The Impact of Therapeutic Hypothermia Used to Treat Anoxic Brain Injury After Cardiopulmonary Resuscitation on Organ Donation Outcomes

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Therapeutic hypothermia (TH) is clinically used to improve neurologic outcomes in patients with anoxic brain injury after cardiopulmonary resuscitation (CPR). For patients that regress and become organ donors after neurologic determination of death (DNDDs), the impact of TH received before determination of death on organ donation outcomes remains unknown. A prospective observational study of all adult DNDDs that received CPR and had anoxia as a cause of death from March 2013 to December 2014 was conducted across 20 organ procurement organizations (OPOs) in the United States. Main outcome measures included organs transplanted per donor (OTPD), specific organ transplantation rates, and recipient graft outcomes. One thousand ninety eight DNDDs met inclusion criteria, with 46% having received TH before determination of death. DNDDs with hypothermia before death had a similar number of OTPD (2.74 vs. 2.69, $p=0.61$) and similar transplantation rates of individual organs. With regards to recipients, there was significantly less delayed graft function (DGF) in kidney grafts from donors who received TH before death (24% vs. 30%, $p=0.02$). After adjusting for donor, recipient, and graft related factors, the protective effect of TH on DGF persisted (OR 0.75, 95%CI [0.56–0.995], $p=0.046$). TH before death in the donor is independently associated with a 25% decrease in DGF among kidney recipients. This should be considered a protective donor selection factor in guiding the decision to accept or reject an organ for transplantation.

Keywords: hypothermia, deceased donation, cardiopulmonary resuscitation, delayed graft function

Introduction

THE INDUCTION OF mild therapeutic hypothermia (TH) has been found to improve outcomes after anoxic brain injury in adults with out-of-hospital cardiac arrest (Bernard *et al.*, 2002; Hypothermia after Cardiac Arrest Study, 2002). As such, after anoxic brain injury, some patients will improve and survive. Others, however, may regress with eventual

brainstem herniation and have the potential to become organ donors after neurologic determination of death (DNDDs). For those patients who neither survive nor regress to brainstem herniation and whose family withdraws life-sustaining measures, donation after circulatory determination of death (DCDD) may be a possibility.

Recently, a large prospective, randomized controlled trial assessed the impact of TH in organ donors *after* determination

This article was presented at the 88th Annual Meeting of the Pacific Coast Surgical Association, Indian Wells, California, on February 19, 2017.

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of death by neurologic criteria (Niemann and Malinoski, 2015). Specifically, this study found that in transplant recipients receiving renal allografts from donors treated with mild hypothermia (34°C to 35°C), the relative odds of delayed graft function (DGF) was 38% lower than those receiving kidneys from donors maintained at normothermia (36.5°C to 37.5°C) during the donor management process (Niemann and Malinoski, 2015). Furthermore, greater relative benefit was noted in recipients of organs from expanded-criteria donors, suggesting that the subsequent ischemia-reperfusion injury in recipients of these higher risk organs can potentially be ameliorated with mild hypothermia (Niemann and Malinoski, 2015).

Currently, the impact that TH *before* death has on organ donation outcomes remains unknown. Given this, and the known clinical use of TH in patients with anoxic brain injury after cardiopulmonary resuscitation (CPR), we sought to investigate whether TH *before* determination of death impacts organ donation outcomes.

Materials and Methods

Study design

Twenty organ procurement organizations (OPOs) across the United States (US; see Acknowledgments section for list of participating organizations) prospectively collected data on all adult (≥ 18 years old) DNDDs who received CPR and were noted to have anoxia as a cause of death (Fig. 1). Data were collected from March 2013 to December 2014. Stan-

dard criteria donors (SCDs), as well as expanded criteria donors (ECDs), were included, whereas DCDDs were excluded. Furthermore, this study used data from the Organ Procurement and Transplantation Network (OPTN), which includes data on all donors, wait-listed candidates, and transplant recipients in the US and has been described elsewhere (Leppke et al., 2013). The Health Resources and Services Administration (HRSA), US Department of Health and Human Services provides oversight to the activities of the OPTN. Finally, this study was determined to be nonhuman subjects' research by the Portland VA Medical Center (PVAMC) Research and Development Committee, and each OPO obtained approval from their local research oversight entity. All DNDDs were managed per OPO-specific donor management protocols based on the United Network for Organ Sharing (UNOS) clinical pathway.

Data collection and outcome measures

Data were collected by each OPO using a standardized electronic form that was completed by OPO personnel at the bedside of each patient during donor management or through medical chart review while assessing suitability of potential organ donors. Data obtained included donor demographics, treatments received before neurologic determination of death (TH and CPR), donor type (SCD or ECD), and organs transplanted (heart, lung, kidney, liver, intestine, and/or pancreas). Completed data forms were sent to the coordinating center (VAPORHCS) upon completion. To assess

FIG. 1. Clinical criteria for including donors after neurologic determination of death.

TABLE 1. DEMOGRAPHICS OF DONORS AFTER NEUROLOGIC DETERMINATION OF DEATH

Variable	All DNDDs (n = 1098)	Without hypothermia before death (n = 588)	With hypothermia before death (n = 510)	p-value
Age (years)	41.7 ± 14.4	41.6 ± 14.6	41.8 ± 14.2	0.81
Gender (female)	519 (47%)	288 (49%)	231 (45%)	0.22
Ethnicity				
White	798 (73%)	423 (72%)	375 (74%)	0.08
Black	143 (13%)	88 (15%)	55 (11%)	
Hispanic	119 (11%)	62 (11%)	57 (11%)	
Other	38 (4%)	15 (3%)	23 (5%)	
Donor Type				
SCD	892 (81%)	479 (82%)	413 (81%)	0.84
ECD	206 (19%)	109 (19%)	97 (19%)	

CPR, cardiopulmonary resuscitation; DNDD, donor after neurologic determination of death; SCD, standard criteria donor; ECD, expanded criteria donor.

graft outcomes, linkage to the OPTN database was performed. Main outcome measures included the following: overall number of organs transplanted per donor (OTPD), the proportion of donors with ≥ 4 OTPD (as this represents a higher average OTPD goal compared to the national goal of 3.75 OTPD established by the Donation and Transplantation Community of Practice [<http://healthcarecommunities.org/>]), individual organ transplantation rates, and recipient graft outcomes (for heart, lung, kidney, and liver allografts). Regarding transplant recipient graft outcomes, follow-up of graft status was assessed at 1 year through OPTN data and was categorized as either functioning or nonfunctioning based on reported graft failure or recipient death (and the date of such failure/death if failed/deceased) or lack thereof. For kidney grafts, DGF was also assessed based on reported OPTN data and given clinically applicability, as well as simplicity, was defined as the need for dialysis within the first week after transplantation (Mallon *et al.*, 2013).

Statistical analysis

Differences in donor characteristics, OTPD, organ transplantation rates, and graft outcomes between donors receiving TH after CPR and before determination of death were compared to those not receiving TH using Pearson's χ^2 and analysis of variance (ANOVA) for categorical data and the independent *t*-test for continuous data. For graft outcomes noted to have a $p < 0.2$ on univariate analysis, a multivariable analysis was performed. Specifically, this adjusted analysis aimed to assess if TH remained an independent predictor of graft outcome when the donor, recipient, and graft-related covariates that are utilized in the Scientific Registry of Transplant Recipients (SRTR) risk adjustment models were included in the analysis (<http://tools.srtr.org/PSRModelVisApp>). Variables with a $p < 0.05$ on multivariable analysis were felt to be independent predictors. Statistical analysis was performed using SPSS versions 22.0 and 23.0 (SPSS, Armonk, NY: IBM Corporation).

Results

Over the 22-month study period, 1098 DNDDs met inclusion criteria with 46% (510) having received TH before neurologic determination of death. The average overall age

was 41.7 ± 14.4 years, with 47% (519) being female and the majority (81%) being SCDs. Donor characteristics between treatment groups were similar with regards to age, gender, ethnicity, and donor type (Table 1). In DNDDs receiving hypothermia before brainstem herniation, the average duration of hypothermia was 31.9 ± 14 hours.

With regards to organ transplantation rates, there were a similar number of heart, lung, kidney, liver, and pancreas transplanted from DNDDs across treatment groups (Table 2). Intestines, however, were more often transplanted from DNDDs who received hypothermia before brainstem herniation (8% vs. 5%, $p = 0.03$). Overall, the mean OTPD for all DNDDs was 2.71 ± 1.77 , with 31% (336) having ≥ 4 OTPD. There was no significant difference across treatment groups with regards to these outcome measures (Table 2).

Upon analysis of graft outcomes, 1-year graft survival for heart, lung, kidney, and liver allografts was noted to be 91%, 86%, 95%, and 92%, respectively. These rates were noted to be similar on comparison across treatment groups (Table 3). For kidney transplant recipients, the overall occurrence of DGF was found to be 28% for the 1211 grafts analyzed. Furthermore, there was significantly less DGF in kidney grafts from donors who received TH to treat their primary neurologic injury before death (24% vs. 30%, $p = 0.02$,

TABLE 2. ORGAN TRANSPLANTATION RATES OF DONORS AFTER NEUROLOGIC DETERMINATION OF DEATH

Variable	Without hypothermia before death (n = 588)	With hypothermia before death (n = 510)	p-value
Transplantation rates			
Heart (n = 289)	146 (25%)	143 (28%)	0.23
Any lung (n = 207)	112 (19%)	95 (19%)	0.86
Any kidney (n = 726)	383 (65%)	343 (67%)	0.46
Liver (n = 788)	422 (72%)	366 (72%)	0.99
Intestine (n = 66)	27 (5%)	39 (8%)	0.03
Pancreas (n = 144)	75 (13%)	69 (14%)	0.71
≥ 4 OTPD	172 (29%)	164 (32%)	0.30
Mean OTPD	2.69 ± 1.81	2.74 ± 1.72	0.61

OTPD, organs transplanted per donor.

TABLE 3. GRAFT OUTCOMES OF DONORS AFTER NEUROLOGIC DETERMINATION OF DEATH

Variable	Without hypothermia before death (n=588)	With hypothermia before death (n=510)	p-value
1-year graft outcomes*			
Heart graft survival (n=289)	90%	92%	0.72
Lung graft survival (n=64)	83%	91%	0.41
Kidney graft survival (n=1211)	96%	95%	0.74
Liver graft survival (n=754)	92%	91%	0.62
Delayed graft function			
Kidney graft (n=1211)	30%	24%	0.02

*Only recipients with complete data included.

Table 3). After adjusting for known donor, recipient, and graft-related factors, the protective effect of hypothermia on DGF persisted (OR 0.75, 95% CI [0.56–0.995], $p=0.046$, Table 4). Of note, the number of kidney grafts pumped by the OPO or transplant center was similar between the hypothermia and normothermia groups (42% vs. 44%, $p=0.38$, respectively).

Discussion

In the United States, DNDDs that receive CPR account for greater than 1000 organs transplanted per year (Orioles *et al.*, 2013). Despite having a lower number of OTPD compared to non-CPR donors (Orioles *et al.*, 2013), recent reports suggest that there are no differences in immediate or long-term graft function in organs from donors who received CPR (Orioles *et al.*, 2013; West *et al.*, 2016). This study explored the previously unknown effects of TH before determination of death by neurologic criteria in patients with anoxic brain injury after CPR. Although TH before brainstem herniation did not impact overall or individual organ transplantation rates, a statistically significant and clinically relevant protective effect was noted as kidney transplant recipients were found to have a 25% decrease in DGF after adjusting for donor, recipient, and graft-related factors.

TH, or a controlled reduction in core body temperature, has been used clinically to ameliorate secondary organ damage

following a variety of primary insults (Moore *et al.*, 2011). Although the most substantial evidence to date on the beneficial effects of TH has been in neuroprotection, theoretical advantages to other organs, such as the heart and kidney, have been suggested given the systemic effect of hypothermia (Moore *et al.*, 2011; Polderman, 2008). Many potential mechanisms have been implicated in explaining the protective effects of TH, including reduction in metabolic rate; alteration in electrolyte shifts; decreased apoptosis and mitochondrial dysfunction; reduction in ischemia-induced inflammatory and immune reactions; decreased release of free radicals; reduced toxic metabolite accumulation and acidosis; and increased early protective gene activation (Moore *et al.*, 2011; Polderman, 2008, 2009; Yenari and Han, 2012). These mechanisms may be conferred in patients receiving TH for anoxic brain injury after CPR and, thus, provide a potential explanation for the finding that TH before determination of death by neurologic criteria leads to decreased DGF in kidney transplant recipients. It should be noted that despite TH, similar 1-year graft outcomes for heart, lung, kidney, and liver transplant recipients across exposure groups were noted. This suggests that, at least in the short term, TH in the potential organ donor does not seem to negatively impact graft survival.

The rate of DGF after kidney transplantation has been noted to vary substantially in the literature, likely due to the heterogeneity of diagnostic criteria and thresholds used in its

TABLE 4. MULTIVARIABLE ANALYSIS: INDEPENDENT PREDICTORS OF DELAYED GRAFT FUNCTION IN KIDNEY TRANSPLANT RECIPIENTS

Variable	Odds ratio	95% confidence interval for odds ratio	p-value
Therapeutic Hypothermia Before Death	0.75	0.56–0.995	0.046
Donor - Age (per year)	1.02	1.004–1.03	0.008
Donor - Weight (per kg)	0.998	0.99–1.004	0.48
Donor - Hypertension	1.20	0.85–1.70	0.30
Donor - Terminal Serum Creatinine	1.67	1.50–1.86	<0.001
Recipient - Age (per year)	0.995	0.98–1.01	0.410
Recipient - Gender (Male)	1.83	1.34–2.51	<0.001
Recipient - BMI (per point)	1.02	0.998–1.04	0.08
Recipient - Diabetes	1.41	1.03–1.92	0.03
Recipient - Dialysis Time Before Transplant (per year)	1.10	1.06–1.15	<0.001
Recipient - Pretransplant Transfusion	1.25	0.88–1.76	0.22
Recipient - Calculated Panel Reactive Antibodies	1.002	0.998–1.01	0.343
Donor and Recipient–HLA mismatch	1.07	0.97–1.19	0.16
Graft - Cold Ischemia Time	1.03	1.02–1.05	<0.001
Graft - Pump Utilized	0.68	0.50–0.93	0.01

HLA, human leukocyte antigen.

definition, as well as differences in donor and recipient characteristics across different studies (Mallon *et al.*, 2013). As previously mentioned, in this study, dialysis in the first postoperative week was used given its simplicity and clinical applicability (Mallon *et al.*, 2013). Using this definition, a previous large registry study of deceased donor recipients approximated DGF to occur in 25–28% of patients (Huaman *et al.*, 2016), a rate that is similar to that found in the current investigation. Clinically, DGF is relevant as it has been associated with negative recipient outcomes (Butala *et al.*, 2013; Fonseca *et al.*, 2015; McLaren *et al.*, 1999; Tapiawala *et al.*, 2010; Yarlagadda *et al.*, 2009). First and foremost, DGF increases resource consumption, total cost of care, and emotional distress (Buchanan *et al.*, 2008; Jordan *et al.*, 2018; Mannon, 2018; Serrano *et al.*, 2018; Zens *et al.*, 2018). In addition, results of a large systematic review and meta-analysis of 33 studies have suggested that DGF is associated with a 38% higher risk of acute rejection and 41% increased risk of graft loss compared to recipients without DGF at 3.2 years of follow-up (Yarlagadda *et al.*, 2009). In the current study, hypothermia was not noted to have a protective effect on graft loss.

Given the significant negative consequence of DGF in kidney transplant recipients and the overall incidence of its occurrence, attempts to prevent DGF through donor management have been investigated. Specific strategies include adopting an approach of standardized care of potential organ donors to meet preset donor management goals (Malinoski *et al.*, 2013), the use of low-dose dopamine infusion in the donor (Schnuelle *et al.*, 2009), and avoidance of hydroxyethyl starch during donor management (Patel *et al.*, 2015). In addition, as mentioned above, a prospective, randomized controlled trial noted a significantly decreased rate of DGF in donors that had been preconditioned with mild hypothermia (34°C to 35°C) after declaration of death and during donor management compared to those that were maintained at normothermia (36.5°C to 37.5°C; 28% vs. 39%, $p=0.02$) (Niemann *et al.*, 2015). Furthermore, with regard to donor graft preservation, studies comparing hypothermic machine perfusion to simple cold storage have found that the former leads to a significant reduction in DGF for both SCD and more marginal ECD grafts (Gill *et al.*, 2014; Jiao *et al.*, 2013; Moers *et al.*, 2009). Although the aforementioned strategies have been shown to have significant impact in reducing DGF, universal adoption and implementation is challenged due to the need for change in donor management protocols across multiple sites/regions and the need for alignment of multiple providers in the care spectrum (intensivist, OPOs, transplant surgeons, etc.).

This current investigation is the first to evaluate the impact of TH that occurs before neurologic determination of death on donation outcomes. The significant reduction noted in DGF in kidney transplant recipients suggests that the use of TH in potential donors should be considered as a criterion in risk-adjusted models that help guide the utilization of kidney grafts. Specifically, a refined model for predicting DGF after renal transplantation has been created on the basis of multivariable regression analysis (an associated web-based calculator is available at www.transplantcalculator.com/DGF) (Irish *et al.*, 2010). Using this model, a greater than 50% DGF risk has been associated with a twofold increase in graft failure (Irish *et al.*, 2010). Donor related factors include ter-

minal creatinine, age, weight, donor type, history of hypertension, and cause of death. Furthermore, graft related factors include total number of human leukocyte antigen mismatches, cold and warm ischemia time, and the use of machine perfusion. Given the notable protective effect of TH before determination of death on DGF in the current study, inclusion of this variable in future models should be considered.

This study is limited by the availability of additional donor and recipient data that could potentially help further discern notable findings. First, although included DNDDs received CPR before brainstem herniation, it is unknown whether the CPR was secondary to out-of-hospital or in-hospital cardiac arrest. In addition, details on the length of CPR time and number of CPR events were not recorded. Second, hypothermia was actively targeted by each donor hospital's critical care team while the donors were still alive and efforts were being made to save them. Local hospital protocols were followed, and the OPOs were not involved in that phase of care. As such, specific details regarding mean temperature and duration of cooling were not recorded by the OPOs. Finally, although there were no negative outcomes noted by TH on follow-up of recipients, the occurrence of specific side effects, including electrolyte disturbances, hyperglycemia, and potential for infection, would be interesting to note and associate with graft utilization and outcomes.

Conclusion

The use of TH before determination of death in patients with anoxic brain injury after CPR is independently associated with decreased DGF in kidney transplant recipients. This finding corroborates prior evidence from a randomized control trial that evaluated the impact of TH after determination of death and authorization for organ donation (Niemann and Malinoski, 2015). Given the potential long-term consequences of DGF after renal transplantation, consideration should be given to incorporating exposure to TH as a protective donor selection factor in prediction models which evaluate for DGF, as well as other graft outcomes, and thus guide the decision to accept or reject an organ for transplantation.

Authorship Contributions

Study conception and design: Wright, Patel, Gao, Witt, Crutchfield, Neidlinger, and Malinoski

Acquisition of data: Wright, Gao, Witt, Groat, Crutchfield, Neidlinger, Pilot, and Malinoski

Analysis and interpretation of data: Wright, Patel, Gao, Witt, Sally, and Malinoski

Drafting of article: Wright, Patel, Gao, and Malinoski

Critical revision: Wright, Patel, Witt, Sally, Groat, Crutchfield, Neidlinger, Pilot, and Malinoski

Acknowledgments

The authors thank and acknowledge the members of the Organ Donation Research Consortium (ODRC) Anoxic Organ Donor Study Group, as well as the donors, recipients, staff, and leadership of the 20 organ procurement organizations, for their support of this study and assistance in collection, as well as management, of data: Bill Tower (Donor

Network of Arizona); Nikole Neidlinger (Donor Network West); Rick Ash, Scott Bunting, Melissa LeGree, Markeith Pilot (OneLegacy); Jeffrey Trageser (Lifesharing); Matthew Wadsworth (Indiana Donor Network); Dana Green (Louisiana Organ Procurement Agency); Charles Wright (LifeLink of Florida); Shri Bharadwaj (LifeLink of Georgia); Bill Payne (Life Source Upper Midwest Organ Procurement); Emily Stahlschmidt (Mid-America Transplant Services); Jami Gleason (Midwest Transplant Network); Donna Croezen (Carolina Donor Services); Briana Torrey (New England Organ Bank); Kristin Deli Carpini (LiveOnNY); Dan Lebovitz (Lifebanc); Dorrie Dils and Mindy Zoll (Lifeline of Ohio); Chad Muse (LifeShare Transplant Donor Services of Oklahoma); David McCloskey (Pacific Northwest Transplant Bank); Ben Keebler (Southwest Transplant Alliance); and Greg Russell (Intermountain Donor Services).

This research was supported by a grant from the Organ Donor Research Consortium. Furthermore, this research was supported, in part, by an appointment to the Postgraduate Research Participation Program at the Division of Transplantation, U.S. Health Resources and Services Administration (HRSA), U.S. Department of Health and Human Services administered by the Oak Ridge Institute for Science and Education (ORISE) through an interagency agreement between the U.S. Department of Energy and HRSA.

Disclaimer

Although the data reported here have, in part, been supplied by HRSA, the interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy of or interpretation by the U.S. Government.

Author Disclosure Statement

Dr. Malinoski received consulting fees and travel reimbursement from Symic.

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