



# Use of Lung Allografts from Brain-Dead Donors after Cardiopulmonary Arrest and Resuscitation

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**Rationale:** Patients who progress to brain death after resuscitation from cardiac arrest have been hypothesized to represent an underused source of potential organ donors; however, there is a paucity of data regarding the viability of lung allografts after a period of cardiac arrest in the donor.

**Objectives:** To analyze postoperative complications and survival after lung transplant from brain-dead donors resuscitated after cardiac arrest.

**Methods:** The United Network for Organ Sharing database records donors with cardiac arrest occurring after brain death. Adult recipients of lung allografts from these arrest/resuscitation donors between 2005 and 2011 were compared with nonarrest donors. Propensity score matching was used to reduce the effect of confounding. Postoperative complications and overall survival were assessed using McNemar's test for correlated binary proportions and Kaplan–Meier methods.

**Measurements and Main Results:** A total of 479 lung transplant recipients from arrest/resuscitation donors were 1:1 propensity matched from a cohort of 9,076 control subjects. Baseline characteristics in the 1:1-matched cohort were balanced. There was no significant difference in perioperative mortality, airway dehiscence, dialysis requirement, postoperative length of stay ( $P \geq 0.38$  for all), or overall survival ( $P = 0.52$ ). A subanalysis of the donor arrest group demonstrated similar survival when stratified by resuscitation time quartile ( $P = 0.38$ ).

**Conclusions:** There is no evidence of inferior outcomes after lung transplant from brain-dead donors who have had a period of cardiac arrest provided that good lung function is preserved and the donor is otherwise deemed acceptable for transplantation. Potential expansion of the donor pool to include cardiac arrest as the cause of brain death requires further study.

**Keywords:** lung transplantation; organ donation; heart arrest; cardiopulmonary resuscitation

More than 1,800 lung transplants were performed in the United States in 2011; however, more than 2,200 new lung transplant candidates were added to the waitlist during that same time,

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## AT A GLANCE COMMENTARY

### Scientific Knowledge on the Subject

Patients who progress to brain death after resuscitation from cardiac arrest have been hypothesized to represent an underused source of potential organ donors; however, there is a paucity of data regarding the viability of lung allografts after a period of cardiac arrest in the donor.

### What This Study Adds to the Field

The authors present the collective, national experience analyzing outcomes after lung transplantation from donors who had progressed to brain death after undergoing cardiac arrest and resuscitation. This study provides further guidance in donor selection and identifies potential implications for expanding the existing donor pool. In addition, clinicians involved in managing terminally ill patients after cardiac arrest should be aware of the organ donation prospects in this population.

far surpassing the available donors (1). Not surprisingly, the waitlist death rate has also increased, with more than 150 pre-transplant deaths per 1,000 waitlist years in 2010–2011 (1, 2). Given that less than 20% of eligible deaths result in lung donation (1, 3, 4), heightened awareness of acceptable donors is needed to improve the use of the currently available pool of deceased donors (5–7).

Adult patients who progress to brain death after resuscitation from cardiac arrest have been hypothesized to represent an underused source of potential organ donors (8–10). Approximately 450,000 Americans have a cardiac arrest each year (11), of which approximately 5–10% will be resuscitated with return of spontaneous circulation (12), and 8–16% of those (or approximately 1,800–7,200 patients) will result in brain death (13). Furthermore, care is withdrawn from many cardiac arrest patients before the evolution to brain death occurs (14, 15), which could further increase the estimated number of potential organ donors via this mechanism. At present, these donors are underrepresented in the organ donation pool, which is dominated by cerebrovascular cause of death and head trauma (1).

Brain-dead donors who have subsequently suffered cardiac arrest with successful resuscitation (referred to as “arrest/resuscitation donors”) represent a dilemma for solid-organ transplant teams given concerns for ischemic organ injury and the potential for impaired posttransplant graft function (9, 16–18). Cardiac arrest may occur before and directly contribute to brain death or occur after brain death (19). The current body of literature to guide clinical decisions in managing this donor population for lung transplant is limited. In a systematic review of solid organs transplanted from brain-dead patients due to cardiac arrest, these donor organs had acceptable recipient

outcomes; however, only two lung transplant recipients were included (20). In the only study focused on lung transplant, a single-center analysis also showed acceptable outcomes but the sample size was limited to 22 recipients (21). Although reassuring that arrest/resuscitation donors may be acceptable for lung transplant, these studies are limited by single-center practices and small sample size, and thus increase the risk of a type II error. To date there has not been a multicenter or national study to evaluate postoperative complications and overall survival after lung transplant from these donors. Furthermore, there is a paucity of information in the literature regarding potential differences in the outcome profile based on the duration of resuscitation.

The United Network of Organ Sharing (UNOS) database records cardiac arrest occurring after brain death in lung donors, representing what is likely the best available source of information to evaluate the viability of lung transplantation after a period of cardiac arrest in the donor. Previous research from our institution has analyzed this donor population for purposes of heart transplantation, demonstrating equivalent outcomes (22). Interestingly, this study also demonstrated higher survival among donors with a brief period of cardiac arrest compared with non-arrest donors. This provides important insight into potentially broadening the acceptable donor pool for heart transplantation, and raises the possibility that similar advancements could be made in lung transplantation. Our objective was therefore to analyze the usage of arrest/resuscitation donors in a cohort of all U.S. lung transplantations since 2005, with a comparison of postoperative complications and overall survival to nonarrest donors. Second, we sought to evaluate the impact of resuscitation time on postoperative survival as well as differing levels of lung function parameters after resuscitation in these donors.

## METHODS

The Institutional Review Board at Duke University Medical Center (Durham, NC) approved this study.

### Study Population

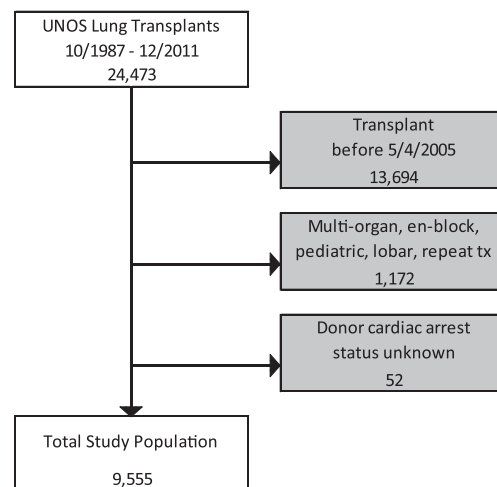
The Organ Procurement and Transplantation Network's national computerized database of donor, waitlist, organ-matching, transplant, and posttransplant information as maintained by the UNOS was used for this analysis (referred to as the UNOS database) (23). Our study population included all U.S. adult lung transplantations as recorded in the UNOS database subsequent to the initiation of the lung allocation score (24) (effective May 4, 2005) through December 2011 to reflect current practice patterns for organ allocation and recipient demographics. Multiorgan transplants, pediatric recipients, and patients undergoing repeat transplantation were excluded. Patients were categorized on the basis of whether the donor had a "cardiac arrest since neurological event that led to declaration of brain death" (this is a yes/no field on the "Deceased Donor Registration Worksheet" [Office of Management and Budget approved form number 0915-0157]). Patients with unknown or missing donor arrest information were excluded.

### Primary and Secondary Outcomes

The primary outcome variable was overall survival compared between recipients of lung allografts from arrest/resuscitation donors and control subjects. Secondary outcome measures included perioperative mortality, airway dehiscence before discharge, dialysis before discharge, and postoperative length of stay greater than 25 days (75th percentile).

### Propensity Matching

Patients receiving a lung allograft from a brain-dead arrest/resuscitation donor were matched 1:1 with the control group on the basis of propensity score matching (25, 26). The propensity score is the probability of treatment



**Figure 1.** Study inclusion algorithm. tx = transplant; UNOS = United Network of Organ Sharing.

assignment (in this case the use of an arrest/resuscitation donor) conditional on observed baseline characteristics to mimic a randomized controlled trial with respect to similarity in the distribution of observed baseline covariates between comparison groups (27). Of the various techniques using propensity scores (28), both the statistical literature (25, 26) as well as the lung transplant literature specific to the use of the UNOS database (29) advocate the use of propensity matching in situations in which a sufficiently large sample of control subjects is available relative to the size of the study group of interest, as is the case in the current analysis.

Covariates selected for the propensity model included variables that affect the exposure (use of an arrest/resuscitation donor) as well as variables that do not affect exposure but affect the primary outcome (survival) in accordance with previously established methodology advocating this approach (27, 29, 30). We therefore included baseline variables related to (1) recipient sociodemographic characteristics: age, sex, ethnicity, year of transplant, geographic region, functional status (need assistance with activities of daily living vs. not), employment status (working vs. not), and insurance carrier (private/self-pay, Medicaid, Medicare, other [Veterans' Affairs, U.S. government, privately donated care, pending payment, free care, or foreign government payment]); (2) donor/waitlist characteristics: donor age, donor sex, donor ethnicity, donor cause of death, and waitlist days; and (3) recipient risk characteristics: primary diagnosis (obstructive disease, restrictive disease, cystic fibrosis or immunodeficiency, pulmonary vascular disease), cytomegalovirus status at transplant, ABO match level, human leukocyte antigen mismatch level, medical condition before transplant (hospitalized, intensive care unit, or neither), life support before transplant (intravenous inotropes, ventilator, intraaortic balloon pump, or ventricular assist device), ventilator at transplant, transplant type (single vs. double lung), diabetes, body mass index ( $\text{kg}/\text{m}^2$ ), serum creatinine level at transplant, preoperative 6-minute walk distance, and lung allocation score.

Consistent with previously established methods specific to addressing missing data in propensity score calculations (29, 31), a separate category for "unknown" was created for missing data for nominal variables. For continuous missing covariates, we added a binary variable for whether or not each variable was missing and imputed a value of 0 for missing values for each of these covariates. A forward, stepwise method was used for variable selection based on the minimum corrected Akaike information criterion (32). Optimal matching was performed without replacement (27). Balance in baseline characteristics between the matched cohorts was assessed using standardized difference, which is calculated by determining the difference in the mean between the two groups being compared and dividing this mean by the square root of the pooled variance, with modification to reflect proportions for categorical variables (33). A standardized difference less than 0.1 is generally accepted to indicate a negligible difference in the mean or prevalence of a covariate between treatment groups (27).

TABLE 1. DONOR, RECIPIENT, AND TRANSPLANT CHARACTERISTICS

Characteristic	Donor Arrest (n = 479)	No Donor Cardiac Arrest (Each Compared against Donor Arrest Group)			
		Full Sample (n = 9,076)	P Value	1:1 Matched (n = 479)	Standardized Difference*
<b>Donor characteristics</b>					
Donor age	30 (21, 44)	32 (21, 46)	0.041 <sup>†</sup>	33 (22, 45)	-0.088
Donor diabetes	35 (7.3%)	561 (6.2%)	0.32	31 (6.5%)	0.032
Donor smoking history	62 (13.1%)	1,105 (12.3%)	0.62	55 (11.6%)	0.046
Donor cocaine use	67 (14.1%)	988 (11.1%)	0.039 <sup>†</sup>	55 (11.6%)	0.075
Terminal creatinine, mg/dl	1.0 (0.8, 1.6)	1.0 (0.8, 1.3)	<0.001 <sup>†</sup>	1.0 (0.8, 1.4)	-0.011
Donor BMI, kg/m <sup>2</sup>	25.1 (22.1, 28.7)	24.7 (22.1, 28.0)	0.05	24.7 (22.1, 27.7)	0.089
Po <sub>2</sub> on 100% inspired oxygen, mm Hg	405 (214, 488)	422 (256, 493)	0.001 <sup>†</sup>	421 (195, 492)	-0.021
<b>Recipient characteristics</b>					
Age	58 (47, 63)	58 (49, 64)	0.17	58 (47, 64)	0.005
Female sex	200 (41.8%)	3,742 (41.2%)	0.82	200 (41.8%)	0.000
White ethnicity	421 (87.9%)	7,659 (84.4%)	0.039 <sup>†</sup>	408 (85.2%)	0.079
<b>Diagnosis</b>					
Obstructive	154 (32.2%)	3,194 (35.2%)		143 (29.9%)	0.050
Restrictive	229 (47.8%)	4,458 (49.1%)		231 (48.2%)	-0.008
CF or immunodeficiency	71 (14.8%)	1,135 (12.5%)		75 (15.7%)	-0.025
Pulmonary vascular	25 (5.2%)	289 (3.2%)		30 (6.3%)	-0.047
Diabetes	87 (18.2%)	1,600 (17.8%)	0.79	91 (19.1%)	-0.023
BMI (kg/m <sup>2</sup> ) at transplant	24.9 (21.1, 28.4)	25.1 (21.3, 28.5)	0.49	25.1 (21.2, 28.7)	-0.015
Requiring ventilator at transplant	34 (7.1%)	510 (5.6%)	0.17	24 (5.0%)	0.088
<b>Pulmonary function</b>					
FEV <sub>1</sub> , % predicted	34 (20, 54)	34 (20, 52)	0.54	36 (21, 56)	-0.046
FVC, % predicted	46 (36, 59)	46 (36, 59)	0.88	46 (36, 61)	-0.061
FEV <sub>1</sub> /FVC	0.91 (0.47, 1.11)	0.86 (0.46, 1.10)	0.30	0.87 (0.49, 1.10)	-0.009
Lung allocation score	39.7 (34.7, 50.0)	38.9 (34.3, 47.9)	0.021 <sup>†</sup>	40.6 (34.7, 49.7)	0.010
Days on waitlist	73 (23, 211)	74 (22, 233)	0.76	65 (21, 211)	0.001
<b>Transplant characteristics</b>					
Bilateral transplant	330 (68.9%)	5,868 (64.7%)	0.06	329 (68.7%)	0.004
Sex mismatch	142 (29.7%)	2,833 (31.2%)	0.47	164 (34.2%)	-0.097
Donor/recipient race mismatch	187 (39.0%)	3,811 (42.0%)	0.20	187 (39.0%)	0.000
CMV mismatch	118/439 (26.9%)	2,141/8,449 (25.3%)	0.47	109/451 (24.2%)	0.062
Ischemic time, h	5.2 (4.1, 6.3)	5.0 (3.9, 6.0)	0.030 <sup>†</sup>	5.2 (4.1, 6.3)	0.018

Definition of abbreviations: BMI = body mass index; CF = cystic fibrosis; CMV = cytomegalovirus; Po<sub>2</sub> = arterial partial pressure of oxygen.

Shown are the median (interquartile range) for nonparametric continuous variables; n (%) for categorical variables. If data are missing for more than 5% of the study population, the denominator is given for categorical variables and "n" is given for continuous variables. The Wilcoxon signed-rank test was done for continuous variables, and the Pearson chi-squared test was done for categorical variables. Note that matched-pair comparisons of balance using standardized differences are explained in text.

\* Standardized difference is the difference in mean between the two groups divided by the square root of the pooled variance, with modification to reflect proportions for categorical variables (33).

<sup>†</sup> Statistical significance.

## Primary Analysis

Baseline recipient and donor characteristics were described for the full study population and the 1:1-matched sample, stratified by the presence or absence of cardiac arrest in the donor, using medians and interquartile range (IQR) for continuous variables and proportions (frequency, percentage) for discrete variables. Comparisons for continuous variables in the full sample were made using Kruskal-Wallis tests, and unordered categorical variables were compared using the Pearson chi-squared test. Comparisons in the 1:1-matched sample were made using standardized difference, as described previously. The trend in use of arrest/resuscitation donors was assessed using the Cochran-Armitage trend test.

Overall survival rates for the original total sample were estimated using the product-limit (Kaplan-Meier) method and compared by the log-rank test. Survival estimates for the 1:1-matched cohort were also estimated by the Kaplan-Meier method and comparisons in this case were made using the test described by Klein and Moeschberger to account for the matched nature of the data (34). Comparisons of perioperative mortality and complications (secondary outcome measures listed previously) were made using McNemar's test for correlated binary proportions, again to account for the matched nature of the data (35).

## Secondary Analysis

For donors who underwent cardiac arrest, a secondary analysis of resuscitation time was performed for the subset of cases for whom this information was available (n = 428/479 [89.4%]). Survival curves were constructed by resuscitation time quartile using the Kaplan-Meier method and compared by the log-rank test.

To better assess the impact allograft quality in comparing arrest/resuscitation donors with control subjects, donor Po<sub>2</sub> on 100% oxygen was stratified into quartiles and the 1:1-matched cohorts were separately compared for each quartile, using Kaplan-Meier methods and the Klein and Moeschberger test to account for the matched nature of the data as described previously. Note that only cases in which both members of the matched pair were in the same Po<sub>2</sub> quartile were included.

For all statistical comparisons, P values less than or equal to 0.05 were considered significant. Statistical analyses were performed with JMP version 10.0 (SAS Institute Inc., Cary, NC).

## RESULTS

### Arrest/Resuscitation Donor Characteristics

Of the 24,473 lung transplants included in the UNOS database, 13,694 transplants were outside the timeframe of our analysis and 1,224 transplants met exclusion criteria (Figure 1). This resulted in a study population of 9,555 lung transplants, of which 479 (5.0%) were from arrest/resuscitation donors. Of these 479 donors suffering cardiac arrest after the neurologic event leading to the declaration of brain death, the inciting cause of death was anoxia for 186 donors (39%) (information as to whether the anoxia was related to cardiac arrest was not available), head trauma for 156 (32%), cerebrovascular/stroke for 124 (26%), central nervous system tumor for 5 (1%), and "other" for 8 (2%). When compared with the entire cohort

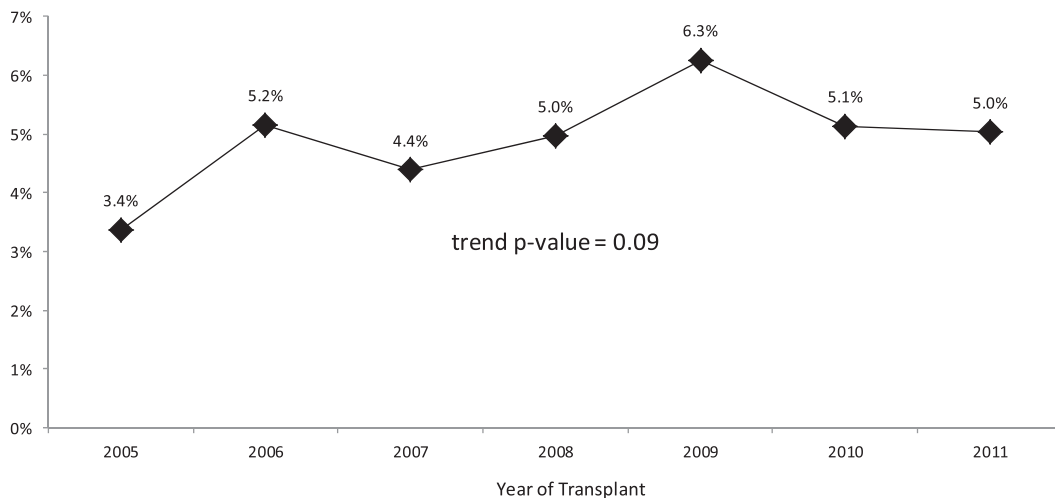


Figure 2. Trend in usage of lung donors who have suffered cardiopulmonary arrest.

of donors without cardiac arrest, arrest/resuscitation donors were significantly younger (median 30 yr, IQR 21–44 vs. median 32, IQR 21–46;  $P = 0.041$ ) with a higher incidence of cocaine use (14.1 vs. 11.1%;  $P = 0.039$ ), higher terminal creatinine (median 1.0 mg/dl, IQR 0.8–1.6 vs. median 1.0, IQR 0.8–1.3;  $P < 0.001$ ), and lower  $PO_2$  on inspired oxygen of 100% (median 405 mm Hg, IQR 214–488 vs. median 422, IQR 256–493;  $P < 0.001$ ) (Table 1).

The use of arrest/resuscitation donors as a percentage of all lung transplants ranged from a low of 3.4% in 2005 to a high of 6.3% in 2009; however, overall there was no significant change in the trend of arrest/resuscitation donor use over time ( $P = 0.09$ ) (Figure 2).

### Recipient Characteristics

On comparison of the full sample, recipients of lung allografts from arrest/resuscitation donors had a higher likelihood of white ethnicity (87.9 vs. 84.4%;  $P = 0.039$ ), a lower incidence of obstructive lung disease (32.2 vs. 35.3%;  $P = 0.029$ ), and a higher lung allocation score (median 39.7, IQR 34.7–50.0 vs. median 38.9, IQR 34.3–47.9;  $P = 0.021$ ) (Table 1). Allografts from arrest/resuscitation donors demonstrated longer ischemic time (median 5.2 h, IQR 4.1–6.3 vs. median 5.0, IQR 3.9–6.0;  $P = 0.030$ ). After 1:1 propensity score matching, the baseline characteristics between groups were balanced with a standardized difference of less than 0.1 for all characteristics.

### Primary Analysis

When comparing recipients of lung allografts from arrest/resuscitation donors with control subjects from the total original sample, there was no difference in unadjusted survival based on Kaplan–Meier analysis (median survival 4.96 vs. 5.10 yr for the control group;  $P = 0.62$ ) (Figure 3A). In addition, there was no difference in recipient survival in the 1:1-matched cohort (median survival 4.96 vs. 5.04 yr for the control group;  $P = 0.52$ ) (Figure 3B).

In comparing postoperative complications in the 1:1-matched cohort, there was no significant difference in 30- or 90-day mortality ( $P = 0.63$  and  $P = 0.78$ , respectively), airway dehiscence ( $P = 1.00$ ), postoperative dialysis requirement ( $P = 0.38$ ), or postoperative length of stay greater than 25 days ( $P = 0.76$ ) (Table 2).

### Secondary Analysis

Information regarding the duration of resuscitation was available for 89.4% (428 of 479) of arrest/resuscitation donors (first quartile, 1–6 min; second quartile, 7–14 min; third quartile, 15–30 min; and fourth quartile, >30 min). When comparing Kaplan–Meier unadjusted recipient survival stratified by donor resuscitation time quartile, the longest recipient survival was observed in the fourth quartile (>30 min of donor resuscitation time); however, this did not meet statistical significance based on log-rank comparison ( $P = 0.38$ ; Figure 4).

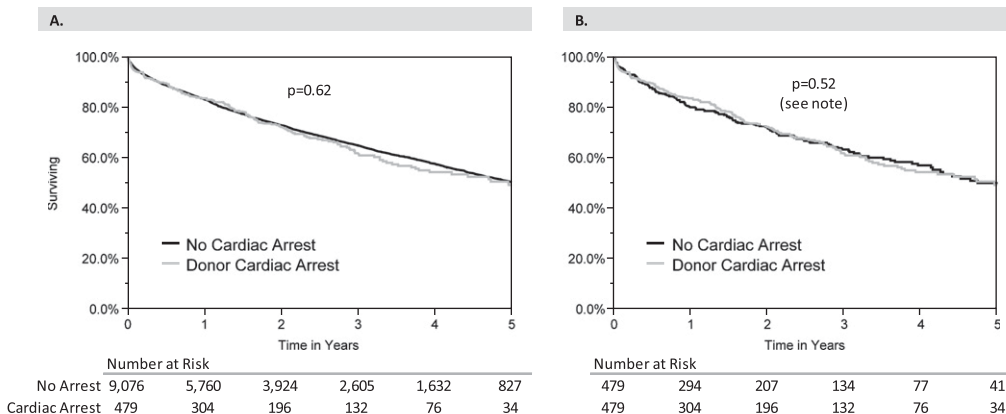


Figure 3. Kaplan–Meier survival curves by donor cardiac arrest status. (A) Original total sample; (B) 1:1-matched cohort. Note: Statistical comparison for the original total sample was performed using the log-rank test, and for the 1:1-matched cohort was performed using the test described by Klein and Moeschberger to account for the matched nature of the data (34).

**TABLE 2. COMPARISON OF PERIOPERATIVE MORTALITY AND COMPLICATIONS IN 1:1-MATCHED COHORT**

Complication	n Pairs	Comparison of Propensity-matched Pairs				P Value*
		Both = No	Both = Yes	Donor Arrest = Yes Matched Control = No	Donor Arrest = No Matched Control = Yes	
30-Day mortality	457	417 (91.2%)	2 (0.4%)	21 (4.6%)	17 (3.7%)	0.63
90-Day mortality	447	386 (86.4%)	6 (1.3%)	29 (6.5%)	26 (5.8%)	0.78
Airway dehiscence before discharge	456	443 (97.1%)	0 (0.0%)	6 (1.3%)	7 (1.5%)	1.00
Dialysis before discharge	467	419 (89.7%)	1 (0.2%)	20 (4.3%)	27 (5.8%)	0.38
Postoperative length of stay > 25 d	462	246 (53.2%)	43 (9.3%)	84 (18.2%)	89 (19.3%)	0.76

\*Statistical comparisons were performed using McNemar’s test for correlated binary proportions.

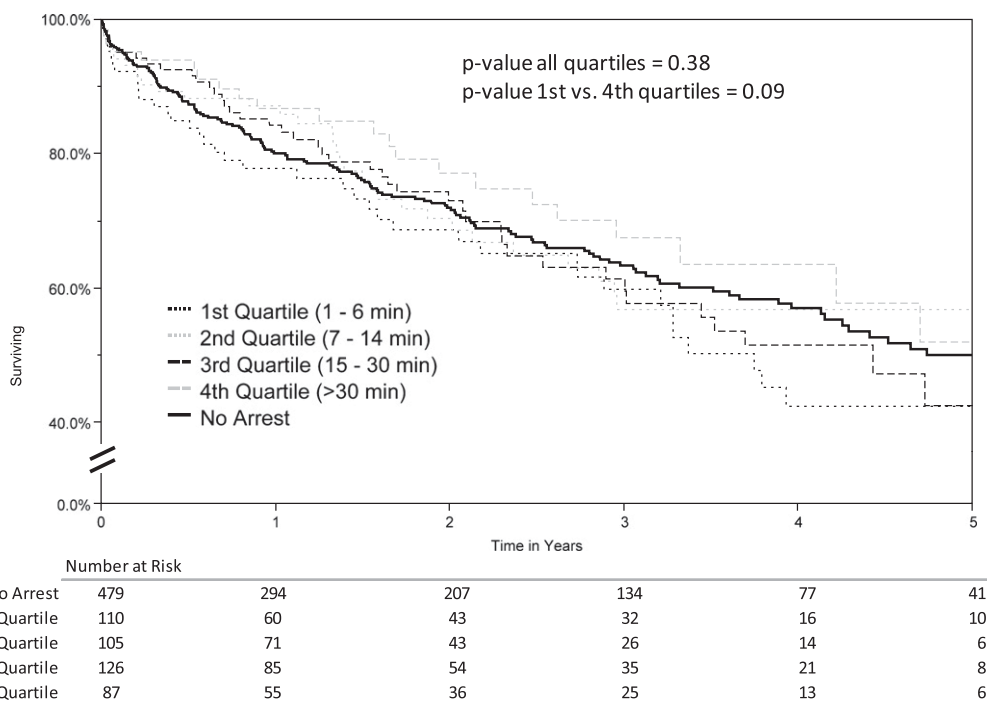
Across both groups in the 1:1-matched cohorts, donor PO<sub>2</sub> on 100% inspired oxygen was distributed as follows: first quartile, less than 198 mm Hg; second quartile, 199–411 mm Hg; third quartile, 412–491 mm Hg; and fourth quartile, greater than 491 mm Hg. In 181 of the matched pairs both members were in the same PO<sub>2</sub> quartile and therefore included in this subanalysis. In comparing propensity-matched subjects stratified by donor PO<sub>2</sub>, there was significantly increased survival in arrest/resuscitation donor lung recipients in the first PO<sub>2</sub> quartile (*P* = 0.013) (Figure 5). Survival in the second, third, and fourth quartiles was similar (*P* = 0.09, *P* = 0.67, and *P* = 0.92, respectively).

**DISCUSSION**

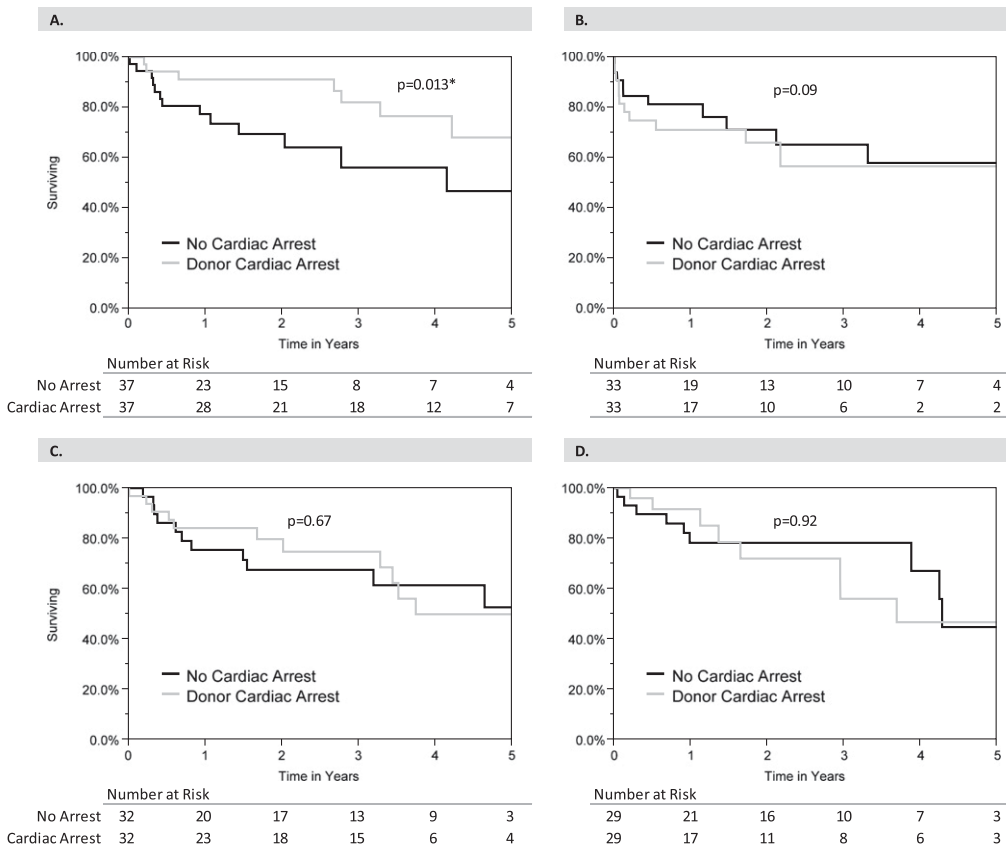
The availability of lung transplantation as an option to treat end-stage lung disease continues to be limited by the lack of sufficient donor organs to meet demand. In the current study, we report equivalent short- and long-term outcomes in lung transplant recipients receiving allografts from brain-dead donors who have subsequently suffered cardiopulmonary arrest and resuscitation with return of spontaneous circulation. These findings persisted regardless of the duration of resuscitation and also at varying levels of donor lung function as measured by arterial oxygen pressure on 100% inspired oxygen. This evidence provides further guidance in donor selection as well as potential implication for expanding the donor pool.

Our findings of equivalent short- and long-term survival with arrest/resuscitation donors are consistent with studies of other solid organ transplants using such donors. In heart transplantation, no evidence of inferior survival was demonstrated in two separate single-center reviews composed of 38 and 25 patients following transplant after cardiac arrest in the organ donor (17, 36). A national study of 930 cardiac arrest donors confirmed these findings of equivalent outcomes for heart transplant recipients (22). Similarly, a single-center review of 37 orthotopic liver transplants from arrest/resuscitation donors (37), as well as a separate review of 12 intestinal transplant recipients from such donors (38), both demonstrated equivalent outcomes when compared with control groups, each study concluding that cardiac arrest should not automatically exclude the use of an arrest/resuscitation graft for transplantation. Furthermore, a systematic review of brain-dead donors after cardiac arrest demonstrated equivalent survival rates for kidneys (*n* = 29), liver (*n* = 14), heart (*n* = 45), and intestine (*n* = 12) (20).

In the current study demonstrating the largest series of lung transplantation after donor arrest/resuscitation yet reported in the literature, our data confirm that cardiac arrest in the donor should not preclude lung donation, provided the allograft is otherwise deemed acceptable. It is important to note that the arrest/resuscitation donors used for lung transplant in our study demonstrated excellent lung function (median PO<sub>2</sub> on 100% oxygen of >400 mm Hg) and therefore likely represent the subset of



**Figure 4.** Kaplan–Meier survival curves by resuscitation time quartile. Note: The “No Arrest” group is displayed for reference. The statistical comparison relates only to the resuscitation time quartile groups.



**Figure 5.** Survival comparison stratified by donor arterial oxygen pressure. (A) First quartile ( $PO_2 \leq 198$  mm Hg). (B) Second quartile ( $PO_2 199-411$  mm Hg). (C) Third quartile ( $PO_2 412-491$  mm Hg). (D) Fourth quartile ( $>491$  mm Hg). \*Statistical significance. Statistical comparison was performed using the test described by Klein and Moeschberger to account for the matched nature of the data (34).  $PO_2$  = arterial oxygen pressure on 100% inspired oxygen.

patients who arrested, were resuscitated, and continued to have good lung function. There may well be a large cohort of patients never made available for donation that were resuscitated and had poor lung function. However, the subanalysis stratified by donor  $PO_2$  quartile provides interesting information by demonstrating longer survival in the arrest/resuscitation group compared with propensity-matched control subjects with donor  $PO_2$  not exceeding 198 mm Hg. This may indicate that the upper stratum of lung function for arrest/resuscitation donors may not be necessary when compared with criteria for conventional donors, although caution should be taken when interpreting these data given the small sample sizes in the  $PO_2$  strata.

Successful use of lung allografts after cardiac arrest in the donor raises the possibility of further expanding the donor pool. Patients suffering out-of-hospital cardiac arrest have been hypothesized to represent an underused source of organ donors (8, 9). Many of these patients have care withdrawn at early stages, potentially precluding evolution to brain death (8, 14, 15). Moreover, concern persists regarding the suitability of such organs because of potential ischemic injury (20). Although our study population consists of patients suffering cardiac arrest after brain death (not before), this is nonetheless the strongest evidence yet reported in the literature to demonstrate that the insult to lung allografts after a period of cardiac arrest in the donor does not preclude successful lung transplantation when the donor is otherwise acceptable. These findings may serve as the foundation for advances in lung transplantation pertaining to organ donation from individuals who have suffered a cardiac arrest/resuscitation. Moreover, clinicians involved in the care of the critically ill patient subsequent to cardiac arrest may benefit from information regarding organ donation prospects to guide terminal management in accordance with the patient's wishes

should he or she have wanted to be an organ donor. In addition, advances in *ex vivo* lung perfusion technology may further expand the feasibility of lung transplantation from high-risk out-of-hospital cardiac arrest donors (39).

Interestingly, our study demonstrated numerically longer survival in the highest resuscitation time quartile ( $>30$  min), when compared with other resuscitation time quartiles as well as when compared with nonarrest donors (Figure 4). Although this did not meet statistical significance (possibly related to sample size), these findings raise the possibility of ischemic preconditioning, as previously reported in the literature (40-45). This concept has also been hypothesized to play a role in the function of heart allografts from donors with a brief period of cardiac arrest (22). In animal models, ischemic preconditioning has been shown to ameliorate the effects of ischemia-reperfusion injury on lung parenchyma (46, 47). Proposed mechanisms include antiinflammatory response, altered cell energy metabolism, nitric oxide production, and involvement of nuclear transcription factors (48, 49). These proposed mechanisms may in part explain the observed recipient survival with arrest/resuscitation donors, further supporting viability of these organs for lung transplantation. An alternative explanation for these findings is that lungs from donors with prolonged cardiac arrest that recovered to otherwise meet criteria for transplantation may be naturally more resistant to ischemic injury and subsequent primary graft dysfunction. Further delineation of a potential impact of resuscitation time on outcomes would require further study.

Successful transplantation with donor lungs having recovered from a period of warm ischemic injury encourages further advancement in expanding the donor pool beyond brain-dead donors to include donation after determination of circulatory

death (DCD) (50, 51). Between 2008 and 2011, only 0.8 to 1.9% of lung transplants in the United States were from DCD donors (1). Preliminary results with the use of such donors are encouraging (52–54); however, barriers to widespread adoption have included concerns over diminished quality of the organ as well as ethical considerations (6, 55). Although the physiological alterations observed with DCD organ procurement are likely different from those of a brain-dead arrest/resuscitation donor, the results of the current study nonetheless contribute to alleviating concerns about DCD organ quality and the viability of successful lung transplantation after a period of brief warm ischemic injury.

An important limitation to this analysis is that the number of potential donors excluded from organ procurement due to arrest/resuscitation events, as well as the number of out-of-hospital cardiac arrest patients for whom care is withdrawn before evolution to brain death, are not well captured. This precludes definitive quantification of the potential impact of more liberal inclusion of such donors into the organ allocation pool. Moreover, given that our data source only includes information for arrest/resuscitation donors used for transplant, we are unable to determine whether these donors are physiologically more functional than the overall arrest/resuscitation cohort, or what factors determine whether an arrest/resuscitation donor should be used.

Several other limitations should be considered when evaluating the results of the current study. Given the retrospective nature of this review, unmeasured confounders that impact post-operative outcomes and/or the decision to use or decline an arrest/resuscitation donor may exist. For arrest/resuscitation donors, the time between return of spontaneous circulation and organ harvest was unavailable for analysis, and this may directly impact willingness to use these organs. Moreover, our analysis is limited to donors suffering cardiac arrest after the index event causing brain death. We have not analyzed donors for whom brain death was the subsequent result of cardiac arrest.

## Conclusions

Recipients of lung transplants from brain-dead arrest/resuscitation organ donors have equivalent outcomes when compared with the general UNOS cohort as well as matched control subjects in the UNOS database. Brain-dead donors subsequently suffering cardiac arrest should not be excluded from lung procurement when good lung function is preserved and the donor is otherwise deemed acceptable for transplantation. The potential effect of ischemic preconditioning on lung allograft function, as well as the potential expansion of the donor pool to include cardiac arrest as the cause of brain death, require further study.

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