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Lung size mismatch and primary graft dysfunction after bilateral lung transplantation

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BACKGROUND: Donor-to-recipient lung size matching at lung transplantation (LTx) can be estimated by the predicted total lung capacity (pTLC) ratio (donor pTLC/recipient pTLC). We aimed to determine whether the pTLC ratio is associated with the risk of primary graft dysfunction (PGD) after bilateral LTx (BLT).

METHODS: We calculated the pTLC ratio for 812 adult BLTs from the Lung Transplant Outcomes Group between March 2002 to December 2010. Patients were stratified by pTLC ratio >1.0 ("oversized") and pTLC ratio ≤ 1.0 ("undersized"). PGD was defined as any ISHLT Grade 3 PGD (PGD3) within 72 hours of reperfusion. We analyzed the association between risk factors and PGD using multivariable conditional logistic regression. As transplant diagnoses can influence the size-matching decisions and also modulate the risk for PGD, we performed pre-specified analyses by assessing the impact of lung size mismatch within diagnostic categories.

RESULTS: In univariate analyses oversizing was associated with a 39% lower odds of PGD3 (OR 0.61, 95% CI, 0.45-0.85, $p = 0.003$). In a multivariate model accounting for center-effects and known PGD risks, oversizing remained independently associated with a decreased odds of PGD3 (OR 0.58, 95% CI 0.38 to 0.88, $p = 0.01$). The risk-adjusted point estimate was similar for the non-COPD diagnosis groups (OR 0.52, 95% CI 0.32 to 0.86, $p = 0.01$); however, there was no detected association within the COPD group (OR 0.72, 95% CI 0.29 to 1.78, $p = 0.5$).

CONCLUSION: Oversized allografts are associated with a decreased risk of PGD3 after BLT; this effect appears most apparent in non-COPD patients.

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Primary graft dysfunction (PGD) is a major cause of early mortality after lung transplantation (LTx) and is associated with the development of bronchiolitis obliterans, which is a major cause of long-term mortality.[1,2] Improved survival associated with graft oversizing in bilateral lung

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transplantation (BLT) has been demonstrated in several studies.[3–9] The most common indications for transplantation affect the size-matching preference, with a general preference toward oversizing in chronic obstructive pulmonary disease (COPD) and undersizing in idiopathic pulmonary fibrosis (IPF).[4,9] However, data from studies limited to patients transplanted for idiopathic pulmonary arterial hypertension (IPAH), a condition in which no sizing preference exists, demonstrate the same association between size matching and survival.[4]

The mechanisms by which oversizing improves outcomes after transplant remain unknown, but the survival difference may be observed in the early post-transplant period.[8] It is conceivable that differences in PGD rates are responsible for these early survival differences and that lung undersizing predisposes to PGD through mechanisms involving both the pulmonary vasculature as well as through potentially injurious tidal volumes during mechanical ventilation. A significantly undersized pulmonary vasculature could result in higher pulmonary arterial pressure at reperfusion, which is a risk factor for PGD.[2,10] Alternately, variability in size matching could result in different rates of PGD through differences in mechanical ventilation tidal volumes compared with donor lung size during the period of mechanical ventilation during and after LTx. It is common practice to set mechanical ventilation tidal volumes after LTx according to recipient rather than donor characteristics.[11,12] Therefore, undersized allografts could potentially receive tidal volumes that are high when considered according to donor lung size.[11,12] Lung protective strategies of low tidal volume ventilation clearly established to be beneficial in acute respiratory distress syndrome (ARDS)[13] are also beneficial to patients at risk for ARDS.[14,15] Likewise, low tidal volume ventilation is also associated with better outcomes, even when exposure is limited to the relatively brief intra-operative period in patients undergoing abdominal surgery.[14]

We hypothesized that an oversized allograft would be associated with a lower risk of PGD. To address this hypothesis, we conducted a study ancillary to the Lung Transplant Outcomes Group (LTOG) to characterize lung size mismatch and its association with the occurrence of PGD.

Methods

Study design and subject selection

The LTOG study is a U.S. National Institutes of Health (NIH)-sponsored, multicenter, prospective cohort study designed to evaluate risk factors for PGD. Details of the LTOG cohort have been described previously.[2] In this LTOG ancillary study, we included patients aged 18 to 80 years undergoing BLT at 10 U.S. transplant centers between March 2002 and December 2010. Clinical parameters were collected prospectively. Additional information was verified by United Network for Organ Sharing data.

Stratification according to lung size matching. Estimates of lung and chest wall size were calculated from gender, age and height, as the predicted total lung capacity (pTLC) (refer to Supplementary Material 1 available online at www.jhltonline.org).[8,16,17] Donor lung size was compared with the size of a recipient's thorax by calculating the ratio of the donor's pTLC to the recipient's pTLC (pTLC ratio). The pTLC ratio was analyzed as a continuous variable. To assess for non-linearity, we analyzed according to quintiles of pTLC ratio. Patients were further stratified by pTLC ratio ≤ 1.0 ("undersized") and pTLC ratio > 1.0 ("oversized"), as previously reported.[3,9] A propensity score estimating the likelihood of receiving an oversized allograft (pTLC ratio > 1.0) was created using logistic regression based on 17 potential predictors (see Supplementary Material 2 online).

Definition of PGD. PGD was graded according to ISHLT criteria, which is based on PaO_2/FIO_2 ratio and the presence of diffuse parenchymal infiltrates in the allograft on chest radiograph.[1] Chest radiographs were interpreted independently by two physicians unaware of other clinical variables, with adjudication of conflicts by a third reviewer (Grade 3 PGD [PGD3] classification kappa = 0.95).[1,2] The primary outcome was the presence of PGD3 (PaO_2/FIO_2 ratio <200) at any point within 72 hours of transplantation.[1,2]

Analytical plan. Logistic regression was used to estimate odds ratios (ORs) for the association between pTLC ratio and PGD. Transplant center was evaluated as a fixed effect using conditional logistic regression. As transplant diagnoses can influence the size-matching decisions and also modulate the risk for PGD, we performed pre-specified analyses assessing the impact of lung size mismatch with the following transplant indications: (a) within chronic obstructive pulmonary disease (COPD) vs non-COPD; and (b) within COPD, idiopathic pulmonary fibrosis (IPF) and idiopathic pulmonary arterial hypertension (IPAH). An interaction analysis was performed between diagnoses (COPD vs non-COPD, and COPD, IPF, IPAH and "other") and pTLC ratio upon the outcome of PGD3 (see Supplementary Material 3 online). Potential confounders were selected into multivariable models based on risk factors previously identified in the literature and plausible association with pTLC ratio or PGD.[2] Recipient body mass index (BMI) was included as a categorical variable (quintiles of BMI) in multivariable modeling because of its observed non-linearity.[18] The risk of PGD by pTLC ratio strata was further assessed in a second multivariable model incorporating ordinal quintiles of the propensity score (likelihood of receiving an oversized allograft based on 17 predictors; see Supplementary Material 2 online). Potential problems of missing data were approached as described previously.[2]

Characteristics of mechanical ventilation at reperfusion. Recipient tidal volumes (TVs) at reperfusion were expressed as absolute values in milliliters (ml). As a general goal is to set tidal volume to match lung size, TVs are commonly set according to predicted body weight (PBW), not measured body weight.[13] TVs were expressed in relation to PBW of the recipient and PBW of the donor (see Supplementary Material 1 online).

Results

Of 1,255 total LTxs, there were 812 BLT subjects, and PGD3 developed in 31% of the patients. The histogram of the pTLC ratio is shown in the Supplementary Material (see Figure S2).

In univariate conditional logistic regression models, each 0.1 increase in pTLC ratio was associated with a 14% lower odds of PGD3 (odds ratio [OR] 0.86, 95% confidence interval [CI] 0.78 to 0.96, $p = 0.005$; Table 1). The