Published in final edited form as:

Anesth Analg. 2016 September ; 123(3): 795–796. doi:10.1213/ANE.0000000000001374.

In Response to a Letter to the Editor

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Colombo et al. note that more inotropic and vasopressor support was required in patients who developed grade-3 primary graft dysfunction (PGD), and ask whether our analysis adjusted for the imbalance in these variables. Using standard statistical techniques, all baseline and perioperative characteristics listed in Table 2 were considered as potential confounders and evaluated for inclusion in the multivariable logistic regression model. Although inotropic agents and vasopressor use were univariably associated with grade-3 PGD ($P<0.05$), these variables were removed from the model during backward selection procedures when their effect was not significant. Thus the effect of inotropic and vasopressor use with grade 3 PGD was considered in our analysis, but was not found to be significant.

With regards to the preoperative cardiac function, there are data that pulmonary arterial hypertension is indeed associated with PGD^{i,ii}. Although echocardiographic measures of right and left ventricular function were not included in our model, we captured hemodynamic variables after lung reperfusion including cardiac index, pulmonary arterial pressures, and central venous pressure. None differed significantly in our groups.

We agree that more detail on the overall perioperative fluid balance of patients would be helpful. But inherent limitations of our retrospective study design included the fact that accurate recording of postoperative fluid balance was unavailable. Regarding our

hemodynamic management protocol, intraoperative management for lung transplantation at the Cleveland Clinic is standardized and the algorithm for hemodynamic management and mechanical ventilation was described in the methods section of our paper.

Inadequate intravascular volume can harm the heart and kidneys, and we certainly do not recommend fluid restriction to point of organ malperfusion and dysfunction. However, our results are consistent with two other reports, that fluid administration and blood transfusion are associated with development of PGD after lung transplantation.^{iii,iv} And finally, minimizing fluid administration improves outcomes in conditions with similar pathophysiology including severe ARDS, lung trauma, and thoracic surgery.^v

Retrospective analyses cannot establish causality with certainty. Thus while the association between fluid and graft failure is clear, it remains unknown whether restricting fluid will actually improve graft survival. The value of our analysis is in identifying a potentially valuable therapeutic intervention that is easy to implement and costs nothing. We agree that a randomized trial is needed to prove whether fluid restriction reduces risk of PGD, and our results provide an excellent basis for estimating treatment effect (and thus sample size) for such trial. However, in light of our results and others^{iv, v, vi} and the general consensus that increased fluid administration is detrimental, patient enrollment and clinician participation for a randomized study examining liberal vs. restrictive fluid strategies may be challenging.

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