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Hearts With Cardiac Arrest History Safe For Transplant In The Context Of Donor And Recipient Factors

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Hearts With Cardiac Arrest History Safe For Transplant in the Context Of Donor And Recipient Factors

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by

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Abstract

***Background*:** Cardiac arrest, or downtime, can result in ischemic damage to myocardial tissue, which prompts caution in accepting hearts with such a history for transplant. Our aim is to provide guidance about whether these hearts are suitable and which among them confer optimal outcome.

***Methods*:** We analyzed all first-time adult cardiac transplantations in the United States between 1988 and 2010 as reported in the United Network of Organ Sharing (UNOS) database. Stratification was between donors with downtime history prior to brain death versus those without such a history for univariate and multivariate analyses.

***Results*:** Of 17,941 donors that met inclusion criteria, 700 experienced downtime. Recipients of these hearts were sicker pre-transplant: at waitlist status 1A, hospitalized, supported by ECMO, on IV inotropes, and supported by LVAD ($p<0.05$). They were more likely to be black, to be cigarette users, and to have had prior cardiac surgery ($p<0.05$). In univariate and multivariate analysis, downtime history was not associated with differences in 30-day, 1-year, or 10-year graft survival. Independent risk factors for outcome were donor age, donor BMI, donor cigarette use, recipient ECMO use, recipient use of RVAD, TAH, or bi-VAD, and black recipient ethnicity ($p<0.05$). Subset analysis of recipients of downtime hearts showed that donor cigarette use and black or Hispanic recipient ethnicity were associated with worse outcomes within this group ($p<0.05$).

***Conclusions*:** Donor downtime does not influence survival or mortality overall; however, donor smoking history and non-white recipient ethnicity confer a worse outcome within the cohort.

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Introduction

This introduction will serve to provide broad, detailed context for the research undertaken for this thesis project, which sought to answer the question of whether or not donor hearts with a history of cardiac arrest are safe to use for transplant. It will set the stage for the reader to understand the current system and state of cardiac transplantation in this country and why expanding the donor pool to include "marginal" organs is an endeavor that is both necessary and worthwhile. It will also discuss the specific problem of cardiac arrest and how such events are addressed. Finally, it will discuss the existing body of research speaking directly to the question at this thesis attempts to answer.

A Brief History of Cardiac Transplantation

The roots of modern cardiac transplantation stretch to the early 20th century (1), when French physician Alexis Carrel and American physiologist Charles Claude Guthrie – working at the University of Chicago in 1904 – transplanted a canine heart into the neck of a larger dog and successfully restored muscle contraction in the transplanted organ an hour and fifteen minutes after it was removed from the donor animal (2). The researchers halted their collaboration, and with it the earliest work in heart transplantation, when the pair took jobs across the country from one another.

The next group to take up the cause didn't begin work until the 1930s. Frank Mann, at the Mayo Clinic, and his collaborators also focused their energy on transplanting canine hearts into recipient dogs' necks. They were able to sustain one graft (i.e. transplanted organ) for eight days. Their work elucidated host rejection as a cause of graft failure – though immunosuppression had not yet been developed in

any meaningful way to combat this – in addition to describing the use of heparin in this context as well as the importance of ventricular distension and air embolism in the technical success of the operation (3). Again, however, work in this area stalled for another two decades as Mann's research group transitioned its focus.

Cardiac transplantation research saw resurgence, however, as Russian physiologist Vladimar Demikhov undertook numerous canine-based experiments, including transplantation of a second heart into a dog's thorax, removal of host heart and subsequent transplant of donor heart (orthotopic transplantation), and transplantation of heart and lungs. He was first successful in 1951, when he transplanted heart and lungs from one canine into another and the animal was able to live six relatively normal days before dying of respiratory complications. Five years later, he was able to keep a German shepherd alive for 32 days (4).

Further animal experimentation continued by groups in numerous institutions in North America and Europe alike for the next ten years. Owing largely to the development of cardiopulmonary bypass, these groups were able to advance surgical techniques at an accelerated pace during this period. Moreover, in the early 1960s, American physicians Richard Lower and Norman Shumway made several substantial advances in the field. In the course of their experimentation, they developed the method of cold cardioplegia, in which surgeons pump cold solution through the coronary circulation in order to induce organ hypothermia, thereby reducing the metabolic demand of the donor tissues and thus tissue death. In addition, they began implementing critical strategies for combating graft rejection. By treating recipient animals with the immunosuppressant medications 6-

mercaptopurine, azathioprine, and prednisone, they were able to increase survival to 250 days in recipients of orthotopic transplants, though drug toxicity and infection were problematic side effects of the medications (5). With these advances in hand, the possibility of human cardiac transplantation came into reach.

The first attempted human heart transplant took place in 1964 by Dr. James Hardy at the University of Mississippi Medical Center. Because the concept of brain death was not formally recognized at the time, it was nearly impossible to find a suitable human donor whose heart would be appropriate for transplant at the time of surgery. As a result, a chimpanzee heart was implanted into 68-year-old patient with severe ischemic cardiovascular disease and intractable hypotension. Unfortunately, the relatively small primate heart could not handle the venous return demanded by the recipient, and the patient died approximately one hour after the chimpanzee heart was transplanted. Though human experimentation ceased for three years after this failure, participating researchers learned several important lessons: that they could effectively preserve the donor heart for at least an hour prior to transplant, that their surgical technique was adequate, that they could induce a heartbeat after defibrillation, and that a lower primate's heart was too small to support an adult human's circulation (6).

On December 3,1967, the first human-to-human orthotopic heart transplant was performed in Cape Town, South Africa by Dr. Christiaan Barnard. The donor was a woman who had suffered catastrophic cerebral injuries in an accident and whose family had consented to donation if her heart stopped. In the early hours of the morning of transplant, it did, and her heart was successfully implanted into a 54-

year-old man using the surgical techniques developed over the previous two decades in the laboratory. Immunosuppression for the patient consisted of steroids, azathioprine, and actinomycin C as well as local radiation. The patient developed *Pseudomonas* pneumonia – a common opportunistic infection in immunosuppressed patients – and passed away about two-and-a-half weeks later (7).

Following this success, a substantial uptick in heart transplant attempts occurred in the following year. However, most of these patients had died by the end of 1968 and many hospitals became hesitant to continue transplant programs. The major problems of donor availability and graft rejection also loomed large over the budding transplant community. But in 1968, the Ad Hoc Committee of the Harvard Medical School to Examine the Definition of Brain Death was formed, creating a standardized definition of brain death – thus protecting surgeons from the ethical dilemmas surrounding obtaining donor hearts (8). Another enormous milestone was marked in the 1970s with the discovery of the immunosuppressant cyclosporine (9), which was introduced to practice in the early 1980s and has since substantially improved survival and reduced mortality post-transplant. These advances moved transplantation toward its modern state, which finds itself contending with issues of donor shortage, post-transplant malignancies, and chronic rejection in place of the old challenges of surgical technique, infection, and acute rejection.

While we will discuss the prognosis of transplant recipients at greater length later in the introduction, along with known factors that improve and hinder survival, it should be noted that modern transplant patients experience a median survival of 11 years after transplant, compared with 5.3 years even in 1980 (10).

Indications and Eligibility for Transplant

At present, orthotopic cardiac transplantation is the destination therapy for patients with severe heart failure that has proven refractory to medical management. In practical terms, several major societies have created guidelines for referral for transplantation in potentially eligible patients. So that the reader has an understanding of the recipient population examined in this research, I will give a brief overview of one set of guidelines.

The American College of Cardiology and American Heart Association (ACC/AHA) guidelines (11) stratify their recommendations into three categories: absolute, relative, and insufficient indications for transplant. Absolute indications for transplant include the following: 1) hemodynamic compromise due to heart failure (including refractory cardiogenic shock, dependence on intravenous inotropes to maintain organ perfusion, or a peak VO_2 of less than 10 mL/kg per minute during anaerobic metabolism); 2) severe, symptomatic ischemia that limits activity and is not amenable to percutaneous coronary intervention or coronary artery bypass grafting; or 3) recurrent, symptomatic ventricular arrhythmias that are refractory to all other therapeutic options. Relative indications for transplant include 1) peak VO_2 of 11-14 mL/kg per minute; 2) recurrent unstable angina that is not treatable by other intervention; and 3) recurrent fluid balance instability unrelated to patient compliance with medication. Insufficient indications are 1) low left ventricular ejection fraction, 2) history of functional class II or IV symptoms of heart failure, and 3) peak VO_2 of greater than 15 mL/kg per minute.

Equally as important as the inclusion criteria for transplant are the exclusion criteria for receiving a transplant (12). These factors have all been determined to correlate too strongly with unsuccessful outcomes for the benefit to be sufficient to proceed. Characteristics that are considered absolute contraindications include a systemic illness that would confer a less than two-year life expectancy even in the absence of heart failure and fixed pulmonary hypertension. Situations that would fall within this first category include active malignancy; AIDS (HIV and well-controlled hepatitis infections do not always contraindicate transplant); autoimmune conditions like lupus, sarcodosis, or amyloidosis that are active with multisystem involvement; end-stage renal or hepatic dysfunction if not a candidate for multi-organ transplant; and end stage obstructive pulmonary disease.

Recipient characteristics that are considered relative contraindications but that are assessed on a case-by-case basis include age >72 years, active infection, active peptic ulcer disease, severe diabetes mellitus with end organ damage, severe peripheral vascular or cerebrovascular disease, morbid obesity, recent pulmonary infarction, irreversible neurologic or neuromuscular disorder, and heparin induced thrombocytopenia within 100 days. Importantly, all transplant candidates are carefully screened for mental illness and psychosocial stability as well as lack of drug, tobacco, and alcohol use within six months of potential transplant.

Mechanical Circulatory Support

Mechanical circulatory support devices have exploded onto the scene as an option for patients with heart failure that has been refractory to medical management. These devices can serve as a bridge to transplant (given wait times

and supply and demand imbalances for donor organs), a bridge to decision regarding transplant eligibility, an alternative destination therapy for those ineligible for transplant, or a bridge to recovery of cardiac function. While there are multiple device options, the vast majority of patients receive support via a left ventricular assist device (LVAD), while less than 15% get either a total artificial heart (TAH) or a biventricular assist device (BiVAD).

LVADs can be used as a bridge to transplant in those patients whose clinical status is deteriorating too quickly to wait for transplant without circulatory support, meaning that they generally have heart failure classified as New York Heart Association Class IV – disease causing an inability to engage in any physical activity without discomfort – despite inotropic and intraaortic balloon pump (IABP) support. Use of an LVAD in these patients can also improve the patient's overall health before transplant, thus improving their chances of post-transplant success. Specifically, LVAD therapy can improve function of other organs, reduce pulmonary hypertension, and allow the patient to build up their nutritional reserve. This strategy has picked up substantially over the last twenty years, with pre-transplant LVAD use increasing from 13.4% to 20.1% between 1992 and 2009, according to The International Society for Heart and Lung Transplantation (ISHLT) (13).

As outlined above, there are a number of situations in which a patient's end organ dysfunction or comorbid medical conditions may contraindicate transplantation. However, with improved perfusion of said organs, it is possible to improve the patient's overall status and therefore reverse the contraindication. As a result, many patients will receive an LVAD as a "bridge to decision" in an effort to

make them eligible for transplant. According to the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS), 42% of LVADs registered between 2006 and 2010 were used for this purpose (14).

Given that survival rates with LVAD have improved, using such devices as permanent measures to support patients who are ineligible for transplantation has become increasingly common. As LVAD technology has improved, the devices have become more durable and now experience lower rates of device failure, making them a viable long-term option for many patients. According to the INTERMACS database, between 2006 and 2011, the proportion of LVADs used as destination therapy increased from 16% to 34%, with a corresponding decrease in use of LVAD as bridge to transplant during that period from 44% to 23%. Causes of death for patients receiving LVADs for destination therapy generally correspond to pre-existing comorbidities, many of which preclude eligibility for transplant. INTERMACS identified critical cardiogenic shock, elevated BUN, the need for concomitant surgery at the time of implantation, and the need for BiVAD as risk factors for early death. Advanced age, diabetes, pulmonary hypertension, low sodium, and use of a pulsatile flow device (vs. continuous flow) were identified as continuous risk factors for having an LVAD in this population (14).

The Waiting List and Donor Allocation

Unfortunately, these alternate therapy options for heart failure patients are extremely relevant: according to the United Network of Organ Sharing (UNOS), the body that oversees transplant in the United States, approximately 2,300 heart

transplants are performed annually in our country. And at present, there are 4,030 patients on the waiting list for a new heart (15).

UNOS, which is a private organization that reports to the US government, is charged with ensuring the equitability of organ allocation as well as with managing the mechanics of the waitlist. They have created an organ allocation system known as the Organ Procurement and Transplantation Network (OPTN), which outlines the rules that allocate available organs with the input of transplant professionals, organ recipients, and donor families. These rules take into account the geographic distance and blood type compatibility of a potential donor organ as well as the severity of illness and time on the waitlist of a recipient.

It is important to note in transplant that geographic distance plays a major role in organ retrieval, as ischemic times of greater than four hours have been shown to correlate with an increased risk of primary graft failure. Accordingly, UNOS established 11 geographic regions, based on population and physical area, to help guide allocation when a potential organ becomes available.

To organize recipients, OPTN demarcates a series of “Status” categories to prioritize their need for an organ, the criteria for which are as follows (16). Status 1A patients are considered the very sickest of the group. A patient meets this designation if they are currently living in the hospital that will be performing the transplant and either are being supported by mechanical ventilation; are relying on an IABP, total artificial heart, or extracorporeal membrane oxygenation (ECMO); or require hemodynamic monitoring while on intravenous inotropes. A patient can also be considered Status 1A for the 30 days after they have a right and/or left ventricular

assist device implanted in the setting of an acute decompensation or for the 30 days after they have a total artificial heart implanted. Patients with an existing LVAD with a severe device complication (e.g. thromboembolism, infection, mechanical failure, life threatening arrhythmia) can also be considered 1A (16)

Status 1B comprises the next-sickest group of patients. These patients require IV inotropes (but are of lower acuity than 1A patients), have an LVAD or RVAD (after 30 days post-op), or have a TAH (also after 30 days post-op). Status 2 encompasses the remainder of the active waitlist. A Status 7 designation exists for patients who are "inactive," meaning that they are ineligible for transplant at the time. According to the OPTN, there are currently 512 patients at Status 1A (12.7% of the waitlist), 1,641 at Status 1B (40.7%), 970 at Status 2 (24%) and 912 at Status 7 (22.6%). In 2003 – the most recent listed year on the OPTN website for this data – the median waiting time was 50 days for 1A, 78 days for 1B, and 309 for 2 (16). These waiting times vary between transplant regions as well. Much of this wait time can be explained by the relative lack of donor organs available for transplant.

Prognosis After Transplant

As briefly discussed earlier in this introduction, survival after transplant has greatly improved over the last 20 years, with median survival of 11 years as of 2005. Generally, mortality is greatest in the first six months and is followed by approximately 3.4% mortality per year afterward (10). It is estimated that these trends continue to improve as our strategies for decreasing mortality and our understanding of donor and recipient factors that impact mortality strengthen.

In terms of quality of life after transplant, data from The International Society for Heart and Lung Transplantation (ISHLT) describe a very high proportion (approximately 90%) of patients who report no limitation of functional activity at one and five years after surgery. Though this number appears very promising, it should be noted that their data indicates that fewer than 30% of recipients return to work full-time, only 10% resume part-time work, and 40% remain unemployed (whereas they may not have been pre-op) (10).

The ISHLT released a report in 2011 (10) identifying recipient and donor characteristics independently associated with early mortality. Recipient factors included the requirement of mechanical circulatory support prior to transplant, a history of dialysis prior to transplant, mechanical ventilation at the time of transplant, prior transfusion, and infection requiring IV antibiotics within two weeks prior to transplant. The report also identified a number of continuous variables that increased risk: age and weight (which were represented by a u-shaped curve: low and high values represent greater risk), pulmonary vascular resistance, panel reactive antibodies, and serum bilirubin and creatinine. Donor risk factors – including advanced donor age, prolonged organ ischemic time, and anorexia as a cause of donor death – were also described in the report.

Risk factors for mortality at five, ten, and fifteen years are much more poorly described in the literature overall. The ISHLT report described poor immunosuppressive therapy, human leukocyte antigen (HLA) A-locus mismatches, recipient history of hepatitis, recipient history of dialysis, age, pregnancy, diabetes, and infection requiring treatment as risk factors for mortality at five years. Similar risk

factors were identified at 10 years, with the addition of preoperative coronary artery disease and heart size mismatch (usually a female heart given to a male donor). Risk factors at 15 years were similar (10).

These risk factors lead to a discussion of actual causes of death in transplant recipients, which can be grouped into three categories: opportunistic infections, lymphoma or other malignancy, and graft failure, caused by hyperacute, acute, or chronic rejection. Each category, and in the case of rejection, each subcategory, is associated most strongly with a different post-operative time period. Opportunistic infections are the leading cause of death between six months and one year post-transplant. Infection risk at any given time comprises a balance between epidemiologic exposures and the "net state of immunosuppression," which takes into account the patient's exposure to immunosuppressive therapies, comorbidities, the condition of the graft, any invasive devices or catheters in the recipient, the recipient's immune function, and the recipient's current or historical infection with immunomodulatory viruses such as CMV, EBV, HHV-6 and -7, HBV, and HCV (17).

After the first year post-transplant, malignancy becomes a leading cause of death for cardiac transplant recipients. Given the high levels of immunosuppression required in heart transplant patients (the risks associated with organ rejection are more dire than for other types of transplant), the rates of lymphomas and solid tumors surpass those of other solid organ transplant recipients. Mortality for patients who contract post-transplant lymphoproliferative disorders (PTLD) varies widely by the type of disease they develop, with monomorphic PTLD associated with 80% survival and mean survival for all forms as low as 25-35% (18). PTLD development

is associated with immunosuppression using cyclosporine, azathioprine, or polyclonal or monoclonal antilymphocyte antibodies.

Graft failure, as mentioned above, can be attributed to hyperacute, acute, or chronic rejection, each of which results from a different underlying immunologic root. Hyperacute rejection occurs within minutes to hours of transplantation. This type of response is humorally mediated and generally occurs because the recipient has preformed antibodies against the graft due to prior transfusions, pregnancies, or prior transplants. This results in activation of the complement system and subsequent massive thrombosis in the capillaries, forestalling vascularization and thus causing immediate graft failure. Acute rejection occurs over a slightly longer time course – within six months of surgery. This form of rejection is mediated primarily on a cellular level by recipient lymphocytes that become activated against donor antigens or that respond to donor dendritic cells acting as antigen presenting cells. The humoral response plays a smaller role in this form of rejection.

Chronic rejection occurs over months to years following transplantation as a result of both antibody and cell-mediated processes and generally manifests as fibrosis and scarring of the organ and decreasing function. Previous episodes of acute rejection, inadequate immunosuppression, any initial delay in graft function, donor factors like advanced age (19) or a history of hypertension, reperfusion injury to the graft, extended ischemic time, recipient diabetes/hypertension/hyperlipidemia, and post-transplant infection have all been linked to increased risk of chronic rejection (20). The scarring and fibrosis of chronic rejection takes different forms in each solid organ. In hearts, the process is termed cardiac allograft vasculopathy,

also known as transplant coronary artery disease or cardiac transplant vasculopathy (21). This vasculopathy is associated with ischemic sequelae in transplanted hearts, including myocardial infarction, arrhythmia, and sudden cardiac death. Statin therapy is one of the mainstays of preventive treatment from a cardiovascular standpoint (22). Calcineurin inhibitors Everolimus and sirolimus have also been shown to decrease the incidence of this process (23).

How do we try to Reconcile Supply and Demand?

An important and interesting figure to consider is that approximately 8,000 donors become available per year for all organs in the United States but only a quarter or so of those donors have hearts that are deemed appropriate for transplant. Many of the donor factors that make these hearts ineligible – such as donor/recipient size mismatch (24) or systemic infection (25) in the donor – confer increased mortality to recipients and cannot be attenuated or altered as risk factors. However, there are certain factors that have traditionally lead transplant providers to reject heart offers that may in fact be safe for recipients. These “marginal” quality organs represent a potential frontier of expansion for the donor pool (26). One such subsection of marginal organs is the subject of this research: donor hearts with a history of cardiac arrest prior to brain death.

An Overview of Cardiac Arrest

Cardiac arrest, or downtime, results in the cessation of oxygenated blood flow throughout the body, including to the myocardium. The classically described list of patient factors that can lead to cardiac arrest are as follows: hypovolemia, hypoxia, acidosis, hyper- or hypokalemia, hypothermia, hyper- or hypoglycemia, toxins,

cardiac tamponade, tension pneumothorax, myocardial infarction, pulmonary embolism, and trauma. Patients with underlying structural heart disease, conduction abnormalities, or severe coronary artery disease are at increased baseline risk for sudden cardiac arrest. Cigarette smoking (27), chronic inflammation (as measured by elevated serum CRP) (28), and excess alcohol consumption (29) are also associated with downtime.

Pulseless arrest encompasses the rhythms of asystole, pulseless electrical activity (PEA), ventricular fibrillation, and ventricular tachycardia. Each of these rhythms is associated with different chances of successful resuscitation and degrees of myocardial damage. Asystole is associated with the poorest outcomes, with only 10% of patients presenting in this rhythm being resuscitated initially and 0-2% surviving to hospital discharge. This rhythm often reflects prolonged cardiac arrest (more than four minutes), which leads to severe myocardial damage that cannot be attenuated. Witnessed arrest in a younger patient with a shorter time to EMS response (if an out-of-hospital arrest) confers a greater probability of successful resuscitation in this group (30). Patients presenting in PEA also tend to do quite poorly, though their outcomes in one study were slightly better than patients presenting in asystole, with 23% being initially resuscitated and 11% surviving to discharge (31). Outcomes are much better for patients who present in a ventricular tachyarrhythmia – with survival rates of 25-40% to hospital discharge in ventricular fibrillation (32) and 65-70% in ventricular tachycardia (33). The key interventions leading to successful resuscitation in all cases depends on the timing of effective CPR and defibrillation. Success for in-hospital arrest is increased by witnessed

arrest, VT or VF as the initial rhythm, and the re-establishment of pulse within the first 10 minutes of CPR.

Following a successful resuscitation, the major goals of post-cardiac arrest care are to treat the underlying cause of arrest, minimize brain injury, manage any residual cardiovascular dysfunction, and manage and prevent problems associated with reperfusion injury following a period of global ischemia. Unfortunately, even when patients' hearts are successfully resuscitated, many suffer brain death, which puts them in the position to serve as organ donors.

Downtime History and Cardiac Donation

A history of downtime understandably raises concern about ischemic damage to the organ when a transplant program is considering such a donor heart for a potential recipient. As a result, such a history is often grounds to reject an organ offer. However, prior to the commencement of this research, several studies in large animal models as well as small hospital-based cohorts suggested that such hearts are in fact safe options for transplant recipients in need.

The results of one such large animal study performed by a multi-institution group were reported in 2011 (34). Their study assessed cardiac function in pigs after inducing either hypoxic cardiac arrest or brain death and then transplanted these organs into recipient pigs. They began by inducing hypoxic cardiac arrest in one group of donor pigs, followed by 15 minutes of warm ischemia and then resuscitation. They also caused brain death in another cohort of animals via intracerebral balloon inflation. They assessed cardiac function of the hearts of both cohorts and found that the cardiac arrest hearts showed near-normal contractility,

though the stroke volume was slightly reduced compared to that of the other group. They also noted that cardiac enzyme profiles changed significantly during hypoxia, though they returned to baseline after reperfusion. Both sets of animals were sacrificed and their organs transplanted into another group of pigs, after which time the cardiac function of those animals was assessed and documented. It was discovered that cardiac function was comparable between the group that received donor hearts with a history of downtime and the group that did not.

In terms of clinical studies: at the time our research began, there were only two institution-specific analyses that addressed this problem. Ali et al. found in their examination of 38 cases at their institution that cardiac arrest was not a predictor of post-transplant mortality, though donor age, the need for postoperative ventricular assist device support, renal failure, and respiratory failure did confer a significant mortality risk (35). Bonde et al. also found no impact on allograft dysfunction post-operatively or survival and identified donor weight ratio, pre-operative cancer, diabetes, and pre-transplant diagnosis of post-cardiotomy failure as independent predictors of mortality in their group of 284 subjects, 73 of whom had a downtime history. The group also stratified their analysis based on length of downtime and made the general recommendation that an organ from a donor under age 40 with prompt resuscitation following a downtime lasting less than 30 minutes who recovered heart function within two to five days was sound for transplantation (36, 37). During the course of our research, two other groups pursued this research question, using methods quite similar to ours; the differences between our study and theirs will be addressed in the discussion (38, 39).

Statement of Purpose and Hypothesis

As explored in the introduction, the supply and demand for transplantable hearts in the United States is grossly out of balance. Give this need for donor hearts, counterbalanced by a relative dearth of organs deemed fit for transplant, the transplant community has been attempting to expand the donor pool with hearts that have historically been considered marginal in quality. Again, one such group of donor hearts is those with a history of cardiac arrest, or downtime, prior to the declaration of brain death. At the time that we began this research, only large animal studies and small case series had been performed to hint at an answer to whether or not downtime negatively impacted recipient outcome after transplantation.

In the context of this evidence, the hypothesis of this investigation was that donor downtime should not contraindicate transplant. Accordingly, our purpose was not only to lend statistical power to our hypothesis but also to elucidate donor and recipient factors that can improve the palatability of accepting these hearts. We aimed to do so through extensive analysis of the United Network of Organ Sharing (UNOS) database and its more than two decades of transplant data. Furthermore, given the movement toward expanding the donor pool overall through use of organs that had previously been considered “marginal,” we also hoped to shed some light on current allocation practices for such organs.

Methods

Data Source

The United Network for Organ Sharing (UNOS) provided Standard Transplant Analysis and Research (STAR) files with de-identified donor and recipient transplant data from October 1987 to March 2012 as well as recipient follow-up data through December 2011. The database included prospectively collected demographic, donor, operative, and postoperative information for all thoracic transplant recipients in the United States during this time period.

Study Design

We retrospectively reviewed the UNOS database from January 2000 to December 2009. These time-points were chosen in order to identify a modern cohort of heart transplant patients with adequate time for follow-up at the time of analysis, which began during the summer of 2012. All adult (≥18 years) single-organ heart transplants were included (e.g. patients undergoing heart-lung transplants were not eligible for analysis under our study criteria). Transplants were primarily stratified by donor cardiac arrest history prior to declaration of brain death. This variable was defined and reported by UNOS in the dataset. If no data was available about this variable, the transplants were excluded from our analysis.

Outcome Measures

Demographic and clinical characteristics of all heart transplant donors and recipients in this dataset were examined. The primary end-point was all-cause graft failure during the study period. This is to say that organ survival (vs. recipient survival) was the outcome we examined, given that re-transplantation can occur.

Statistical Analysis

Baseline demographic and clinical characteristics between the primary study cohorts (hearts with and without downtime history) were compared using Student's *t*-test for continuous variables and the chi-square test for categorical variables. For all Student's *t*-tests conducted, normality was assessed using skewness and kurtosis. Survival was modeled using the Kaplan-Meier method with statistical differences between survival curves assessed using the log-rank (Mantel-Cox) test.

Univariate, unadjusted 30-day, 1-year, 3-year, 5-year, and 10-year graft survival analysis was conducted using the chi-square test. Multivariate analysis was conducted using both the Cox proportional hazards regression model as well as a logistic regression model. In order to adjust for potential confounders and accurately determine factors associated with decreased graft survival, variables describing baseline demographic and clinical characteristics that were significantly different ($p < 0.05$) between the two study cohorts on univariate analysis were included in the multivariate models.

Statistical significance was established at $p < 0.05$ (2-tailed), and all hazard ratios are presented with 95% confidence intervals. All statistical analysis was generated using SAS software, Version 9.3 of the SAS System for Windows. (Copyright, SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks of SAS Institute Inc., Cary, NC, USA). Oliver Jawitz (Yale School of Medicine, Class of 2015/2016) was instrumental in performing statistical analysis for this program, and Bonde Lab statistician Samira Ghadvani supervised and approved the validity of our findings.

Results

Over the course of the selected study period, 700 transplants occurred that used donors with downtime history, and 17,241 took place that used donors without such a history. The baseline non-cardiac demographic characteristics of the donors are summarized in Table 1; cardiac-specific donor characteristics are summarized in Table 2. Baseline recipient characteristics can be found in Table 3.

Donor cohorts did not differ significantly in age, history of hypertension, history of alcohol use, and total bilirubin. However, donors with downtime history were more likely ($p < 0.05$) to be female, to have a higher body mass index (though the mean value was in the low range of "overweight" for both groups), to have a history of diabetes, and to have a history of cocaine use. They were less likely, however, to have used cigarettes. Their total serum creatinine, Blood Urea Nitrogen, SGOT/AST, and SGPT/ALT were all significantly higher those donors belonging to the cohort without downtime history.

Donor cohorts also differed when examined by causes of death, mechanisms of death, and circumstances of death. In terms of cause of death, downtime donors were significantly more likely ($p < 0.001$) to have "anoxia" (versus "cerebrovascular/stroke, head trauma, or CNS tumor) listed on their death certificates when compared with their counterparts. As far as mechanism of death, downtime donors had significantly ($p < 0.05$) more "drowning," "seizure," "drug intoxication," "asphyxiation," and "cardiovascular" mechanisms than the control group, and significantly lower rates of "gunshot wound," "blunt injury," and "intracranial hemorrhage/stroke." Downtime donors' circumstances of death were

more likely to be undefined and less likely to be the result of a motor vehicle accident ($p < 0.001$).

Certain cardiac characteristics were well matched between donor groups. There was no significant difference ($p < 0.05$) in history of myocardial infarction, abnormal findings on coronary angiogram, or graft ischemic time. Left ventricular ejection fraction (LVEF) was significantly lower in those with a downtime history than those without, but it is important to note that the mean values of 60.79% and 61.59%, respectively, are both well within a normal range, rendering this metric unimportant here. More relevantly, however, donors with downtime history were significantly more likely to have been on three or more inotropes at the time of transplant ($p < 0.01$) than their counterparts.

Recipients were well matched for gender, age, BMI, hemodynamics, viral serostatus at transplant, serum albumin levels, and history of malignancy. Recipients of downtime hearts were more likely ($p < 0.05$) to be black, to have had a history of cigarette use, and to have had prior cardiac surgery ($p < 0.01$). They also were more likely ($p < 0.05$) to be Status 1A on the transplant list and to have been hospitalized, though not in ICU, at time of transplant ($p < 0.01$) and less likely to be Status 2 or out of the hospital than those recipients whose donors did not have such a history. Groups were matched for recipients who were Status 1B or who were in ICU at the time of transplant. Downtime recipients were also more likely to be on ECMO and IV inotropes ($p < 0.05$) and to be supported by LVAD ($p < 0.01$) than the other group at the time of transplant.

Despite the differences noted between donor and recipient cohorts, Table 4 illustrates no significant difference between 30-day ($p = 0.81$), 1-year ($p = 0.81$), 3-year ($p = 0.41$), 5-year ($p = 0.31$), or 10-year ($p = 0.97$) graft survival for transplants using donors with cardiac arrest history and those without this history. A Kaplan-Meier graft survival curve (Figure 1) demonstrates similar degrees of graft survival; the log-rank test showed $p = 0.56$. There was also no difference in the incidence of rejection that required treatment between transplant and discharge between groups ($p = 0.34$), nor was there a difference in mean length of hospital stay between transplant and discharge ($p = 0.63$).

Recipient cause of death was similar between the cohort of recipients whose donors had downtime history and those whose donors did not (Table 5) in the categories of “infection,” “cardiovascular,” “pulmonary,” “cerebrovascular,” “hemorrhage,” and “malignancy.” The only exception is for graft failure ($p = 0.006$), which is more likely to be the cause of death in the former cohort than the latter. This category includes primary graft failure, acute rejection, and chronic rejection; each of these sub categories was, predictably, more likely to be a cause of death in the downtime group as well, though the trends were not statistically significant.

Ten independent predictors of graft survival were identified by the Cox proportional hazards regression model performed during our analysis (Table 6). Increased risk was conferred by advanced donor age ($p < 0.001$); increased donor BMI ($p = 0.01$); positive donor history of cigarette use ($p < 0.001$); recipient ECMO use ($p < 0.001$); recipient use of RVAD ($p < 0.001$), TAH ($p = 0.05$), or BiVAD ($p < 0.001$); and recipient ethnicity being black ($p < 0.001$). Protective factors were being

hospitalized but not in ICU at transplant and not being hospitalized at time of transplant. Again, donor downtime history was not significant.

Multivariate Logistic regression identified three variables of interest that independently predicted graft failure as cause of death. Donor downtime history was again identified as conferring this risk ($p = 0.02$), and recipient ethnicity being black conferred a greater risk of graft failure ($p < 0.001$). Recipient cigarette use had a similar effect ($p = 0.001$).

Subset analysis within the group of donors with downtime history demonstrated that donors without a history of cigarette use were associated with significantly better outcomes than those with such a history ($p = 0.001$; Figure 2a). We found that recipient history of cigarette use did not predict outcome among those who received a downtime heart ($p = 0.65$; Figure 2b). There are also significant differences within the group that received downtime hearts based on recipient ethnicity ($p = 0.04$; Figure 2c). White recipients do the best throughout, and black recipients do comparably at first but then start doing worse within the first year. Hispanic recipients do worse from the outset.

Among the group with donor downtime, those donors who required three or more inotropes were associated, though not significantly ($p = 0.12$) with poorer outcomes (Figure 3a). Male donor gender was weakly associated ($p = 0.38$) with better survival (Figure 3b). Donor cocaine use within the downtime donor cohort did not impact recipient outcome ($p = 0.46$; Figure 3c), and donor mechanism of death also did not impact outcome ($p = 0.49$; Figure 3d).

Tables

Table 1. Donor Characteristics Stratified by History of Downtime

Variable	No Downtime N = 17241[a]	Yes Downtime N = 700[a]	p-Value*	
Female gender	4,864 (28.21%)	233 (31.86%)	0.04	*
Mean (STD) donor age (yr)	31.56 (±12.40)	30.67 (±11.73)	0.06	
BMI	26.35 (±5.31)	27.29 (±6.20)	<0.0001	*
History of hypertension	2,083 (12.14%)	82 (11.78%)	0.78	
History of cancer	312 (1.81%)	6 (0.86%)	0.06	
History of diabetes	387 (2.25%)	24 (3.44%)	0.04	*
Insulin dependence	169 (43.90%)	12 (50%)	0.56	
History of cigarette use	4,447 (25.97%)	153 (22.11%)	0.02	*
History of cocaine use	2,181 (12.89%)	110 (16.15%)	0.01	*
History of heavy alcohol use	1,453 (15.45%)	63 (13.76%)	0.32	
Cause of death				
Anoxia	1,586 (9.20%)	262 (37.43%)	<0.0001	*
Cerebrovascular/stroke	4,436 (25.73%)	116 (16.57%)	<0.0001	*
Head trauma	10,732 (62.25%)	307 (43.86%)	<0.0001	*
CNS tumor	180 (1.04%)	3 (0.43%)	0.11	
Mechanism of death				
Drowning	56 (0.32%)	6 (0.86%)	0.02	*
Seizure	125 (0.73%)	10 (1.43%)	0.03	*
Drug intoxication	456 (2.64%)	67 (9.57%)	<0.0001	*
Asphyxiation	295 (1.71%)	66 (9.43%)	<0.0001	*
Cardiovascular	589 (3.42%)	98 (14%)	<0.0001	*
Electrical	5 (0.03%)	1 (0.14%)	0.11	
Gunshot wound	3307 (19.18%)	109 (15.57%)	0.02	*
Stab	37 (0.21%)	1 (0.14%)	0.69	
Blunt injury	6796 (39.42%)	194 (27.71%)	<0.0001	*
Intracranial hemorrhage/stroke	4993 (28.96%)	121 (17.29%)	<0.0001	*
Natural Causes	142 (0.82%)	8 (1.14%)	0.36	
Circumstance of death				
Motor vehicle accident	5706 (33.10%)	176 (25.14%)	<0.0001	*
Suicide	2183 (12.66%)	101 (14.43%)	0.17	
Homicide	1902 (11.03%)	68 (9.71%)	0.27	
Non-motor vehicle accident	1696 (9.84%)	69 (9.86%)	0.84	
Natural Causes	2836 (16.45%)	111 (15.86%)	0.99	
Other	2918 (16.92%)	175 (25%)	0.68	
Terminal Serum Creatinine	1.21 (±1.06)	1.64 (±1.63)	<0.0001	*
Terminal Blood Urea Nitrogen	14.57 (±11.31)	20.19 (±18.46)	<0.0001	*
Terminal Total Bilirubin	1.13 (±1.44)	1.09 (±1.63)	0.41	

Terminal SGOT/AST	106.1 (±438.4)	192 (±495.6)	<0.0001	*
Ethnicity				
White	11,901 (69.04%)	473 (67.57%)	0.41	
Black	2,216 (12.86%)	109 (15.57%)	0.04	*
Hispanic or Latino	2,669 (15.48%)	108 (15.43%)	0.97	
Asian	254 (1.47%)	5 (0.71%)	0.10	
Terminal SGPT/ALT	89.74 (±353.7)	187.3 (±472)	<0.0001	*

CNS, central nervous system. *p-Value based on Student's t-test for continuous variables and the chi-square test for categorical variables ($p < 0.05$ considered statistically significant).

[a]Some patients were excluded from each analysis due to missing data fields or erroneously inputed data in the database

Table 2. Donor Cardiac Variables Stratified by History of Cardiac Arrest

Variable	No Downtime N = 17241[a]	Yes Downtime N = 700[a]	p-Value*	
History of myocardial infarction	189 (1.10%)	9 (1.29%)	0.39	
Mean (STD) LVEF	61.59 (±7.88)	60.79 (±8.60)	0.01	*
LVEF Method				
Echo	16,134 (97.42%)	646 (97.00%)		
MUGA	10 (0.06%)	0 (0%)		
Angiogram	417 (2.52%)	20 (3%)		
Abnormal coronary angiogram	210 (1.22%)	9 (1.29%)	0.74	
# of vessels with >50% stenosis	109.7 (±312.2)	100 (±315.5)	0.92	
Inotropic agent at procurement (agent 1)				
Dopamine	7022 (68.64%)	232 (53.09%)	<0.0001	*
Dobutamine	103 (1.01%)	7 (1.60%)	0.18	
Epinephrine	67 (0.65%)	1 (0.23%)	0.30	
Levophed	714 (6.98%)	44 (10.07%)	0.01	
Neosynephrine	1660 (16.23%)	76 (17.39%)	0.28	
Other	664 (6.49%)	77 (17.62%)	<0.0001	*
Three or more inotropes at transplant	351 (2.04%)	31 (4.44%)	<0.0001	*
Graft Ischemic Time (hours)	3.21 (±1.04)	3.22 (±1.05)	0.86	

*p-Value based on Student's t-test for continuous variables and the chi-square test for categorical variables ($p < 0.05$ considered statistically significant).

[a]Some patients were excluded from each analysis due to missing data fields or erroneously inputed data in the database

Table 3. Recipient Characteristics Stratified by Donor History of Cardiac Arrest

Variable	No Downtime N = 17241[a]	Yes Downtime N = 700[a]	p-Value*	
Female gender	4,106 (23.82%)	183 (26.14%)	0.16	
Mean (S.D.) recipient age (yr)	51.81 (±12.33)	51.37 (±12.93)	0.36	
BMI	26.91 (±23.44)	27.06 (±5.21)	0.88	
Status before transplant				
ICU	5184 (30.07%)	219 (31.29%)	0.49	
Hospital, not ICU	3239 (18.79%)	159 (22.71%)	0.009	*
Not in hospital	8818 (51.15%)	322 (46%)	0.008	*
Life support at transplant				
ECMO	84 (0.49%)	8 (1.14%)	0.017	*
IABP	923 (5.35%)	47 (6.71%)	0.12	
Prostaglandins	5 (0.03%)	1 (0.14%)	0.11	
IV Inotropes	7763 (45.03%)	349 (49.86%)	0.012	*
Inhaled NO	41 (0.24%)	2 (0.29%)	0.8	
Ventilatory support	489 (2.84%)	20 (2.86%)	0.97	
VAD				
LVAD	2020 (11.72%)	110 (15.71%)	0.001	*
RVAD	35 (0.20%)	1 (0.14%)	0.73	
TAH	56 (0.32%)	5 (0.71%)	0.08	
LVAD & RVAD	400 (2.32%)	15 (2.14%)	0.76	
Not specified	1522 (8.83%)	53 (7.57%)	0.25	
Serum Albumin	3.65 (±0.76)	3.64 (±0.78)	0.79	
Hemodynamics				
Pulm. artery systolic pressure (mm Hg)	41.98 (±14.12)	42.40 (±14.37)	0.46	
Pulm. artery diastolic pressure (mm Hg)	20.27 (±8.51)	20.44 (±8.60)	0.61	
Pulm. artery mean pressure (mm Hg)	28.44 (±10.13)	28.62 (±9.63)	0.67	
Cardiac output (L/min)	4.52 (±1.54)	4.55 (±1.66)	0.59	
History of cigarette use	4317 (25.04%)	227 (32.43%)	<0.0001	*
HCV serostatus positive	338 (1.99%)	14 (2.03%)	0.97	
EBV serostatus positive	10,498 (62.76%)	457 (66.91%)	0.15	
CMV IgG positive	9,858 (57.18%)	381 (54.43%)	0.15	
CMV IgM positive	945 (5.48%)	35 (5%)	0.58	
Ethnicity				
White	12,657 (73.41%)	501 (71.57%)	0.28	
Black	2,763 (16.03%)	134 (19.14%)	0.03	*
Hispanic or Latino	1,242 (7.2%)	47 (6.71%)	0.62	
Asian	401 (2.33%)	12 (1.71%)	0.29	
Waitlist status at transplant				
Status 1A	6,815 (39.53%)	304 (43.43%)	0.04	*
Status 1B	6,678 (38.73%)	285 (40.71%)	0.29	

Status 2	3741 (21.70%)	111 (15.86%)	0.0002	*
History of dialysis	423 (2.45%)	21 (3%)	0.36	
History of cardiac surgery	3,278 (19.01%)	179 (25.57%)	<0.0001	*
History of diabetes	3,897 (22.60%)	161 (23%)	0.81	
Mean (STD) serum creatinine at Tx (mg/dL)	1.31 (±0.57)	1.35 (±0.61)	0.09	
Mean (STD) total bilirubin (mg/dL)	1.25 (±1.97)	1.22 (±1.43)	0.75	
History of malignancy	882 (5.12%)	32 (4.57%)	0.81	

ICU, intensive care unit; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; IV, intravenous; NO, nitric oxide; VAD, ventricular assist device; CMV, cytomegalovirus; IgG, immunoglobulin G; IgM, immunoglobulin M. *p-Value based on Student's t-test for continuous variables and the chi-square test for categorical variables ($p < 0.05$ considered statistically significant).

[a]Some patients were excluded from each analysis due to missing data fields or erroneously inputed data in the database

Table 4. Graft Outcomes Stratified by Donor History of Cardiac Arrest

Variable	No Downtime N = 17241[a]	Yes Downtime N = 700[a]	p-Value*
Survival 30 days	16,229 (94.21%)	657 (93.99%)	0.81
Survival 1 yr	14,886 (86.59%)	604 (86.91%)	0.81
Survival 3 yr	11,484 (75.92%)	428 (74.43%)	0.41
Survival 5 yr	7,830 (62.71%)	266 (60.32%)	0.31
Survival 10 yr	1,286 (17.59%)	46 (17.49%)	0.97
Treated rejection between transplant and discharge	1,474 (8.55%)	67 (9.57%)	0.34
Mean (STD) length of stay, transplant to discharge (days)	20.02 (±25.55)	20.50 (±19.43)	0.63

Survival data based on graft survival time, post-transplant. *p-Value based on Student's t-test for continuous variables and the chi-square test for categorical variables ($p < 0.05$ considered statistically significant).

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Table 5. Recipient Cause of Death Stratified by Donor History of Cardiac Arrest

Variable	No Downtime N = 17241[a]	Yes Downtime N = 700[a]	p-Value*	
Graft failure - all causes	811 (17.84%)	46 (25.99%)	0.006	*
Primary failure	278 (6.12%)	16 (9.04%)	0.11	
Acute rejection	277 (5.86%)	15 (8.47%)	0.2	
Chronic rejection	124 (2.73%)	9 (5.08%)	0.06	
Infection	714 (15.71%)	20 (11.30%)	0.11	
Cardiovascular	882 (19.40%)	35 (19.77%)	0.9	
Pulmonary	297 (6.53%)	7 (3.95%)	0.17	
Cerebrovascular	194 (4.27%)	9 (5.08%)	0.6	
Hemorrhage	111 (2.44%)	4 (2.26%)	0.88	
Malignancy	420 (9.24%)	20 (11.30%)	0.35	
Renal failure	123 (2.71%)	2 (1.13%)	0.2	
Multiple organ failure	481 (10.58%)	14 (7.91%)	0.26	

*p-Value based on the chi-square test for categorical variables ($p < 0.05$ considered statistically significant)

Table 6. Multivariate Cox Proportional Hazards Regression Model | Outcome: Graft Time

Variable	Hazard Ratio (95% Confidence Limits)	p-Value*	
Donor history of cardiac arrest	1.07 (0.92-1.24)	0.39	
Donor gender (vs. female)	0.95 (0.89-1.01)	0.13	
Mean donor age	1.01 (1.01-1.01)	<.0001	*
Donor BMI	0.99 (0.99-0.99)	0.01	*
Donor ethnicity: black (vs. all other)	1.08 (0.99-1.17)	0.1	
Donor history of diabetes	1.04 (0.87-1.25)	0.67	
Donor history of cigarette use	1.12 (1.06-1.20)	0.0003	*
Donor history of cocaine use	0.95 (0.87-1.03)	0.22	
Donor terminal Serum Creatinine	0.98 (0.95-1.02)	0.26	
Donor terminal Blood Urea Nitrogen	1.00 (1.00-1.00)	0.86	
Donor terminal SGOT/AST	1.00 (1.00-1.00)	0.75	
Donor terminal SGPT/ALT	1.00 (1.00-1.00)	0.18	
Donor LV ejection fraction	1.00 (0.99-1.00)	0.24	
Recipient status before transplant (vs. in ICU)			
Hospital, not ICU	0.86 (0.79-0.93)	0.0003	*
Not in hospital	0.81 (0.75-0.88)	<.0001	*
Recipient life support at transplant			
ECMO	2.78 (2.07-3.74)	<.0001	*
IV Inotropes	0.98 (0.91-1.04)	0.46	
VAD (vs. none)			
LVAD	1.09 (0.97-1.22)	0.14	
RVAD	2.90 (1.77-4.75)	<.0001	*
TAH	1.59 (1.00-2.50)	0.05	*
Bi-VAD	1.52 (1.26-1.82)	<.0001	*
Recipient history of cigarette use	1.00 (0.93-1.08)	0.97	
Recipient ethnicity: black (vs. all other)	1.39 (1.29-1.49)	<.0001	*
Recipient waitlist status at transplant (vs. 1A)			
Status 1B	0.96 (0.89-1.03)	0.25	
Status 2	0.99 (0.89-1.10)	0.88	
Recipient history of cardiac surgery	1.09 (0.98-1.20)	0.11	

IV, intravenous; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit.
*p-Value based on multivariate Cox proportional hazards regression model, using factors significant on univariate analysis ($p < 0.05$ considered statistically significant).

Figures

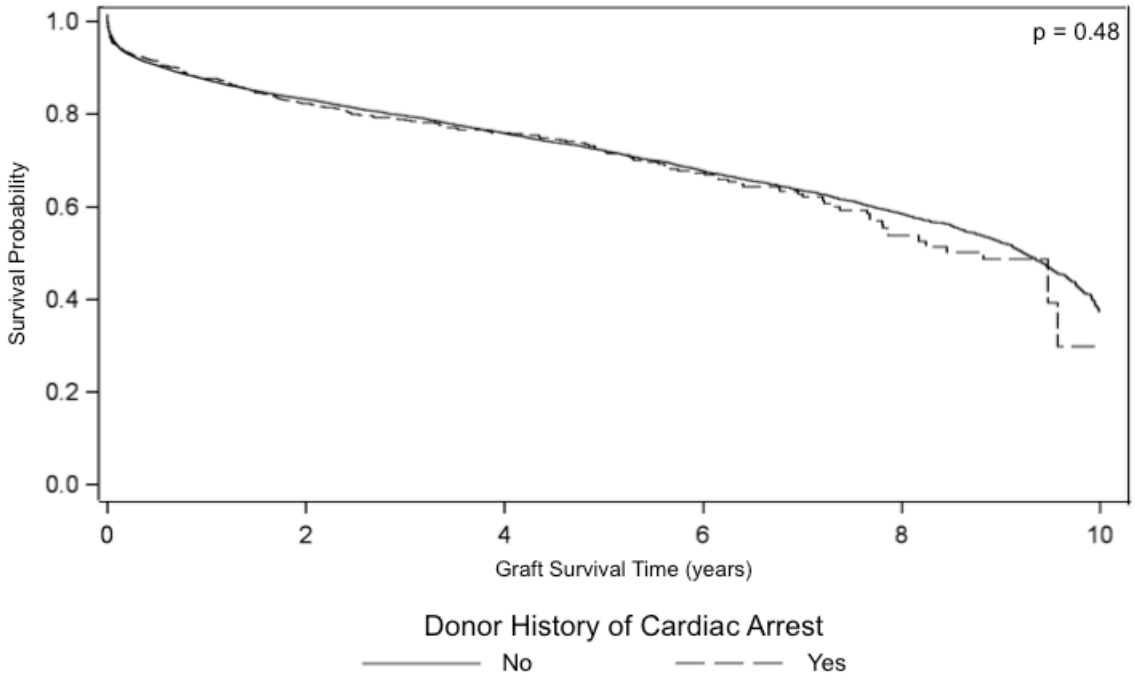
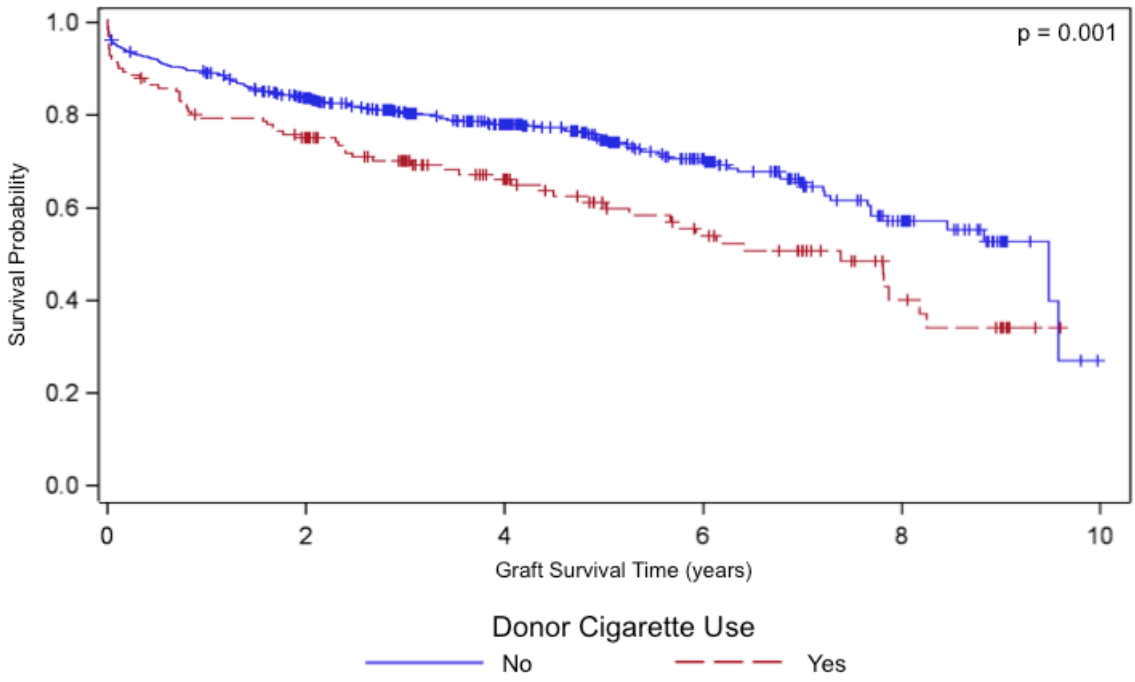
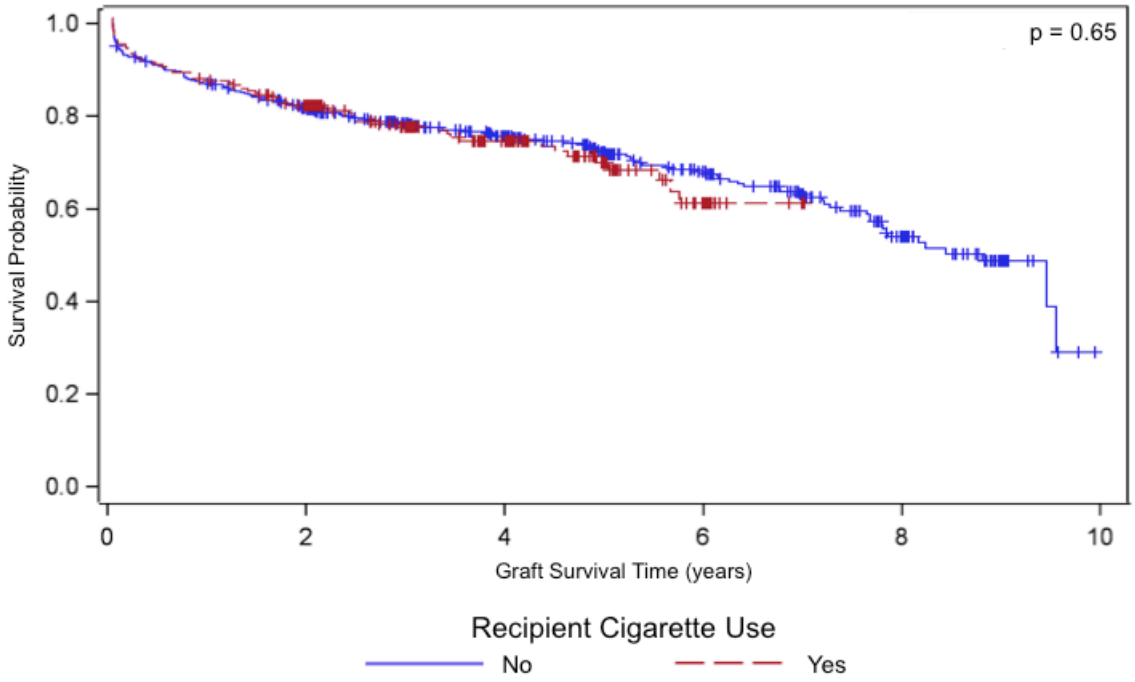


Figure 1. Kaplan-Meier graft survival analysis of all patients. Impact of donor history of downtime. P-value corresponds to Mantel-Cox log-rank test results.

a.



b.



c.

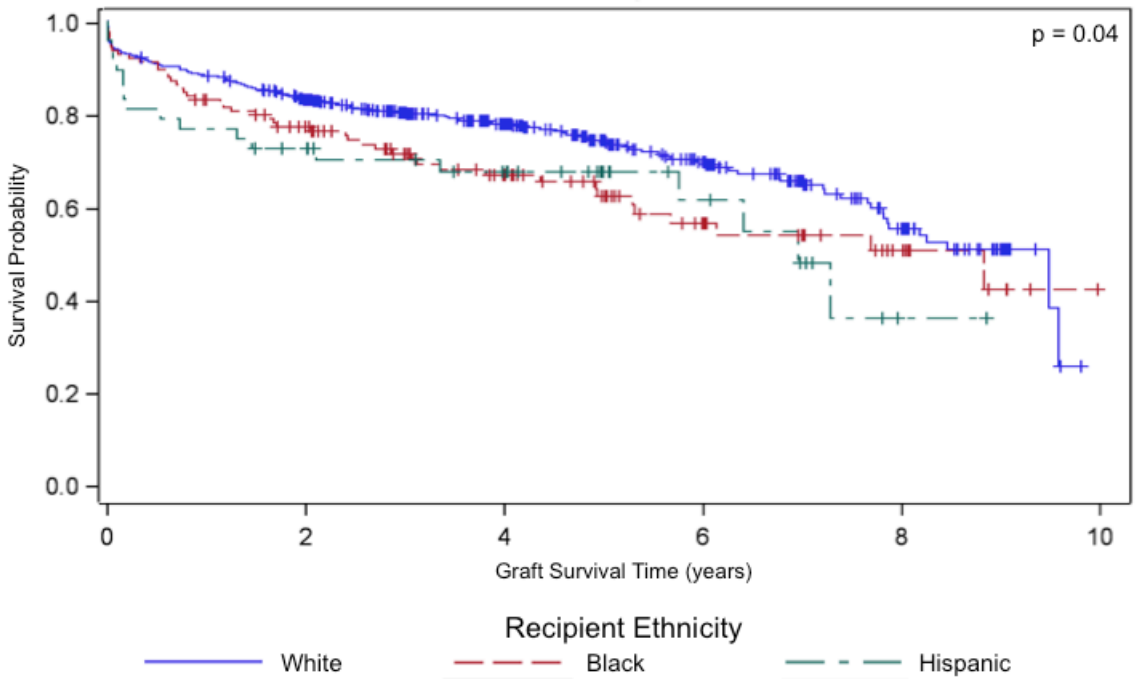
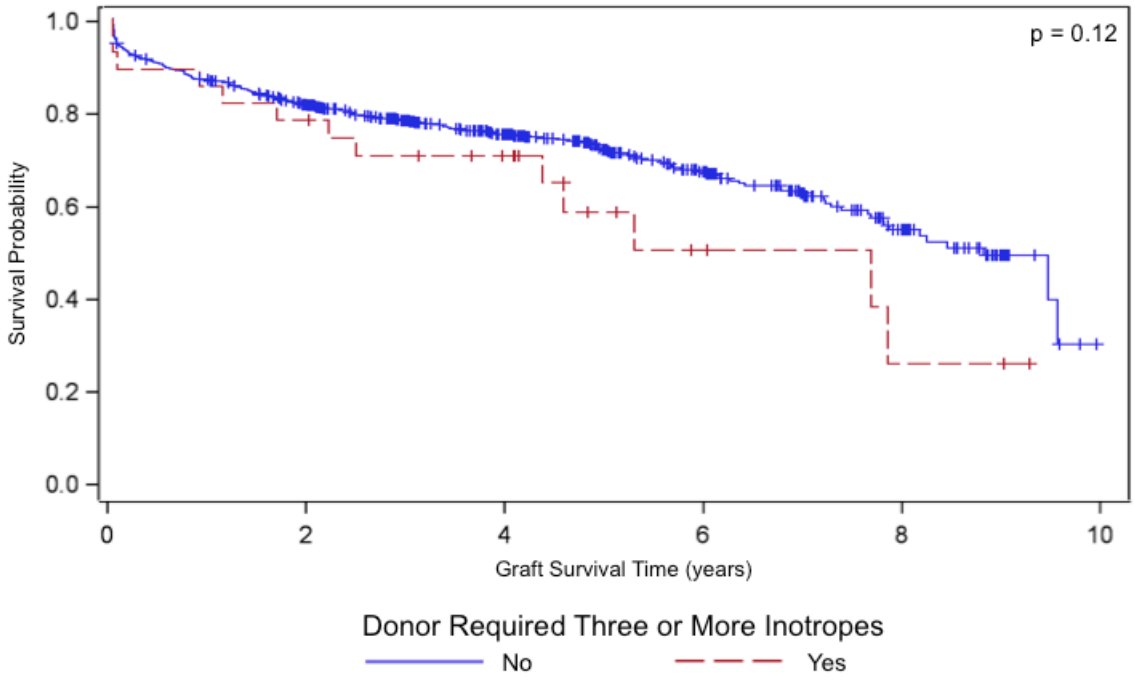
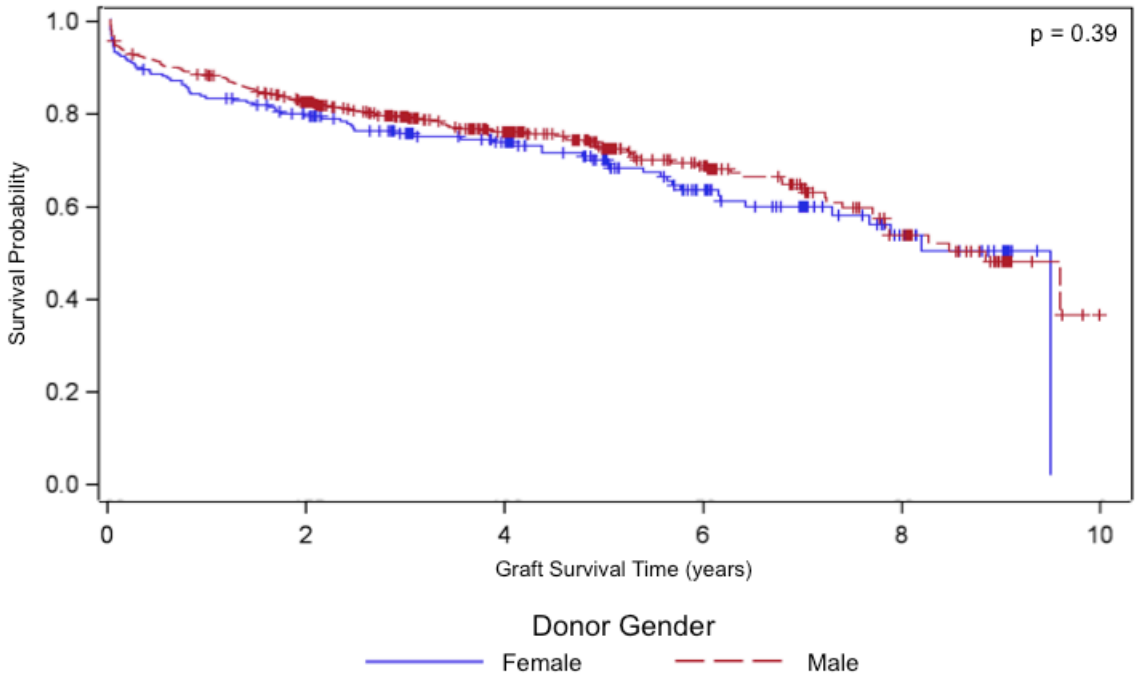


Figure 2. Kaplan-Meier graft survival analysis within recipients of hearts with downtime history. ***2a.*** Impact of donor cigarette use. ***2b.*** Impact of recipient cigarette use. ***2c.*** Impact of recipient ethnicity. P-value corresponds to Mantel-Cox log-rank test results.

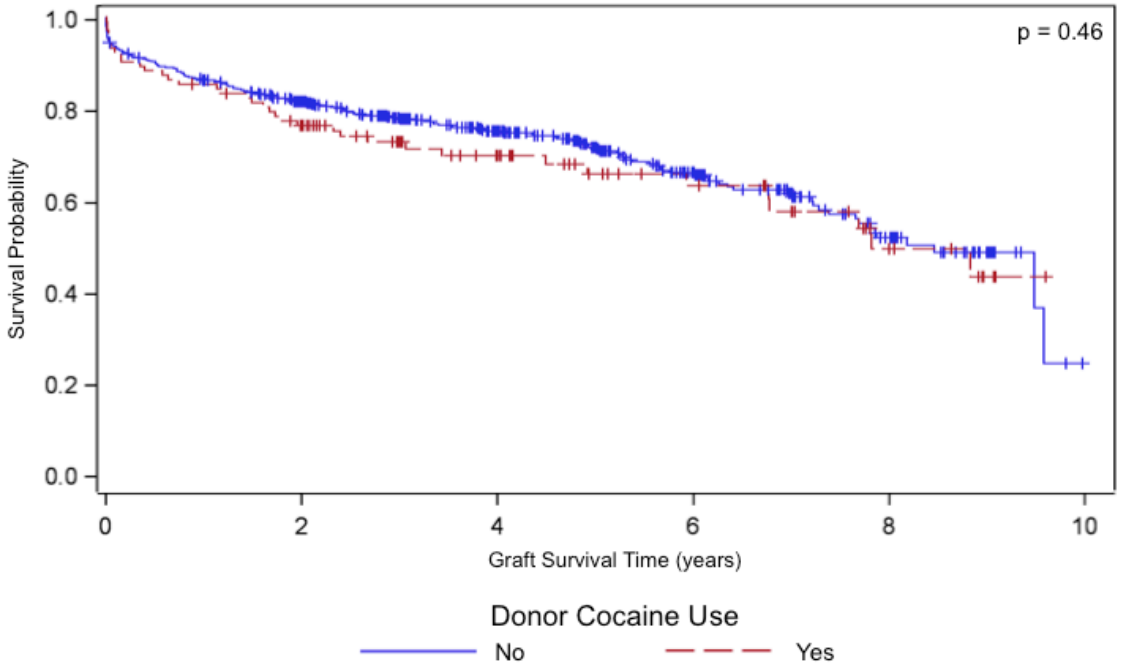
a.


p = 0.12
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
0
2
4
6
8
10
Graft Survival Time (years)
Donor Required Three or More Inotropes
No
Yes

b.


p = 0.39
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
0
2
4
6
8
10
Graft Survival Time (years)
Donor Gender
Female
Male

c.



d.

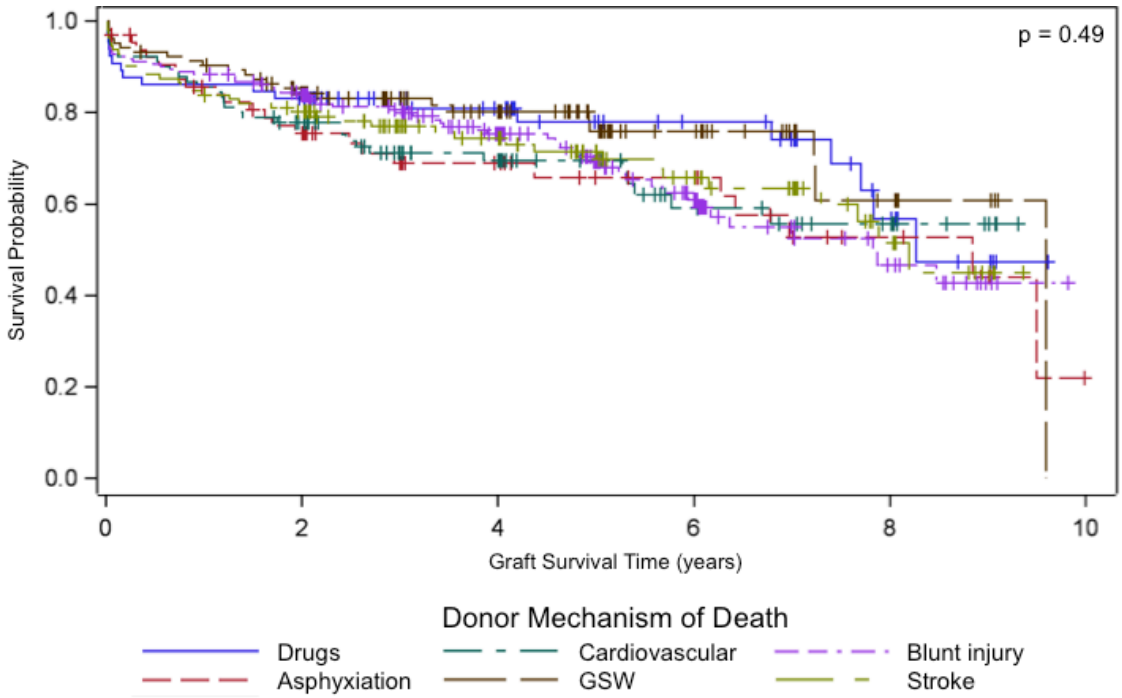


Figure 3. Kaplan-Meier graft survival analysis within recipients of hearts with downtime history. ***3a.*** Impact of donor inotrope requirement. ***3b.*** Impact of donor gender. ***3c.*** Impact of donor cocaine use. ***3d.*** Impact of donor mechanism of death. P-value corresponds to Mantel-Cox log-rank test results.

Discussion

Cardiac transplantation remains the gold standard therapy for patients with heart failure; however, the demand for donor organs continues to exceed supply. Accordingly it is incumbent on the transplant community to make use of all organs that will safely provide desirable outcomes for our patients. Of all the potential donor hearts considered by UNOS during the time period examined, only 35% were actually transplanted (40). Reasons for declining the remainder of the hearts range from non-modifiable qualities – like vascular damage or HIV positivity – to qualities that can, and should, be examined more carefully to determine whether or not they actually impact end organ function, like a history of downtime in the donor.

Indeed, laboratory and preliminary clinical data have suggested that recipient outcomes need not be compromised by such a donor history, especially when organ function is restored before transplant. These hearts, if demonstrated to confer equivalent outcome, have the potential to significantly expand the acceptable pool of donor organs. This project explores, in some spirit, the state of transplant's need to expand the types of donors we find acceptable. We aimed to lend support to the use of donors with a history of downtime with the increased statistical power afforded by the UNOS database and to elucidate donor characteristics that could further assist transplant teams in choosing hearts for their patients.

Our analysis revealed several points of interest. First and foremost, donor downtime history caused no significant impact on long-term survival and rejection of the graft over time. However, there was a slight preponderance of graft failure as cause of death in the downtime group. This is to say that while longevity was not

affected by the history of downtime, cause of death itself was influenced by it. Accordingly, the experience of downtime may indeed have some impact on the organ over its lifespan, but those effects could potentially be mitigated by increasing or modulating the means we already have in place to decrease risk of graft failure (e.g. increasing immunosuppression, monitoring the organ frequently with angiograms).

Potential bias exists towards downtime as can be indirectly inferred from the fact that these hearts predominantly were accepted for very sick patients who likely could not stay on the waiting list for much longer. These patients were more likely to be hospitalized, on ECMO, on IV inotropes, on LVAD support, at Status 1A on the waitlist, and to have had a history of cardiac surgery. Despite this, and despite the fact that being on ECMO was found to be an independent risk factor for outcome, these patients still did comparably to those whose donors did not have a history of downtime in both the short and long term, which lends weight to the argument that downtime hearts should not be viewed as a marginal option.

As an interesting side note – for policy and political considerations – black patients were much more likely to receive a downtime heart than patients of any other ethnicity. Being black was also an independent risk factor for overall outcome and was very strongly associated with having graft failure as cause of death, an observation that has been previously documented. Our data suggests that ethnicity is treated as a risk factor when allocating hearts in the same way that wait list status, hospitalization, and life support usage are considered risk factors. Yet some of those factors do not independently predict outcome, though ethnicity does, likely due to

immune variation. Whether this allocation trend reflects purely an understanding of likely outcome, some degree of racial bias, or some combination of the two, this is an important trend to keep in mind and explore further as a community.

At the time of our analysis, we did not have data about the duration of donor downtime; however, concurrent studies understandably demonstrated that shorter downtime led to better outcomes in this group of donors (38, 39). Quader et al. described a mean downtime of 20 minutes in the successfully resuscitated group and separated the groups into tertiles based on downtime, though they did not find significant differences in survival based on their gradation system (38). Southerland et al. divided the groups into quartiles based on arrest time and found significantly improved survival in patients with arrest time of 0 to 8 minutes when compared with the 9 to 15 minute and >25 minute groups. Their Cox proportional hazard modeling also demonstrated that duration of arrest as a continuous variable was associated with increased mortality (39).

In Quader et al.'s discussion, they brought up the concept of "ischemic pre-conditioning" as a possible explanation for their findings. Essentially, this concept posits that myocardial tissue tolerates ischemia better when it has been previously exposed to ischemia (38). They described work by Murry et al. that demonstrated that myocardial damage was less when a coronary artery was occluded intermittently than when it was blocked off continuously for the same total duration (41). The explanation offered in this case included less depletion of ATP and less accumulation of metabolic waste products, given time to recover between ischemic

episodes. This was confirmed in human studies by taking myocardial biopsies during coronary artery bypass grafting surgery (42).

More relevantly for our purposes, another animal study by Kuzuma et al. demonstrated that that ischemic preconditioning may be protective as late as 24 hours after the initial ischemic insult (43). As a result of the initial ischemic period – in order to clear metabolic waste and repair any initial damage – myocardial tissue synthesizes anti-oxidant enzymes like superoxide dismutase, catalase, and heat shock proteins. Donor hearts always suffer one period of ischemic stress after procurement. Despite storage of the donor organ in a cold solution to decrease the tissue's metabolic rate and thus minimize anaerobic metabolism, some degree of ischemic damage does occur. It may well be that a prior period of ischemic stress during downtime ended up conferring some degree of protection to the organs during this second period of stress.

Our analysis identified additional donor and recipient characteristics that should be factored into evaluation of an organ by transplant providers when a donor offer is made. Certain characteristics conferred independent risk for all groups – regardless of donor cardiac arrest history – donor age, donor BMI, donor cigarette use, recipient ECMO use, recipient use of RVAD/TAH/BiVAD, and black recipient ethnicity.

We delved into certain areas in more detail with subset analysis to clarify the magnitude of impact on outcome and to identify non-significant trends that might guide decision-making. On the issue of donor cigarette use, donors with downtime history were less likely to be smokers, but smoking did confer poorer outcomes

within this group (as expected, given vascular changes associated with smoking). Accordingly, concurrent donor smoking and downtime history should be considered unfavorably. Recipient cigarette use, on the other hand, did not impact overall outcome, so this need not factor into decision-making.

On the issue of ethnicity, we found significant differences in outcome for white, black, and Hispanic recipients of hearts with downtime, with Hispanics doing worse than both other groups from the outset. Cardiac arrest hearts were assigned preferentially to black individuals and with no frequency trend in Hispanics. Black race was an independent predictor of post-transplant mortality, but this was not observed for Hispanics. Given that ethnic influence on transplant outcomes is a complex topic, this issue should be explored further to elucidate an etiology for this trend, but it would seem that Hispanics should not be given these hearts, as they seem to do worse with them.

We also analyzed certain factors that were statistically different between donors with downtime and donors without. Downtime donors required three or more inotropes at a significantly higher rate than the other donor group, and though the impact of requiring this support did not significantly impact outcome within the group ($p = 0.12$), the suggested effect may be large enough to take into account when considering donor organs. Male donor gender conferred a weaker trend toward survival benefit ($p = 0.38$) within the downtime group; it still may be a factor to keep in mind, though the argument is not that strong. Donor cocaine use, though significantly higher in the cardiac arrest group, did not impact outcome among recipients of downtime hearts ($p = 0.46$). Mechanism of death was also different

between donor cohorts, but it did not impact outcome within the cardiac arrest group ($p = 0.49$).

Limitations to generalizability are intrinsic to a study of this structure. Analysis was limited to the variables UNOS collects. Furthermore, the deceased donor's family members provide donor data, so information about substance use – i.e. cocaine, alcohol, tobacco, which can all impact cardiac function – may not be completely reliable, though this is the case for all examined cohorts within the study.

In sum, our recommendations are as follows: donor hearts with a history of downtime (cardiac arrest) are a viable option for transplant, though they may confer a higher risk of graft dysfunction over time, which can be addressed with frequent monitoring and tailored immunosuppression. They should not be treated as a marginal option, assigned more often to sicker patients, and current organ allocation practices treat ethnicity as a risk factor for outcome on par with waitlist status and life support use. Independent risk factors for outcome should be considered when a "riskier" heart is used. These findings have the potential to expand the donor pool substantially and guide decision-making about which hearts are optimal for use and, potentially, to adjust treatment of black recipients.

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