Published in final edited form as:

J Surg Res. 2020 November ; 255: 332–338. doi:10.1016/j.jss.2020.05.072.

Acute Kidney Injury in Patients Undergoing Cardiopulmonary Bypass for Lung Transplantation

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Abstract

Background: Cardiopulmonary bypass (CPB) is often used to support patients undergoing lung transplantation who are intolerant of anatomic manipulation or single lung ventilation during the procedure. However, CPB may be associated with adverse outcomes. We evaluated the hypothesis that CPB is associated with increased acute kidney injury (AKI) and postoperative mortality after lung transplantation.

Materials and Methods: This was a retrospective review of our institutional lung transplant database at the University of Texas Southwestern Medical Center from 2012–2018. Patients were grouped based on their need for CPB. The primary outcome was AKI within 48 hours of transplantation, which was defined as Kidney Disease Improving Global Outcomes (KDIGO) Stage 1 or greater. Secondary outcomes included all-cause mortality.

Results: 426 patients underwent lung transplantation with 39.0% (n=166) requiring CPB. There were no differences in demographics and comorbidities, including baseline renal function, between CPB and no CPB. CPB use was higher in recipients with interstitial lung diseases and primary pulmonary hypertension. Median lung allocation score was higher in those needing CPB

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Author Contributions: Christopher Heid conceptualized the study, presented the findings at the Academic Surgical Congress, and drafted the manuscript. Mitri Khoury performed all statistical analysis and assisted with manuscript preparation. Kayla Maaraoui and Charles Liu assisted with data collection. W. Steves Ring manages the institutional Society of Thoracic Surgeons database and lung transplant database, used for this study. Michael Wait, Matthias Peltz, and Lynn C. Huffman were the surgeons who performed all operations and oversaw the study from start to finish. All authors assisted with manuscript revisions.

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Meeting Presentation: This study was presented at the 15th Annual Academic Surgical Congress on Wednesday, February 5, 2020. Program number: ASC20201316. Session: 66-Clinical/Outcomes: Trauma/Cardiothoracic Patient- Centered Outcomes QuickShot Session.

(47 [IQR 40–59] vs 39 [IQR 35–47]). Patients requiring CPB were significantly more likely to experience AKI (61.44% versus 36.53%, $P<.01$) and post-operative hemodialysis (6.6% vs 0.4%, $P<.01$). On multivariable analysis, CPB was significantly associated with post-operative AKI (OR 1.66, 95% CI 1.01–2.75, $P=.04$). 30-day mortality was higher in patients undergoing CPB (4.2% vs 0.8%, $P=.03$).

Conclusion: CPB for lung transplantation is associated with a higher incidence of AKI, renal failure requiring hemodialysis, and 30-day mortality. CPB should be used selectively for lung transplantation.

Keywords

Lung transplantation; acute kidney injury; cardiopulmonary bypass; renal failure; hemodialysis

Introduction:

End stage lung disease is a complex and heterogeneous clinical entity with poor long-term survival. To date, no pharmacologic therapy exists that can provide meaningful improvements in patient mortality. Therefore, lung transplantation remains the only definitive treatment, providing adult patients a median survival of 6.2 years¹.

Lung transplantation is a technically demanding procedure that requires single lung ventilation and retraction of the heart for exposure; both of which can cause significant cardiopulmonary dysfunction. Cardiopulmonary bypass (CPB) is one solution to the hypoxia, hypercarbia and hypotension that can occur during lung transplantation. By placing the recipient on CPB, adequate arterial perfusion pressures and gas exchange can be maintained, facilitating the operation. However, the use of CPB during lung transplantation is controversial^{2–6}. Some institutions routinely use CPB for lung transplantation, as it is felt to provide a more controlled operative environment for anastomoses and reduced warm ischemic times^{4,6}. Other institutions use cardiopulmonary bypass selectively, as it has been associated with many complications such as coagulopathy⁷, stroke⁸, and renal injury⁹.

The theory behind renal injury from CPB is multifactorial. CPB is felt to result in altered renal blood flow⁹, release of pro-inflammatory cytokines¹⁰, and formation of microemboli⁹, all of which may contribute to renal dysfunction. Despite this, recent studies have called into question that CPB results in renal injury¹¹. The objective of this study is to determine the impact of CPB on post-operative renal function and early mortality in lung transplantation. We hypothesize that the use of CPB increases acute kidney injury (AKI) and perioperative mortality in patients undergoing lung transplantation.

Material and Methods:

Study Design

We performed a retrospective review of our prospectively maintained institutional lung transplant database at the University of Texas Southwestern Medical Center. This study was approved by the institutional review board at the University of Texas Southwestern Medical Center, and the need for informed consent was waived. Patients undergoing unilateral and

bilateral lung transplantation from 2012–2018 were included and grouped by their need for CPB. Patients were excluded if they were undergoing multi-organ transplantation, were less than 18 years of age, or had missing data regarding pulmonary systolic artery pressure. The primary outcome was the development of AKI. Secondary outcome was all cause 30-day mortality.

Study Definitions

AKI was defined as being Kidney Disease Improving Global Outcomes¹² (KDIGO) Stage 1 or greater. This was determined using the peak post-operative creatinine level within 48 hours of surgery. CPB was defined as mechanical circulatory support during transplantation with full cardiopulmonary bypass via either central or peripheral cannulation. Post-operative acute renal failure (ARF) was defined by a new need for renal replacement therapy at least once postoperatively. Intraoperative blood products included transfusion of any blood component during the operation (red blood cells, platelets, fresh frozen plasma, or cryoprecipitate). Selective use of CPB was defined as an intraoperative conversion to CPB after attempts at performing the operation off CPB. Elective use of CPB refers to cases where the patient was put on CPB prior to attempting the first pneumonectomy suggesting preoperative intent.

Institutional Practice Patterns

Institutional practice patterns are to use CPB selectively, and this is an intraoperative decision made in conjunction with cardiac anesthesia based on the patient's physiologic status. Hemodynamic instability, severe pulmonary hypertension and deranged gas exchange are the typical causative factors warranting CPB at our institution. At times, CPB may be used empirically at the surgeon's discretion based on preoperative physiologic parameters. There are no set criteria for elective CPB use. Perioperative immunosuppression at our program typically consists of a preoperative antimetabolite dose (azathioprine or mycophenolate mofetil), intraoperative methylprednisolone bolus, and tacrolimus continuous infusion. For patients with underlying chronic kidney disease or implants performed with CPB, a renal sparing regimen is utilized by replacing the calcineurin inhibitor infusion with a dose of basiliximab¹³. Tacrolimus is started only after stabilization of renal function.

Statistical Analysis

Categorical variables were represented as numbers with proportions. Continuous variables were represented as medians with interquartile ranges. Patients were compared using Pearson's Chi Square and Fisher's Exact Test where appropriate for categorical variables. Wilcoxon rank sum tests were used to compare continuous variables. We performed a binary logistic regression analysis to identify the magnitude of association for variables on AKI. The patient-related factors that demonstrated a univariate association $P \leq .05$ or were considered clinically relevant for AKI were included as covariates in the regression model. All statistical analysis was performed with SPSS v25 (Aramonk, NY). A $P < .05$ was considered statistically significant.

Results:

A total of 426 patients underwent lung transplantation with 39.0% (n=166) requiring CPB. There were notable differences in the baseline characteristics between the two groups (Table 1). The patients that underwent CPB were more likely to have higher body mass index (BMI), lung allocation scores (LAS), and pulmonary artery systolic pressures. There were no differences in baseline renal function between CPB and no CPB groups (Table 2). CPB was more commonly used for pulmonary hypertension and interstitial lung disease (ILD) patients and less commonly for patients with cystic fibrosis, chronic obstructive pulmonary disease and other (Table 3). Operative time and blood product transfusions were higher in the CPB group (Table 4). CPB was more often needed for bilateral compared to unilateral transplants (Table 4).

Patients requiring CPB were significantly more likely to experience an AKI in the postoperative period (Table 5). This held true for both selective and elective use of CPB. Moreover, there were no differences in AKI rates based on elective vs selective CPB (Table 6). 30-day mortality and ARF were also higher in patients undergoing CPB on univariate analysis (Table 5). After adjustment, CPB continued to be significantly associated with acute kidney injury (Table 7).

Discussion:

In this study, we observed that the use of CPB for lung transplantation was associated with higher rates of AKI, ARF, and 30-day mortality despite no significant differences in baseline renal function. CPB was associated with longer operative times, more blood transfusions, and was more frequently used for double versus single lung transplants. When analyzing CPB based on selective compared to elective use, both were associated with AKI. On multivariable analysis, we identified the following to be independent predictors of AKI: LAS, angiotensin converting enzyme inhibitor/angiotensin II receptor blocker (ACEI/ARB) within 48 hours of surgery, and CPB.

The impact of CPB on perioperative complications remains controversial. Prior studies have suggested strong associations with the use of CPB and adverse outcomes^{9,10}. This topic was particularly studied when the use of off-pump coronary artery bypass grafting became in vogue in cardiac surgery. Early literature in the off-pump coronary artery bypass era reported higher rates of renal dysfunction in patients undergoing CPB¹⁴. However, subsequent studies failed to confirm this finding^{11,15}. Recent randomized controlled trials have also found that off-pump coronary artery bypass was associated with worse survival compared to on CPB¹⁶.

In the lung transplant literature, several studies have shown CPB time to be associated with renal injury^{17–19}. In these studies, all patients underwent CPB for their operation and total time on CPB seemed to correlate with renal injury. Since we perform cardiopulmonary bypass selectively at our center, we were able to compare patients based on the use of CPB versus no CPB, and we identified CPB to be significantly associated with AKI. Moreover, when we stratify for selective compared to elective CPB, both are associated with AKI. We believe the pathophysiologic role of CPB on renal function is multifactorial. First, CPB

results in continuous, non-pulsatile flow. Although the goal is to maintain flows at a cardiac index of at least 2.2 liters per kilogram per minute, this is still a state of non-physiologic blood flow to end organs. Secondly, the CPB circuit and cardiotomy suction result in the activation of inflammatory cytokines, which may cause renal damage⁹. Third, coagulopathy related to the necessary anticoagulation for CPB (activating clotting times > 480 seconds) and the dilutional effect of the CPB priming fluid result in a functional anemia that may impair oxygen carrying capacity to end organs.

Aside from CPB, additional predictors for AKI identified by our regression included: LAS and ACEI/ARB within 48 hours of surgery. LAS is the scoring system used for lung allocation²⁰ and has been shown to be a predictor of adverse outcomes after lung transplantation²¹. The only baseline co-morbid diagnosis taken into the LAS is diabetes. The association between diabetes and AKI would be an expected observation due to the underlying pathophysiologic impact of diabetes on renal function²². LAS also accounts for age and hemodynamic parameters, which are known to affect renal function. The association between ACEI/ARB and AKI has been previously documented in cardiac surgery²³ and is felt to be due to intra-operative hypotension resulting in renal hypoperfusion. According to our regression, there is a strong trend between transfusion and AKI, which is likely multifactorial. First, the need for intraoperative blood transfusion may be a marker for intraoperative anemia, which can have detrimental effects on renal function²⁴, as the kidney is an end organ dependent on adequate hemoglobin concentration for oxygen delivery. Additionally, red blood cell storage results in altered cell function and the release of pro-inflammatory mediators, which may impair renal function^{25–28}. Although these factors likely have a role in the development of renal injury, this is undoubtedly a complex process that warrants further investigations, both at the clinical and basic science level.

The decision to use routine CPB bypass for lung transplantation remains controversial and no consensus guidelines exist. There are times when CPB is mandatory, such as cardiopulmonary intolerance, hypoxemia and difficulties with exposure. We observed the diagnosis of primary pulmonary hypertension (WHO Class I) and interstitial lung disease required higher rates of CPB use. The association of primary pulmonary hypertension and the need for CPB was not surprising. Pulmonary hypertension leads to various degrees of right ventricular strain and right ventricular dysfunction. These patients often tolerate unilateral pulmonary artery clamping poorly, necessitating CPB. Similarly, progressive ILD often leads to the development of pulmonary hypertension and severe hypoxia.

In our patient population, both elective and selective CPB use were associated with AKI despite a renal protective immunosuppression regimen¹³. We believe these data highlight the potential untoward effects of CPB, including increased rates of renal dysfunction and 30-day mortality. For these reasons, we advocate for selective over routine use of CPB in lung transplantation, keeping in mind that there are times when CPB will be required.

There are several limitations in this study to consider. First, this study is subjected to all the inherent biases of this being a retrospective review. Another limitation of this study is that we only examined patients with full CPB support. A growing body of literature is suggesting improved outcomes with extracorporeal membrane oxygenation (ECMO) support over full

CPB^{29–30}. In theory, ECMO results in less systemic inflammation due to its smaller circuit interface and lack of cardiotomy suction. Moreover, ECMO requires less anticoagulation resulting in less coagulopathy^{29–30}. This study is underpowered to stratify CPB into elective/selective in a multivariable regression, and we recognize that as a limitation to the study as the selective patients presumably required CPB in order to receive a transplant. Nevertheless, our data shows no difference in AKI rates between the elective and selective group by univariate analysis, thus analyzing CPB in a binary fashion still supports the argument that CPB is associated with AKI. In addition, our study likely underestimates the true incidence of renal injury, since our analysis only identified AKI based on biochemical parameters. KDIGO guidelines¹² also have criteria based on urine output, which is not available in our database. Lastly, although CPB was significantly associated with 30-day mortality on Chi-Square analysis, no regression was conducted due to the low number of events (n=9), which would undoubtedly lead to small sample bias and large variability in the logistic regression coefficients.

Conclusion:

Lung transplantation can result in intra-operative cardiopulmonary dysfunction manifested as hypotension, hypoxia, and/or hypercarbia. CPB is a tool that can circumvent these issues. Some lung transplant centers routinely use CPB on all lung transplantations, whereas others advocate for a selective use of CPB. The literature on CPB in lung transplantation is controversial, and there are no consensus guidelines. This study showed that CPB during lung transplantation is associated with increased rates of AKI, post-operative ARF, and increased 30-day mortality. CPB use was identified as an independent predictor of AKI on multivariable analysis. For these reasons, we advocate for a selective use of CPB during lung transplantation.

Acknowledgements

Disclosures:

Funding: Research reported in this publication was supported by the National Heart, Lung, And Blood Institute of the National Institutes of Health under Award Number T32HL110853 (MK). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

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Highlights:

- Cardiopulmonary bypass for lung transplant can be used selectively or empirically
- Cardiopulmonary bypass is a risk factor for AKI in lung transplantation
- Cardiopulmonary bypass for lung transplant is associated with higher dialysis requirements
- Cardiopulmonary bypass for lung transplant is associated with higher 30d mortality

Table 1.

Baseline characteristics

	No CPB (n=260)	CPB (n=166)	P-Value
Age	61 [54–66]	60 [50–66]	0.3
Male Sex, n (%)	155 (59.6%)	107 (64.5%)	0.36
BMI	25.4 [21.2–28.6]	26.6 [23.6–29.0]	0.02
Comorbidities			
Diabetes	72 (27.7%)	52 (31.3%)	0.45
Hyperlipidemia	143 (55.0%)	80 (48.2%)	0.2
Hypertension	124 (47.7%)	85 (51.2%)	0.49
Liver Disease	14 (5.4%)	16 (9.6%)	0.12
Immunocompromised	175 (67.3%)	115 (69.3%)	0.75
Mediastinal Radiation	2 (0.8%)	4 (2.4%)	0.21
Peripheral Vascular Disease	9 (3.5%)	9 (5.4%)	0.33
Chest Wall Deformity	1 (0.4%)	1 (0.6%)	1
Cerebrovascular Accident	11 (4.2%)	3 (1.8%)	0.27
Coronary Artery Disease	33 (12.7%)	23 (13.9%)	0.77
Previous Drug Use	13 (5.0%)	9 (5.4%)	0.83
LAS Score	39.0 [34.6–46.7]	47.0 [39.9–58.9]	<.01
Prior Thoracic Surgery	61 (23.5%)	49 (29.5%)	0.17
Ejection Fraction	62 [57–66]	63 [57–68]	0.2
PA Systolic Pressure	35 [31–42]	48 [36–63]	<.01
Preoperative Medication Use			
ACEI or ARB	63 (24.2%)	27 (16.3%)	0.05
Aspirin	86 (33.1%)	56 (33.7%)	0.92
Clopidogrel	2 (0.8%)	0 (0%)	0.94

Median [Interquartile range]

CPB, Cardiopulmonary bypass; ACEI; Angiotensin converting enzyme inhibitor; ARB, Angiotensin receptor blocker

Table 2.

Preoperative renal function parameters

	No CPB (n=260)	CPB (n=166)	P-Value
Chronic Kidney Disease	13 (5.0%)	14 (8.4%)	0.16
eGFR	96.0 [79.5–116.7]	97.3 [77.1.–123.2]	0.83
Preoperative Dialysis	1 (0.4%)	2 (1.2%)	0.56

CPB, Cardiopulmonary bypass; eGFR, Estimated glomerular filtration rate

Table 3.

Indications for transplant

	No CPB (n=260)	CPB (n=166)	P-Value
Chronic Obstructive Pulmonary Disease	89 (34.2%)	16 (9.6%)	<.01
Interstitial Lung Diseases	128 (49.2%)	107 (64.5%)	<.01
Cystic Fibrosis	28 (10.8%)	7 (4.2%)	0.02
Pulmonary Hypertension	6 (2.3%)	26 (15.7%)	<.01
Other	9 (3.5%)	10 (6.0%)	0.23

CPB, Cardiopulmonary bypass

Table 4.

Operative characteristics

	No CPB (n=260)	CPB (n=166)	P-Value
Operative Time	307 [239–356]	375 [328–435]	<.01
Cardiopulmonary Bypass Time		193 [141–234]	
Lowest Temperature Intra Op	35.7 [35.3–36.2]	36.0 [35.0–36.1]	0.45
Number of Lungs Transplanted			<.01
1	84 (32.3%)	9 (5.4%)	
2	176 (67.7%)	157 (94.6%)	
Intraoperative Blood Products	96 (36.9%)	148 (89.2%)	<.01
Redo Transplant	3 (1.2%)	1 (0.6%)	1

^aMedian [Interquartile range]

CPB, Cardiopulmonary bypass

Table 5.

Post-operative renal function parameters and 30-day mortality

	No CPB (n=260)	CPB (n=166)	P-Value
Acute Kidney Injury	95 (36.5%)	102 (61.4%)	
Stage 1	66 (25.4%)	61 (36.7%)	0.02
Stage 2	25 (9.6%)	22 (13.3%)	0.27
Stage 3	4 (1.5%)	19 (11.4%)	<.01
Acute Renal Failure	1 (0.4%)	11 (6.6%)	<.01
30-day Mortality	2 (0.8%)	7 (4.2%)	0.03

CPB, Cardiopulmonary bypass

Table 6.

Univariate analysis for AKI based on selective, elective or no CPB

	No AKI	AKI	P-Value
CPB Type			
None	165 (72.1%)	95 (48.2%)	<.01
Elective	28 (12.2%)	50 (25.4%)	<.01
Selective	36 (15.7%)	52 (26.4%)	<.01

CPB, Cardiopulmonary bypass

AKI, Acute kidney injury

Table 7.

Multivariable analysis for acute kidney injury

Variable	aOR	95% CI	P-Value
Hypertension	1.09	.69–1.71	.72
Liver Disease	1.49	.66–3.35	.34
Peripheral Vascular Disease	0.7	.25–1.95	.49
Lung Allocation Score	1.03	1.01–1.04	<.01
CKD Stage 3 or greater	1.91	.79–4.60	.15
ACEI/ARB	2.34	1.34–4.11	<.01
Operative Time	1.0	.99–1.01	.46
Two vs One Lung	1.29	.70–2.39	.41
Intra-Operative Blood Products	1.59	.96–2.64	.07
Cardio-Pulmonary Bypass	1.66	1.01–2.75	.04

aOR, Adjusted odds ratio; CI, Confidence interval; ACEI, Angiotensin converting enzyme inhibitor; ARB, Angiotensin receptor blocker