Reduced Cerebral Perfusion Pressure during Lung Transplant Surgery Is Associated with Risk, Duration, and Severity of Postoperative Delirium

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Abstract

Rationale: Delirium is common following lung transplant and is associated with poorer clinical outcomes. The extent to which intraoperative hemodynamic alterations may contribute to postoperative delirium among lung transplant recipients has not been examined.

Objectives: To examine the impact of intraoperative hemodynamic changes on neurobehavioral outcomes among lung transplant recipients.

Methods: Intraoperative hemodynamic function during lung transplant was assessed in a consecutive series of patients between March and November 2013. Intraoperative cerebral perfusion pressure was assessed every minute in all patients. Following lung transplant, patients were monitored for the presence and severity of

delirium using the Confusion Assessment Method and the Delirium Rating Scale until hospital discharge.

Measurements and Main Results: Sixty-three patients received lung transplants, of whom 23 (37%) subsequently developed delirium. Lower cerebral perfusion pressure was associated with increased risk of delirium (odds ratio [OR], 2.08 per 10-mm Hg decrease; 95% confidence interval [CI], 1.02–4.24; $P = 0.043$), longer duration of delirium (OR, 1.7 d longer per 10-mm Hg decrease; 95% CI, 1.1–2.7; $P = 0.022$), and greater delirium severity ($b = -0.81$; 95% CI, -1.47 to -0.15 ; $P = 0.017$).

Conclusions: Poorer cerebral perfusion pressure during lung transplant is associated with greater risk for delirium following transplant, as well as greater duration and severity of delirium, independent of demographic and medical predictors.

Keywords: cerebral perfusion pressure; delirium; lung transplantation

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Delirium is a frequent complication following cardiothoracic surgery and is associated with adverse clinical outcomes (1, 2). It has been estimated that between 14% and 42% of patients undergoing cardiothoracic surgery will experience at least one episode of delirium during their hospital stay (2). The presence of postoperative delirium has been associated with longer hospital stay (3), long-term cognitive impairment (4, 5), and greater mortality following discharge (6),

independent of other medical risk factors. Among cardiac patients, poorer intraoperative cerebral oxygenation has been associated with increased risk of neurocognitive dysfunction following coronary bypass surgery (7). Moreover, cerebral oxygen desaturation predicted cognitive decline and longer hospital stay following cardiac surgery (7).

Delirium is common following lung transplant and has been shown to be

associated with poorer clinical outcomes (8) and future cognitive impairment (9). Several recent studies have suggested that poorer intraoperative hemodynamic function may be associated with adverse neurocognitive outcomes among patients undergoing surgical procedures requiring single-lung ventilation (10, 11). Tang and colleagues (10) demonstrated that reduced cerebral oxygen saturation predicted early cognitive dysfunction as determined by using the Mini

Mental State Examination in a sample of 76 surgical patients. Similarly, Suehiro and Okutai (11) found that longer duration of cerebral desaturation was associated with greater impairment in cognitive function following pulmonary lobectomy.

Despite the importance of delirium, no studies have determined the relationship between cerebral perfusion pressure changes and postoperative delirium among lung transplant recipients. We conducted a prospective study in which we examined cerebral perfusion pressure changes and postoperative delirium in lung transplant recipients. In the present study, we sought to determine if alterations in perfusion pressure were associated with risk, duration, and severity of delirium experienced during patient hospitalization.

Methods

Our sample consisted of 63 consecutive patients who underwent lung transplant at Duke University Medical Center between March and November 2013 and was previously described in detail. All patients listed for transplant or who had relocated to Durham, NC, to participate in pulmonary rehabilitation as a prerequisite to listing were approached for participation. The protocol was approved by the Duke Institutional Review Board. All patients who were approached provided written informed consent.

Because significant cognitive impairment is a contraindication for transplant, patients who had dementia or exhibited significant cognitive impairment were not eligible for participation. Within this patient cohort, we previously demonstrated that poorer pretransplant neurocognitive function was predictive of postoperative delirium and that the presence of post-transplant delirium was associated with longer duration of hospitalization. In addition, we previously found that neurocognitive performance declined following transplant among individuals who developed postoperative delirium.

All patients received similar pharmacologic management, both during transplant and during the immediate postoperative period. Anesthesia was induced with propofol or etomidate and maintained with isoflurane, propofol, midazolam, and fentanyl as needed. The target oxygen saturation was greater than 90% in all patients, and systolic blood

pressure was maintained above 90 mm Hg using phenylephrine, vasopressin, and epinephrine as needed. Patients were sedated postoperatively with propofol infusions until they were ready to be extubated, at which point all sedatives were discontinued and thoracic epidural analgesia was provided. All patients were free from benzodiazepines before transplant, as recommended by Duke lung transplant guidelines.

Intraoperative Hemodynamics

Intraoperative hemodynamic levels were recorded at 1-minute intervals during transplant and stored on a networked hard drive for all patients during transplant. These data were recorded in and later retrieved from the electronic medical records. Mean arterial pressure (MAP) was measured from an arterial catheter routinely placed for intraoperative monitoring from either the radial or the femoral artery. Central venous pressure (CVP) was obtained from a pulmonary arterial catheter. Cerebral perfusion pressure was calculated as the difference between MAP and CVP (MAP – CVP). To eliminate potentially erroneous values due to measurement error, MAP values below 15 mm Hg or above 200 mm Hg were eliminated, as were CVP values above 60 mm Hg.

Medical Variables

Primary graft dysfunction. Primary graft dysfunction data were obtained through retrospective chart review. Grading of primary graft dysfunction was determined according to International Society of Heart and Lung Transplant guidelines (12) using the ratio of partial oxygen pressure to

fraction of inspired oxygen assessed at 72 hours after transplant (13, 14). Because chest X-rays could not be visually inspected for some patients, we did not differentiate between primary graft dysfunction grades 0 and 1. Patients were therefore graded as either 0 or 1, 2, or 3 on the basis of laboratory values obtained as close to 72 hours as possible.

Charlson comorbidity index. The Charlson comorbidity index (15) incorporates multiple chronic conditions, including history of heart disease, diabetes, liver disease, and others, to calculate a predicted 10-year mortality score. Medical background information was collected during patients' pretransplant clinic assessments.

Lung allocation score. The lung allocation score is used to prioritize patients for transplant on the basis of a quantitative risk metric determined by a combination of native disease, pulmonary function, functional capacity, and other disease markers. Scores range from 0 to 100, with higher scores suggesting a greater net transplant benefit (16).

Postoperative Morbidity

Postoperative morbidity was assessed with the Postoperative Morbidity Survey (POMS) (17), a validated system used to document the presence of postoperative morbidity in multiple organ systems. POMS criteria were evaluated through direct patient questioning and examination, review of clinical notes and charts, retrieval of data from the hospital clinical information system, and/or consultation with the patient's caregivers. The POMS incorporates postoperative morbidity data

Table 1. Background and clinical characteristics of the sample (n = 63)

Variable	Delirious (n = 23)	Nondelirious (n = 40)	Total Cohort (n = 63)
Mean age (SD), yr	54.2 (16.7)	52.3 (16.9)	52.7 (16.8)
Male sex, n (%)	17 (74%)	6 (26%)	23 (35%)
White race, n (%)	18 (78%)	34 (85%)	52 (83%)
Charlson comorbidity index	1.30 (0.6)	1.35 (0.5)	1.27 (0.5)
Diabetes, n (%)	0 (0%)	4 (10%)	4 (6%)
Heart disease history, n (%)	3 (13%)	6 (15%)	9 (14%)
Lung allocation score at transplant	44.4 (13.6)	47.9 (18.3)	46.8 (17.4)
Native disease			
Cystic fibrosis	3 (27%)	8 (73%)	11 (17%)
Chronic obstructive pulmonary disease	6 (43%)	8 (57%)	14 (22%)
Idiopathic pulmonary fibrosis	9 (39%)	14 (61%)	23 (37%)
Other	5 (33%)	10 (67%)	15 (24%)

Figure 1. Consolidated Standards of Reporting Trials chart showing flow of participants.

that include information on pulmonary, renal, gastrointestinal, hematologic, cardiovascular, and infectious diseases; wound complications; and pain. Neurologic morbidity information, including delirium, is typically obtained as part of this assessment; however, it was not included in calculating the POMS score for the present study, because delirium was the primary outcome of interest.

Interim Assessments during the Perioperative Period

In the days immediately following transplant, patients were assessed daily for the presence and severity of postoperative delirium using two clinical instruments: the Confusion Assessment Method (CAM) and the Delirium Rating Scale-Revised-98 (DRS-R-98).

Confusion Assessment Method. The CAM is a bedside test of delirium based on a checklist of symptoms that requires less than 5 minutes to administer (18). The CAM was administered daily for the first week post-transplant. For patients assessed in the intensive care unit (ICU), the CAM-ICU was used. Beginning 1 week following transplant (Postoperative Day 8), the CAM was discontinued if the patient exhibited three consecutive negative screens for delirium. Otherwise, the CAM was administered on a daily basis. The CAM has good reliability, with excellent sensitivity and specificity (19).

Delirium Rating Scale. The DRS-R-98 was administered following transplant to assess for delirium severity (20, 21). The DRS-R-98 is a 16-item scale used to assess the severity of delirium on the basis of all

available information derived from patient interviews, family and nurse reports, and cognitive and medical tests measured over a 24-hour period. The DRS-R-98 was administered at Postoperative Days 3, 5, and 7 and immediately following any positive CAM result.

Statistical Analyses

Analyses were performed using SAS 9.3 (SAS Institute, Cary, NC) and R 3.1.3 (<http://cran.r-project.org/>) software. To examine the relationship between intraoperative hemodynamic changes and post-transplant delirium, we used a logistic model with intraoperative hemodynamic measures serving as predictors and post-transplant delirium serving as a binary outcome (present or absent). Within this model, we controlled for native disease and primary graft dysfunction grade. We also examined the impact of these intraoperative factors on duration of delirium, with the total number of days with delirium modeled as the outcome variable and the same covariates as in the models above, as well as the POMS and total number of post-transplant days in the ICU (log transformed). A regression model in which a negative binomial distribution was specified for the outcome was used in this analysis. We also examined the relationship between each predictor and the severity of delirium

Table 2. Comparison of intraoperative variables for patients with and without delirium

Variable	Delirious (n = 23)	Nondelirious (n = 40)	Total Cohort (n = 63)
Intraoperative hemodynamics, mean (SD)			
Mean arterial pressure (MAP), mm Hg	73.7 (8.7)	75.9 (7.5)	75.1 (8.0)
Minimum MAP, mm Hg	28.7 (11.2)	33.0 (8.5)	31.4 (9.7)
Maximum MAP*, mm Hg	146.0 (34.6)	151.7 (31.6)	149.6 (32.6)
Central venous pressure (CVP), mm Hg	13.1 (6.6)	11.7 (3.7)	12.3 (5.0)
Minimum CVP, mm Hg	1.4 (2.9)	0.9 (1.7)	1.1 (2.2)
Maximum CVP*, mm Hg	37.0 (16.2)	30.3 (14.1)	32.7 (15.2)
Cerebral perfusion pressure (CPP), mm Hg	60.5 (11.4)	64.2 (8.4)	62.8 (9.7)
Minimum CPP*, mm Hg	8.8 (17.2)	16.0 (14.7)	13.4 (15.9)
Maximum CPP, mm Hg	133.5 (35.0)	143.2 (32.1)	139.7 (33.2)
Duration with CPP <50 mm Hg*, h	2.1 (1.6)	1.4 (1.3)	1.7 (1.6)
Other surgical characteristics			
Bilateral transplant, n (%)	20 (87%)	31 (78%)	63 (81%)
ECMO during hospitalization, n (%)	4 (17%)	6 (15%)	10 (16%)
Preoperative	1 (4%)	3 (8%)	4 (%)
Intraoperative*	3 (13%)	1 (3%)	4 (%)
Postoperative	2 (9%)	3 (8%)	5 (%)
Cardiopulmonary bypass, n (%)	3 (13%)	4 (17%)	7 (11%)
Surgery duration, mean (SD), h	9.2 (2.3)	8.6 (2.4)	8.9 (2.4)
Postoperative mechanical ventilation, h, median (IQR)	45.5 (242)	41.7 (210)	43.3 (221)
Intensive care unit stay†, mean (SD) d	13.3 (15.5)	5.1 (7.6)	8.2 (11.9)
Primary graft dysfunction grade†, n (%)			
0/1	10 (44%)	27 (68%)	37 (59%)
2	7 (30%)	11 (28%)	18 (29%)
3	6 (26%)	2 (5%)	8 (13%)

Definition of abbreviations: ECMO = extracorporeal membrane oxygenation; IQR = interquartile range. Comparisons between delirious and nondelirious groups are unadjusted.

*Delirious and nondelirious groups differ at $P \leq 0.10$.

†Delirious and nondelirious groups differ at $P \leq 0.05$.

Figure 2. Cerebral perfusion pressure during surgery and risk of delirium, adjusted for native disease and primary graft dysfunction assessed 72 hours following transplant. Lower cerebral perfusion pressure was associated with an increased risk of post-transplant delirium, with every 10-mm Hg decrease roughly doubling the odds of delirium (odds ratio, 2.08/10-mm Hg decrease; 95% confidence interval, 1.02–4.24; $P = 0.043$).

using general linear models, controlling for the same covariates as above, with the mean DRS-R-98 score used as the outcome variable.

Cerebral perfusion pressure was scaled in 10-point increments to allow for meaningful interpretation of parametric estimates. Model assumptions were evaluated and found to be acceptable across all analyses. Complete data were available for all 63 participants, and all estimates were generated without the need for imputation of missing data. Given the number of candidate predictors in relation to the number of delirium cases in our model of delirium risk, we used the bootstrap validation procedure in the rms package within R (<http://cran.r-project.org/>) to evaluate the extent to which overfitting may have influenced our estimates (22).

Results

Demographic and clinical characteristics of the study sample are presented in Table 1. Sixty-four individuals underwent lung transplant during the study, of whom 63 were available for assessment (Figure 1). The most common native diseases of these lung transplant recipients were idiopathic pulmonary fibrosis (37%), followed by chronic obstructive pulmonary disease (22%) and cystic fibrosis (17%). Patients tended to have low levels of comorbidity, and the majority of patients were white. The frequency of intraoperative

measurements varied across the sample (median, 418 measurements; interquartile range [IQR], 169; range, 152–823). Patients with cystic fibrosis exhibited lower cerebral perfusion pressure levels during surgery than patients with other native diseases (mean cerebral perfusion pressure, 56.1 mm Hg; SD 11.1; $P = 0.006$), followed by patients in the “other” category (mean cerebral perfusion pressure, 60.4 mm Hg; SD, 22.8), idiopathic pulmonary fibrosis (mean cerebral perfusion pressure, 64.3 mm Hg; SD, 9.4), and chronic obstructive

pulmonary disease (mean cerebral perfusion pressure, 66.5 mm Hg; SD, 7.9) (Table 2). Cerebral perfusion pressure levels were not associated with any other patient background or medical predictors. Patients with and without delirium did not differ in use of intraoperative vasopressors or blood product administration.

Intraoperative Predictors of Delirium

Twenty-three (37%) of 63 patients developed delirium during the first week of hospitalization. More than half of the occurrences of delirium were observed during the first 1–3 days following transplant; 30% of patients were not initially delirious but developed delirium on Postoperative Day 4. On average, the duration of delirium was 1 day (mean duration, 1.1 d; SD, 2.1; range, 0–10 d). In our full model of delirium risk, we found that lower cerebral perfusion pressure levels were associated with a greater likelihood of delirium, with every 10-mm Hg decrease in cerebral perfusion pressure more than doubling the odds of developing postoperative delirium (odds ratio [OR], 2.08 per 10-mm Hg decrease; 95% confidence interval [CI], 1.08–4.24; $P = 0.043$) (Table 3; Figure 2). Within this model, higher primary graft dysfunction grade also was associated with a higher likelihood of delirium. The estimated optimism for fit was modest for this final model (15.8%), suggesting that our

Figure 3. Cerebral perfusion pressure during surgery and duration of postoperative delirium, adjusted for native disease, primary graft dysfunction assessed 72 hours following transplant, postoperative morbidity, and time in the intensive care unit. Lower cerebral perfusion pressure was associated with longer duration of post-transplant delirium, with every 10-mm Hg decrease corresponding to a 1.7-day (95% confidence interval, 1.1–2.7) increased duration of delirium.

Table 3. Cerebral perfusion pressure and postoperative delirium

Predictor	Odds Ratio (95% Confidence Interval)	P Value
Native disease		
CF vs. IPF	0.97 (0.16–5.90)	0.779
COPD vs. IPF	2.51 (0.51–12.35)	0.155
Other vs. IPF	0.73 (0.15–3.44)	0.399
Primary graft dysfunction grade 0/1, 2, or 3	3.38 (1.34–8.56)	0.010
Cerebral perfusion pressure, per 10 mm Hg	2.08 (1.02–4.24)	0.043

Definition of abbreviations: CF = cystic fibrosis; COPD = chronic obstructive pulmonary disease; IPF = idiopathic pulmonary fibrosis.

Lower cerebral perfusion pressure was associated with a greater likelihood of developing post-transplant delirium after adjusting for native disease and primary graft dysfunction score. Parametric estimates were derived from the adjusted model.

estimates were not substantially biased by overfitting.

Duration of Delirium

Duration of delirium ranged from 1 to 10 days (median, 2.0 d; IQR, 3.0). Lower levels of cerebral perfusion pressure ($b = -0.54$; 95% CI, -1.00 to -0.08 ; $P = 0.022$) were associated with longer duration of delirium after accounting for native disease, postoperative morbidity, primary graft dysfunction score, and time spent in the ICU (Figure 3). Within this model, higher primary graft dysfunction score and longer time spent in the ICU were also predictive of longer delirium duration. The association between cerebral perfusion pressure and delirium suggested that every 10-mm Hg decrease corresponded to a 1.7-day (95% CI, 1.1, 2.7) longer duration of delirium (Table 4). Within this model, higher primary graft dysfunction score and

longer time spent in the ICU were also predictive of longer delirium duration.

Delirium Severity

Delirium severity generally tended to be relatively mild (mean DRS-R-98, 8.23; SD, 2.5) among patients with delirium across all administrations. Lower cerebral perfusion pressure level was associated with greater severity of delirium following transplant ($b = -0.81$; 95% CI, -1.47 to -0.15 ; $P = 0.017$). Within this model, longer ICU stay was also associated with greater delirium severity (Table 5).

Discussion

In this consecutive series of 63 lung transplant recipients, we found that lower cerebral perfusion pressure was associated with increased risk, duration, and severity of

postoperative delirium. This relationship appeared to be independent of other background, medical, and surgical predictors.

Our finding that lower cerebral perfusion pressure was associated with increased risk and length of delirium is consistent with previous studies of patients undergoing coronary artery bypass graft which demonstrated that lower cerebral saturation is associated with an increased risk of postoperative cognitive decline and longer duration of hospitalization (7). Similarly, poorer cerebral oxygenation during surgical procedures requiring single-lung ventilation (e.g., lobectomy, wedge resection, pneumonectomy) has been associated with greater likelihood of postoperative cognitive decline (10, 11).

Previous studies among coronary artery bypass graft patients have also shown that intraoperative cerebral perfusion pressure changes exceeding the limits of cerebral autoregulation dramatically increase the risk of postoperative delirium (23). For example, Hori and colleagues (23) found that the presence of delirium was fourfold higher among coronary artery bypass graft patients whose MAP levels exceeded the upper limit of autoregulation capacity during surgery (13% vs. 3%) (23). In addition, avoidance of cerebral desaturation during cardiac surgery is associated with reduced incidence of morbidity and duration of hospital stay following surgery (24), suggesting that techniques designed to minimize reductions in cerebral perfusion during lung transplant may have a beneficial impact on clinical outcomes.

Because individual patients undergoing major cardiothoracic surgery vary widely in their autoregulatory capacity (25, 26), even among solid organ transplant patients (27), interventions tailored to maximize perfusion pressure may have important implications for patient management, as intraoperative hemodynamic fluctuations exceeding autoregulatory capacity appear to impact short-term clinical outcomes as well as increase the risk of postoperative morbidity (28).

Alterations in cerebral hemodynamics may increase the risk of adverse neurobehavioral outcomes in several ways. First, hypoperfusion of the brain has been associated with increased cerebrovascular damage (29–31), cortical atrophy (32), and risk of cognitive impairment (33).

Table 4. Cerebral perfusion pressure and delirium duration

Predictor	Parametric Estimate (95% Confidence Interval)	P Value
Native disease		
CF vs. IPF	−0.98 (−2.6 to 0.64)	0.235
COPD vs. IPF	0.32 (−0.79 to 1.44)	0.570
Other vs. IPF	−0.03 (−1.11 to 1.05)	0.950
Postoperative Morbidity Score	−0.72 (−1.48 to 0.04)	0.064
Primary graft dysfunction grade 0/1, 2, or 3 at 72 h	0.65 (0.02–1.28)	0.043
Time in ICU, log transformed, d	0.51 (0.06–0.95)	0.026
Cerebral perfusion pressure, per 10 mm Hg	−0.54 (−1.00 to −0.08)	0.022

Definition of abbreviations: CF = cystic fibrosis; COPD = chronic obstructive pulmonary disease; ICU = intensive care unit; IPF = idiopathic pulmonary fibrosis.

Lower cerebral perfusion pressure was associated with longer duration of delirium after accounting for native disease, postoperative morbidity, primary graft dysfunction grade, and time in the intensive care unit. Parametric estimates were derived from the adjusted model.

Table 5. Cerebral perfusion pressure and delirium severity

Predictor	Parametric Estimate (95% Confidence Interval)	P Value
Native disease		
CF vs. IPF	−0.61 (−2.44 to 1.22)	0.505
COPD vs. IPF	2.27 (0.62–3.93)	0.008
Other vs. IPF	−0.09 (−1.72 to 1.53)	0.908
Postoperative Morbidity Score	−1.01 (−2.15 to 0.13)	0.082
Primary graft dysfunction grade (0/1, 2, or 3) at 72 h	0.71 (−0.25 to 1.66)	0.145
Time in ICU, log transformed, d	0.90 (0.31–1.49)	0.004
Cerebral perfusion pressure, per 10 mm Hg	−0.81 (−1.47 to −0.15)	0.017

Definition of abbreviations: CF = cystic fibrosis; COPD = chronic obstructive pulmonary disease; IPF = idiopathic pulmonary fibrosis.

Lower cerebral perfusion pressure was associated with greater severity of delirium after accounting for native disease, postoperative morbidity, primary graft dysfunction grade, and time in the intensive care unit. Parametric estimates below were derived from the adjusted model.

Numerous brain imaging studies among individuals undergoing coronary artery bypass graft have demonstrated an increased prevalence of silent cerebral ischemic lesions following surgery (34, 35), suggesting that hypoperfusion may increase cerebrovascular damage in some patients. Second, it is possible that reductions in perfusion also are associated with underlying cardiovascular disease and/or endothelial dysfunction, which have been associated with both a prolonged neuroinflammatory response and increased blood–brain barrier permeability (36–39). Reduced cerebral perfusion may also increase the risk of cerebral metabolic dysfunction, which has been shown to worsen following coronary artery bypass graft and correspond to changes in postoperative cognitive performance (35) or increase postoperative neuroinflammation (40–42).

Reductions in cerebral perfusion pressure result from either reductions in MAP or increases in CVP. Although MAP was held relatively constant and above autoregulatory thresholds (e.g., 50–150 mm Hg), it is possible that increased CVP due to surgical retraction resulted in lower cerebral perfusion pressure levels. For example, mechanistic studies in animal models have demonstrated that experimental venous obstruction of the

superior vena cava results in significant decreases in cerebral perfusion (43), which may be alleviated through either pharmacologic intervention or partial obstruction relief (44). These findings suggest that future studies may benefit from examining potential treatment strategies to mitigate superior vena cava obstruction during lung transplant, as the presence of postoperative delirium has been shown to improve clinical outcomes following hospitalization (6, 8, 45). It is also possible that elevated CVP resulted in increased edema or passive congestion, as elevated CVP has been associated with prolonged mechanical ventilation time and higher mortality among lung transplant recipients (46). Finally, it is also possible that individual variations in cerebral autoregulation may have resulted in some individuals' experiencing greater susceptibility to delirium (47).

Limitations

Our sample size was relatively small, and data were collected at a single medical center, which may limit the generalizability of our findings. We also examined a relatively limited number of intraoperative hemodynamic mechanisms, and future studies would benefit from collection of additional markers (e.g., cerebral

saturation) to further elucidate the relationship between intraoperative changes and delirium outcomes. In future studies, researchers should collect a more comprehensive array of intraoperative hemodynamic factors to clarify the relationship between intraoperative changes and neurobehavioral outcomes.

We note that, due to the small number of participants in our sample, there may be important native disease differences that we were unable to detect because of low statistical power. However, we considered alternative modeling strategies to better appreciate native disease differences in intraoperative and delirium outcomes, which did not alter the reported pattern of findings. In future studies, researchers should also examine the impact of postoperative sedation as a possible predictor of postoperative delirium among lung transplant recipients.

It is possible that other postoperative medical factors may have contributed to the development of delirium, including infection, metabolic abnormalities, or polypharmacy during the postoperative period. In addition, higher levels of sedation resulting in hypotension should be examined as a potential mechanism in future studies.

Conclusions

Our study demonstrates that decreased cerebral perfusion pressure is associated with higher incidence, longer duration, and greater severity of delirium following lung transplant, independent of demographic and clinical predictors. Future studies could benefit from the collection of neuroimaging markers that would help further elucidate the impact of lung transplant on brain function. If our findings are confirmed, strategies to maintain cerebral perfusion pressure during surgery should be examined as a possible means of reducing the incidence and severity of postoperative delirium. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

References

- McPherson JA, Wagner CE, Boehm LM, Hall JD, Johnson DC, Miller LR, Burns KM, Thompson JL, Shintani AK, Ely EW, *et al.* Delirium in the cardiovascular ICU: exploring modifiable risk factors. *Crit Care Med* 2013;41:405–413.
- Koster S, Hensens AG, Schuurmans MJ, van der Palen J. Risk factors of delirium after cardiac surgery: a systematic review. *Eur J Cardiovasc Nurs* 2011;10:197–204.
- Zhang Z, Pan L, Ni H. Impact of delirium on clinical outcome in critically ill patients: a meta-analysis. *Gen Hosp Psychiatry* 2013; 35:105–111.

- 4 Pandharipande PP, Girard TD, Jackson JC, Morandi A, Thompson JL, Pun BT, Brummel NE, Hughes CG, Vasilevskis EE, Shintani AK, *et al.*; BRAIN-ICU Study Investigators. Long-term cognitive impairment after critical illness. *N Engl J Med* 2013;369:1306–1316.
- 5 Saczynski JS, Marcantonio ER, Quach L, Fong TG, Gross A, Inouye SK, Jones RN. Cognitive trajectories after postoperative delirium. *N Engl J Med* 2012;367:30–39.
- 6 Ely EW, Shintani A, Truman B, Speroff T, Gordon SM, Harrell FE Jr, Inouye SK, Bernard GR, Dittus RS. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. *JAMA* 2004;291:1753–1762.
- 7 Slater JP, Guarino T, Stack J, Vinod K, Bustami RT, Brown JM III, Rodriguez AL, Magovern CJ, Zaubler T, Freundlich K, *et al.* Cerebral oxygen desaturation predicts cognitive decline and longer hospital stay after cardiac surgery. *Ann Thorac Surg* 2009;87:36–45.
- 8 Smith PJ, Rivelli SK, Waters AM, Hoyle A, Durham MT, Reynolds JM, Flowers M, Davis RD, Palmer SM, Mathew JP, *et al.* Delirium affects length of hospital stay after lung transplantation. *J Crit Care* 2015;30:126–129.
- 9 Smith PJ, Rivelli S, Waters A, Reynolds J, Hoyle A, Flowers M, Davis RD, Palmer SM, Mathew J, Durham M, *et al.* Neurocognitive changes after lung transplantation. *Ann Am Thorac Soc* 2014;11:1520–1527.
- 10 Tang L, Kazan R, Taddei R, Zaouter C, Cyr S, Hemmerling TM. Reduced cerebral oxygen saturation during thoracic surgery predicts early postoperative cognitive dysfunction. *Br J Anaesth* 2012;108:623–629.
- 11 Suehiro K, Okutai R. Duration of cerebral desaturation time during single-lung ventilation correlates with Mini Mental State Examination score. *J Anesth* 2011;25:345–349.
- 12 Prekker ME, Nath DS, Walker AR, Johnson AC, Hertz MI, Herrington CS, Radosevich DM, Dahlberg PS. Validation of the proposed International Society for Heart and Lung Transplantation grading system for primary graft dysfunction after lung transplantation. *J Heart Lung Transplant* 2006;25:371–378.
- 13 Diamond JM, Lee JC, Kawut SM, Shah RJ, Localio AR, Bellamy SL, Lederer DJ, Cantu E, Kohl BA, Lama VN, *et al.* Clinical risk factors for primary graft dysfunction after lung transplantation. *Am J Respir Crit Care Med* 2013;187:527–534.
- 14 Snyder LD, Wang Z, Chen DF, Reinsmoen NL, Finlen-Copeland CA, Davis WA, Zaas DW, Palmer SM. Implications for human leukocyte antigen antibodies after lung transplantation: a 10-year experience in 441 patients. *Chest* 2013;144:226–233.
- 15 Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373–383.
- 16 Gries CJ, Rue TC, Heagerty PJ, Edelman JD, Mulligan MS, Goss CH. Development of a predictive model for long-term survival after lung transplantation and implications for the lung allocation score. *J Heart Lung Transplant* 2010;29:731–738.
- 17 Grocott MP, Browne JP, Van der Meulen J, Matejowsky C, Mutch M, Hamilton MA, Levett DZ, Emberton M, Haddad FS, Mythen MG. The Postoperative Morbidity Survey was validated and used to describe morbidity after major surgery. *J Clin Epidemiol* 2007;60:919–928.
- 18 Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegel AP, Horwitz RI. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. *Ann Intern Med* 1990;113:941–948.
- 19 Ely EW, Margolin R, Francis J, May L, Truman B, Dittus R, Speroff T, Gautam S, Bernard GR, Inouye SK. Evaluation of delirium in critically ill patients: validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). *Crit Care Med* 2001;29:1370–1379.
- 20 Trzepacz PT. The Delirium Rating Scale: its use in consultation-liaison research. *Psychosomatics* 1999;40:193–204.
- 21 Trzepacz PT, Mittal D, Torres R, Kanary K, Norton J, Jimerson N. Validation of the Delirium Rating Scale-revised-98: comparison with the delirium rating scale and the cognitive test for delirium. *J Neuropsychiatry Clin Neurosci* 2001;13:229–242. [Published erratum appears in *J Neuropsychiatry Clin Neurosci* 2001;13:433.]
- 22 Harrell FE Jr. Regression modeling strategies: with applications to linear modeling, logistic regression, and survival analysis. New York: Springer; 2001.
- 23 Hori D, Brown C, Ono M, Rappold T, Sieber F, Gottschalk A, Neufeld KJ, Gottesman R, Adachi H, Hogue CW. Arterial pressure above the upper cerebral autoregulation limit during cardiopulmonary bypass is associated with postoperative delirium. *Br J Anaesth* 2014;113:1009–1017.
- 24 Murkin JM, Adams SJ, Novick RJ, Quantz M, Bainbridge D, Iglesias I, Cleland A, Schaefer B, Irwin B, Fox S. Monitoring brain oxygen saturation during coronary bypass surgery: a randomized, prospective study. *Anesth Analg* 2007;104:51–58.
- 25 Brady KM, Mytar JO, Lee JK, Cameron DE, Vricella LA, Thompson WR, Hogue CW, Easley RB. Monitoring cerebral blood flow pressure autoregulation in pediatric patients during cardiac surgery. *Stroke* 2010;41:1957–1962.
- 26 Joshi B, Ono M, Brown C, Brady K, Easley RB, Yenokyan G, Gottesman RF, Hogue CW. Predicting the limits of cerebral autoregulation during cardiopulmonary bypass. *Anesth Analg* 2012;114:503–510.
- 27 Zheng Y, Villamayor AJ, Merritt W, Pustavoitau A, Latif A, Bhambhani R, Frank S, Gurakar A, Singer A, Cameron A, *et al.* Continuous cerebral blood flow autoregulation monitoring in patients undergoing liver transplantation. *Neurocrit Care* 2012;17:77–84.
- 28 Ono M, Brady K, Easley RB, Brown C, Kraut M, Gottesman RF, Hogue CW Jr. Duration and magnitude of blood pressure below cerebral autoregulation threshold during cardiopulmonary bypass is associated with major morbidity and operative mortality. *J Thorac Cardiovasc Surg* 2014;147:483–489.
- 29 O'Brien JT. Vascular cognitive impairment. *Am J Geriatr Psychiatry* 2006;14:724–733.
- 30 Román GC. Vascular dementia prevention: a risk factor analysis. *Cerebrovasc Dis* 2005;20:91–100.
- 31 Zlokovic BV. Neurovascular mechanisms of Alzheimer's neurodegeneration. *Trends Neurosci* 2005;28:202–208.
- 32 Allosco ML, Gunstad J, Jerskey BA, Xu X, Clark US, Hassenstab J, Cote DM, Walsh EG, Labbe DR, Hoge R, *et al.* The adverse effects of reduced cerebral perfusion on cognition and brain structure in older adults with cardiovascular disease. *Brain Behav* 2013;3:626–636.
- 33 Liu J, Zhu Y-S, Khan MA, Brunk E, Martin-Cook K, Weiner MF, Cullum CM, Lu H, Levine BD, Diaz-Arrastia R, *et al.* Global brain hypoperfusion and oxygenation in amnesic mild cognitive impairment. *Alzheimers Dement* 2014;10:162–170.
- 34 Bendszus M, Stoll G. Silent cerebral ischaemia: hidden fingerprints of invasive medical procedures. *Lancet Neurol* 2006;5:364–372.
- 35 Bendszus M, Reents W, Franke D, Müllges W, Babin-Ebell J, Koltzenburg M, Warmuth-Metz M, Solymosi L. Brain damage after coronary artery bypass grafting. *Arch Neurol* 2002;59:1090–1095.
- 36 Grammas P. Neurovascular dysfunction, inflammation and endothelial activation: implications for the pathogenesis of Alzheimer's disease. *J Neuroinflammation* 2011;8:26.
- 37 Zlokovic BV. Neurovascular pathways to neurodegeneration in Alzheimer's disease and other disorders. *Nat Rev Neurosci* 2011;12:723–738.
- 38 Hughes CG, Morandi A, Girard TD, Riedel B, Thompson JL, Shintani AK, Pun BT, Ely EW, Pandharipande PP. Association between endothelial dysfunction and acute brain dysfunction during critical illness. *Anesthesiology* 2013;118:631–639.
- 39 Hála M. Pathophysiology of postoperative delirium: systemic inflammation as a response to surgical trauma causes diffuse microcirculatory impairment. *Med Hypotheses* 2007;68:194–196.
- 40 Zakkar M, Taylor K, Hornick PI. Immune system and inflammatory responses to cardiopulmonary bypass. In: Gravlee GP, Davis RF, Stammers AH, Ungerleider RM, editors. *Cardiopulmonary bypass: principles and practice*. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2008. pp. 321–337.
- 41 Kilminster S, Treasure T, McMillan T, Holt DW. Neuropsychological change and S-100 protein release in 130 unselected patients undergoing cardiac surgery. *Stroke* 1999;30:1869–1874.
- 42 Herrmann M, Ebert AD, Galazky I, Wunderlich MT, Kunz WS, Huth C. Neurobehavioral outcome prediction after cardiac surgery: role of neurobiochemical markers of damage to neuronal and glial brain tissue. *Stroke* 2000;31:645–650.

- 43 Tovedal T, Jonsson O, Zemgulis V, Myrdal G, Thelin S, Lennmyr F. Venous obstruction and cerebral perfusion during experimental cardiopulmonary bypass. *Interact Cardiovasc Thorac Surg* 2010;11: 561–566.
- 44 Tovedal T, Myrdal G, Jonsson O, Bergquist M, Zemgulis V, Thelin S, Lennmyr F. Experimental treatment of superior venous congestion during cardiopulmonary bypass. *Eur J Cardiothorac Surg* 2013;44: e239–e244.
- 45 Inouye SK. Delirium in older persons. *N Engl J Med* 2006;354: 1157–1165.
- 46 Pilcher DV, Scheinkestel CD, Snell GI, Davey-Quinn A, Bailey MJ, Williams TJ. High central venous pressure is associated with prolonged mechanical ventilation and increased mortality after lung transplantation. *J Thorac Cardiovasc Surg* 2005;129: 912–918.
- 47 Hori D, Ono M, Rappold TE, Conte JV, Shah AS, Cameron DE, Adachi H, Everett AD, Hogue CW. Hypotension after cardiac operations based on autoregulation monitoring leads to brain cellular injury. *Ann Thorac Surg* 2015;100:487–493.