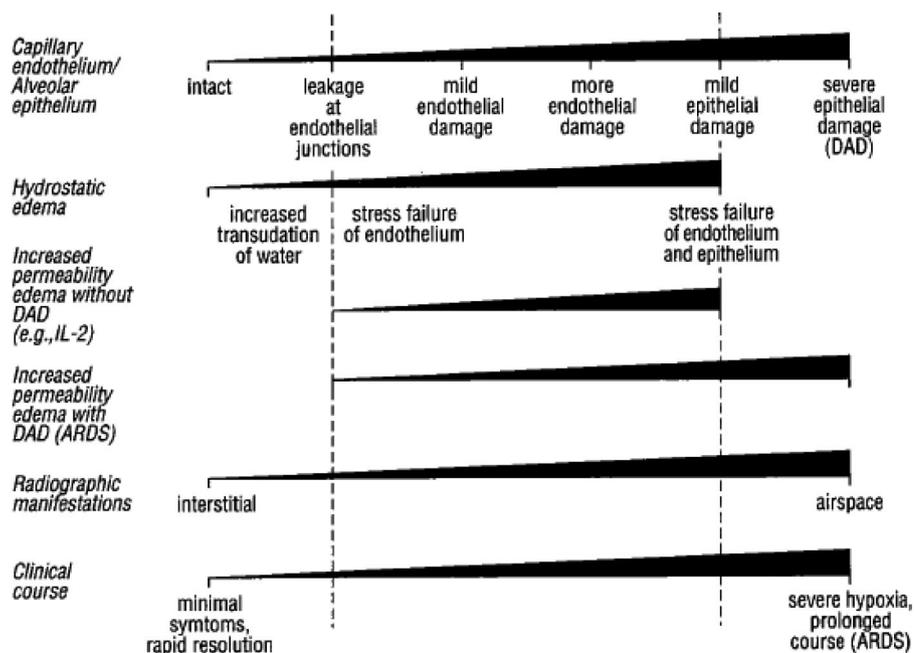
In a recent study, Zhou et al. (39) measured BNP before and after transfusion of red blood cells in 21 patients with clinical suspicion of TACO and in 19 controls, who remained free from respiratory symptoms. A  $\geq 50\%$  increase in BNP following transfusion had a sensitivity of 81% and specificity of 89% for the diagnosis of TACO (Fig. 1). Since none of control patients developed TRALI, the value of BNP in differentiating between TRALI and TACO could not be determined.

**Radionuclide Studies.** Techniques for measuring pulmonary capillary permeability using radioactive colloid tracers are largely confined to the research setting. In a recent study, both positron emission tomographic imaging with (68)Ga-labeled transferrin and gamma-camera scintigraphy with (99m)Tc-labeled albumin yielded disappointing results, and they have no place in clinical practice (40).

**Biomarkers of Acute Lung Injury.** Endothelial and epithelial cell injury and lung inflammation are thought to be at the center of ALI pathogenesis. Although several biomarkers of inflammation and of epithelial and endothelial cell injury have been associated with outcomes of patients with ALI (41), they do not aid in the diagnosis of ALI or its differentiation from hydrostatic pulmonary edema (1).

### Implications for Clinical Practice and Research

In critically ill patients with multiple comorbidities and risks for lung injury, the differential diagnosis between hydrostatic and nonhydrostatic pulmonary edema mechanisms remains a challenge (Fig. 2) (42). This challenge extends to the differentiation between TRALI and TACO and has hampered research on epidemiology and molecular mechanisms of TRALI. In a context of pulmonary edema after transfusion, differentiation between TRALI and TACO is important not only from the perspective of treatment but also for determi-



Journal of Thoracic Imaging, Vol. 13, No. 3, 1998

Figure 2. Spectrum of pulmonary edema with overlapping clinical and pathologic features of hydrostatic and permeability mechanisms. Reprinted with permission from Ref. 42. DAD, diffuse alveolar damage; IL, interleukin; ARDS, acute respiratory distress syndrome.

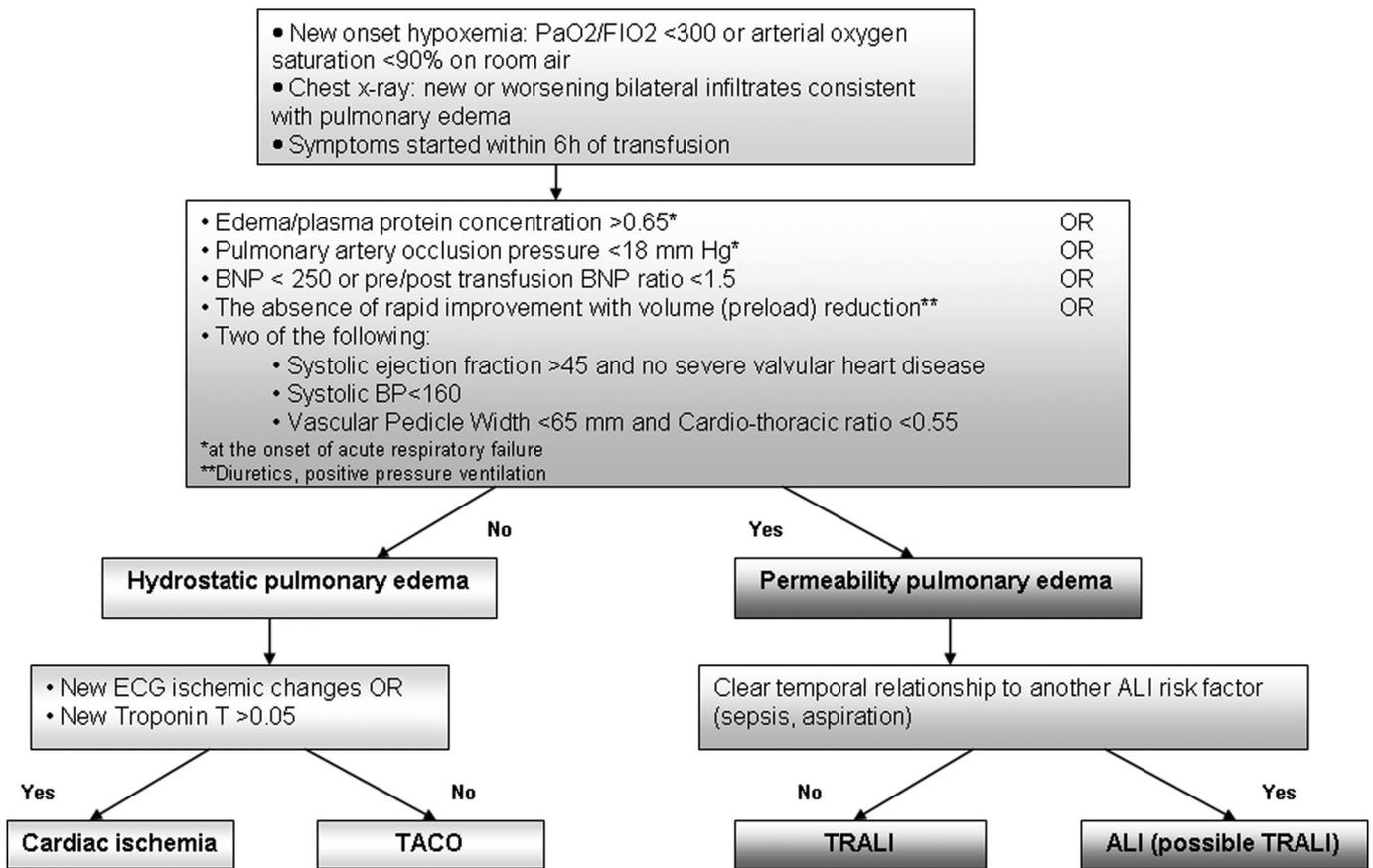


Figure 3. Approach to posttransfusion acute pulmonary edema. *BNP*, B-type natriuretic peptide; *BP*, blood pressure; *ECG*, electrocardiogram; *TACO*, transfusion-associated circulatory overload; *ALI*, acute lung injury; *TRALI*, transfusion-related acute lung injury.

nation of when to trigger complex and expensive TRALI workup and donor exclusions. Both the Canadian consensus conference and the National Heart, Lung, and Blood Institute working group have adopted modified AECC criteria for distinguishing between TRALI and TACO in order to guide such research (4, 5). Yet a clear limitation of the AECC definition and approach to ALI (18) (and hence also TRALI) (4, 5) stems from the implicit assumption that hydrostatic and nonhydrostatic injury mechanisms rarely if ever coexist (15–19, 43). This assumption is probably incorrect. In Figure 3 we have put forth an algorithm clinicians and researchers may wish to consider when managing patients with respiratory symptoms associated with blood transfusions. The algorithm is based on the AECC definition yet is somewhat broader, integrates other diagnostic tests such as the measurement of BNP, and allows for overlap between the two entities. Prospective clinical studies evaluating the accuracy of diagnostic methods for differentiation between hy-

drostatic and permeability pulmonary edema in the setting of blood transfusion (TACO and TRALI) are required.

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