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Broken Hearts and TRALI

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In their seminal article Vlaar *et al*/have eloquently demonstrated that transfusion-related acute lung injury (TRALI) is the result of at least two events, validating its pathogenesis to be similar to other forms of acute lung injury (ALI), including the acute respiratory distress syndrome (1), and supporting the *in vivo* modeling of TRALI in both rodents and sheep (2-6). In their prospective study of patients requiring cardiac surgery and mandatory recovery in the intensive care unit TRALI was associated with increased Euro- and AIA scores, measures of mortality risk, pump time, and IL-6 and IL-8 levels, the latter vs. non-transfused patients alone (1). The patients who developed TRALI were also older, and increased age correlates with increased incidence of ALI. The increased pump time may represent the first clinical event leading to pro-inflammatory activation of the pulmonary endothelium leading to neutrophil adherence, priming, resulting in sequestration. The second event is transfusion of a blood product, which may contain an antibody that recognized an antigen present upon the sequestered PMNs or other biologic response modifiers, e.g. a lipid or soluble CD40 ligand, which could activate the PMN microbicidal arsenal leading to endothelial damage, capillary leak and ALI. The choice to study patients requiring cardiac surgery was excellent for prospective epidemiologic data implicated these patients are at risk for TRALI, and mortality reports from the Food and Drug Administration demonstrated that most TRALI deaths in 2004 were in this patient group (7,8); moreover, data from the Mayo Clinic and Denver demonstrated that patients in the intensive care unit are also at increased risk for TRALI (9,10). TRALI was defined by increases in protein, PMNs, IL-8, IL-6, and elastase- α_1 -antitrypsin (EA) complexes (a marker of PMN activation) in the bronchoalveolar lavage fluid (BALF), indicating that TRALI is PMN-mediated as postulated and demonstrated by many investigators using animal models (2,3,11,12). In addition, pulmonary thrombin-anti-thrombin complexes and plasminogen activator inhibitor-1 (PAI-1) were increased in the BALF with a concomitant decrease in systemic plasminogen activator activity percentage (PAA%) indicating enhanced coagulation with impaired thrombolysis. TRALI was also associated with plasma transfusion and platelet transfusion but not red blood cell transfusion; however, these patients were treated on an RBC transfusion protocol to keep the hemoglobin >5.0 g/dl, which appears restrictive compared to many transfusion triggers, especially in the United States and Canada. Importantly, transfused patients, vs. non-transfused controls, who did not develop TRALI, also

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demonstrated increased plasma levels of TATc, decreased levels of PAA% as well as PMN influx without ALI or evidence of PMN activation (no increase in EA complexes), IL-6, and IL-8 in the BALF. These data indicate that transfusion itself may cause pulmonary sequestration of PMNs as well as a coagulopathy, and impair fibrinolysis similar to previous animal models (13,14). As compared to those patients who did not develop TRALI, whether transfused or not, patients who manifested TRALI had a more clinically severe pro-inflammatory first event. This first event then predisposed them to develop TRALI in response to blood component transfusion.

TRALI, like all other forms of acute lung injury, is the results of at least two events: the first being the clinical condition of the patient and the second the infusion of a biologic response modifier in the transfused components as first postulated in a “look back” series, confirmed in animal models and further refined by the Germans (2,3,6,12). Both antibodies and other biologic response modifiers may cause TRALI as the second event. Those mediators that accumulate with routine storage are difficult to measure and are present with increased activity and/or a greater concentration in implicated units compared to “control” units that did not cause injury with identical storage times (2,8). Furthermore, the role of the coagulation system and activation of innate immunity has been demonstrated in part by Looney *et al* in a murine model with the role of platelets in ALI and by Vlaar invoking the role of changes in plasma-based hemostasis in the current model and their animal data (13-15). Further work determining the role of coagulation, both the cellular and fluid phases, is warranted. Moreover, it may be equally important to examine critically ill patients with pre-existing pulmonary insufficiency for worsening lung function post-transfusion, since the Canadian Consensus Conference definition of TRALI does not encompass such patients. Restrictive transfusion strategies may also decrease TRALI incidence simply by reducing transfusions that are not clinically indicated.

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