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The Role of Donor Chronic Alcohol Abuse in the Development of Primary Graft Dysfunction in Lung Transplant Recipients

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Abstract: Primary graft dysfunction (PGD) following lung transplantation is clinically similar to the acute respiratory distress syndrome. Because alcohol abuse independently increases the incidence of acute respiratory distress syndrome in at-risk individuals, we hypothesized that donor alcohol use is correlated with an increased risk of PGD. As a pilot study, we collected alcohol use histories using a validated instrument, the Alcohol Use Disorder Identification Test questionnaire, from 74 donors and correlated these with the development of PGD in corresponding recipients. Nineteen percent (14/74) of donors were classified as heavy alcohol users, as defined by the Alcohol Use Disorder Identification Test scores ≥8. In the 1st 4 days post-transplantation, similar percentages of recipients developed grade 3 PGD on at least 1 day (heavy alcohol user = 29% [4/14] versus lighter alcohol user = 27% [16/60]); however, recipients receiving a lung from a heavy alcohol user were more likely to have multiple and consecutive days of grade 3 PGD, especially in the 1st 48 hours post-transplant. Both median length of stay in the intensive care unit and hospital were somewhat longer in the heavy alcohol user group (9 versus 7 days and 19.5 versus 17.5 days, respectively). If these preliminary findings are validated in a multi-center study, they would have important implications not only for our understanding of the pathophysiology of PGD but also for the development of novel treatments based on the evolving evidence from experimental and clinical studies on how alcohol abuse renders the lung susceptible to acute edematous injury.

Key Indexing Terms: Primary graft dysfunction; Lung transplantation; Lung donor; Recipient; AUDIT; Alcohol use. **[Am J Med Sci 2015;349 (2):117–123.]**

Primary graft dysfunction (PGD) is the leading cause of death in the immediate period following lung transplantation and has an incidence of 15% to 25%.[1] Unfortunately, there are no effective therapies, and even with supportive care, the mortality can be as high as 43%.[2,3] It had previously been assumed that the factors predisposing to PGD pertain to the surgical procedure or to the allograft recipient.[4] However, compelling experimental and clinical evidence suggests that donor-related risks factors are also important in the development of PGD. For example, it is now recognized that donor characteristics, such as age, smoking and mismatches with the donor in sex or race, contribute to poor recipient outcomes.[4] We recently demonstrated a potential association between elevated donor levels of receptor for advanced glycation end-products and the development of PGD.[5] In addition, other studies have shown that donor biomarkers such as interleukin (IL)-8,[6] vascular endothelial growth factor[7] and certain gene expression profiles[8] are associated with an increased risk of developing PGD. Importantly, because there are no proven medical treatments for PGD, identification of additional biomarkers to accurately identify allografts that are at higher risk for developing this serious condition are needed.[9]

The features of PGD represent essentially a *form fruste* of the acute respiratory distress syndrome (ARDS), the most severe form of acute lung injury (ALI), which occurs within the unique context of lung transplantation.[10] In the past 15 years, a strong independent association between alcohol abuse and ARDS has been identified, and our group at Emory University has been at the forefront of investigating the mechanisms by which alcohol abuse renders the lung susceptible to acute edematous injury. Specifically, alcohol abuse independently and significantly increases the risk of ARDS 2- to 4-fold in critically ill individuals.[11,12] Although the mechanisms underlying this association are still being investigated, we have clear evidence from experimental models and clinical studies that chronic alcohol ingestion causes oxidative stress and depletes the pool of the antioxidant glutathione within the alveolar space.[13,14] Alcohol-induced oxidative stress causes previously unrecognized alveolar epithelial dysfunction, including increased paracellular permeability, decreased liquid clearance, impaired surfactant production and decreased cell viability.[13,15–17]

This "alcoholic lung" phenotype is clinically silent in that the physiological perturbations identified in both experimental models and in otherwise healthy alcoholic individuals are not readily detectable without sophisticated measurements and do not manifest as significant lung dysfunction until an acute inflammatory stress, such as sepsis or aspiration, unmasks them. Specifically, alcohol abuse alone does not cause lung injury but rather it significantly lowers the threshold for its development. This previously unrecognized association between alcohol abuse and ARDS/ALI was identified only when prospective studies were done using accurate alcohol use assessments such as the Alcohol Use Disorder Identification Test (AUDIT).[12] However, this type of prospective investigation has not heretofore been applied in the unique context of lung transplantation and PGD. Therefore, we sought to determine if donor alcohol abuse likewise increased the risk of PGD. As a 1st step and a means of identifying biological plausibility, we demonstrated that chronic alcohol use by the donor exacerbated airway injury in allograft recipients using an experimental

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rat model of heterotopic tracheal transplantation.[18] We then initiated a single-center pilot study within our Emory Alcohol and Lung Biology Center, in collaboration with the McKelvey Center for Lung Transplantation at Emory University, to collect preliminary data in support of such an association that could stimulate the design and implementation of a larger multi-center study. Such information would have enormous implications for both the selection of lung allograft donors and for the development of novel therapeutic approaches to mitigate the devastating consequences of PGD.

We reasoned that this study was important to the lung transplant community, which includes donors, recipients and the tens of thousands of healthcare professionals involved in lung transplantation. Unfortunately, despite advances in lung transplantation techniques and identification of appropriate selection criteria, our ability to predict which lung allograft recipients will develop PGD is at present imprecise,[19] and our limited understanding of the fundamental mechanisms driving the development of PGD has frustrated our attempts to identify effective therapies beyond supportive care. In light of recent experimental and clinical evidence revealing the strong and independent association between alcohol abuse and ALI, we felt that there were compelling reasons to examine whether donor alcohol abuse increased the risk of PGD. To address this hypothesis, we initiated a pilot study at Emory University through our Alcohol and Lung Biology Center to study the relationship between donor alcohol use and the development of PGD in lung transplant recipients.

PATIENTS AND METHODS

Donor and Recipient Characteristics

Eligibility

Between February 2007 and January 2009 at Emory Hospital in Atlanta, GA, 88 consecutive lung transplant recipients and their lung donors were considered for eligibility. Exclusion criteria included being re-transplanted (n = 4), no consent (n = 2) and improper lung preparation (n = 3). Two subjects received a lung from the same donor; 1 subject was randomly selected for inclusion in the analysis. Therefore, in total, there were 78 eligible lung allograft recipients, of whom 74 had their donor's alcohol use quantified using the AUDIT. All analyses are based on these 74 recipients.

Donor Lung Criteria

Lung donors were recruited from brain-dead patients consented for lung donation. Donor lungs used for transplantation at our institution had to meet the following inclusion criteria at the time of organ recovery: (1) compatible ABO blood group, (2) $PaO_2/FiO_2 > 300$ mm Hg, (3) chest radiograph without focal or significant findings consistent with pneumonia or lung contusion and (4) adequate bronchoscopic assessment was performed to ensure that no obvious aspiration was present. Explanted lungs were preserved using Perfadex (Vitrolife, Gothenburg, Sweden). The allograft ischemia time was recorded for all lung transplants.

Lung Recipients Criteria

Recipients listed at our institution received transplants according to their clinical priorities. Clinical data were available for all lung transplant recipients. This study was approved by the institutional review board at Emory University.

Immunosuppressive Therapy

All recipients received a standard immunosuppression protocol following transplantation, consisting of induction with IL-2 receptor antagonist and maintenance with a 3-drug combination with the calcineurin inhibitor tacrolimus, azathioprine and steroids as described previously.[20]

Transplant Infection Prophylaxis

All recipients received antibiotics up to 5 days after surgery, and subsequent antibiotic therapy length was determined based on final donor culture and intra-operative bronchial cultures obtained by swab at the time of surgery. All recipients received prophylaxis after transplantation against cytomegalovirus, *Pneumocystis jirovecii* and *Aspergillus* spp. as previously described.[21]

PGD Treatment

PGD treatment involved administration of diuretics, prolonged mechanical ventilation with adjusted FiO_2 and positive end-expiratory pressure and inhaled NO as required.

Predictor and Outcomes Definitions

Definition of Alcohol Abuse

The AUDIT is a 10-question questionnaire that queries recent alcohol use, alcohol dependence symptoms and alcohol-related problems and has a sensitivity >90% to distinguish hazardous and harmful alcohol use whether the information is self-reported or obtained from a surrogate add.[22,23] Respondents with scores ≥8 are categorized as heavy alcohol users, and those with scores <8 are categorized as light alcohol users.

Scoring of PGD

PGD was scored from 0 to 3 using chest radiographs and PaO_2/FiO_2 ratios per the guidelines of the International Society for Heart and Lung Transplantation. Scores were assigned at regular and/or specified intervals during the 1st 96 hours after lung transplantation.[24] Before removal of their endotracheal tube, all recipients received a bronchoscopy to assess bronchial anastomosis and bronchoalveolar lavage fluid was obtained and submitted for culture. Furthermore, for recipients fitting clinical criteria of PGD, trans-bronchial biopsies were performed to rule out additional potential causes for abnormal radiographs/poor oxygenation.

Covariates Examined

Potential confounding variables were examined that could influence any observed association between donor alcohol abuse and subsequent PGD. These included:

Donor variables: Age, sex, race, smoking history (>1 pack-year) and cause of death.

Recipient variables: Age, race, sex and underlying lung disease, length of stay (LOS) in the intensive care unit (ICU) and overall hospital LOS.

Surgical variables: Transplant procedure, utilization of pulmonary cardiopulmonary bypass, ischemia time and duration of mechanical ventilation

LOS: LOS in the ICU and the overall hospital LOS.

Statistics

As this was a single-center pilot study with a limited number of participants, we recognized that it was unlikely that we would be able to identify a statistically significant difference in the incidence of PGD in allograft from donors with or without alcohol abuse unless that difference was very large. Therefore, the primary goal was to make comparisons that could be used to design a larger multi-center trial if our results suggested that donor alcohol abuse could be associated with