**Incidence of Acute Circulatory Support Prior to Heart Transplantation and Post-Transplant Outcomes**

**Running Title: Circulatory Support Prior to Transplant**

David Ouyang, MD1, Gunsagar Gulati1, Richard Ha2, Dipanjan Banerjee, MD MS1

1. Stanford University School of Medicine, Stanford, CA 94305, USA.2. Division of Adult Cardiac Surgery, Department of Cardiothoracic Surgery.

**Address for Correspondence:**Dipanjan Banerjee, MD MS

300 Pasteur Dr MC 5319

A260

Stanford, CA94305

Tel: (650) 723-6459

Fax: (650) 723-8392 **Email:** dipanjan@stanford.edu

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**Background**: Proposed changes in 2016 to the United Network for Organ Sharing (UNOS) heart transplant allocation protocol will prioritize patients receiving acute circulatory support, including extracorporeal membrane oxygenation (ECMO), percutaneous ventricular assist devices (PVAD), and intra-aortic balloon pumps (IABP). We sought to evaluate contemporary trends in the incidence and outcomes of patients who required acute circulatory support during the hospitalization prior to heart transplantation.

**Methods**: Using the National Inpatient Sample (NIS) from 1998 to 2014, we identified 6,892 patients who received an orthotopic heart transplant (OHT) and classified them based on either pre-transplant ECMO, PVAD, or IABP placement or no pre-transplant acute circulatory support. We compared baseline characteristics and in-hospital outcomes between patients who underwent pre-transplant ECMO, PVAD, or IABP and patients who did not receive acute circulatory support prior to heart transplantation.

**Results**: Of patients who underwent heart transplantation, 456 (6.6%) patients received acute circulatory support prior to transplant. During the study time period, the use of acute circulatory support increased (p < 0.001 for trend), more than doubling from 17 cases per year from 1998-2002 to 40 cases per year from 2012-2014. Of patients with acute circulatory support, 341 (74.8%) were supported by IABP, 130 (28.5%) were supported by ECMO, and 21 (4.6%) were supported by PVAD. Prior to 2007, patients who required acute circulatory support had significantly more mortality than patients who did not require circulatory support prior to transplant(14.3% vs. 7.5%, p = 0.01). In the subsequent era (2007 to 2014), there was no statistically significant difference in mortality (4.7% vs. 5.1%, p = 0.80). There was an improvement in mortality over time for all patients, but most significantly in patients who required acute circulatory support (63% risk reduction comparing the two eras). Patients who had acute circulatory support had less comorbid diabetes, hypertension, or pre-existing renal dysfunction, but during their hospitalization had increased lengths of stays and rates of acute renal, hepatic, and respiratory failure, sepsis, bleeding complications, and surgical reoperations.

**Conclusions**: In this cohort, we found an increasing proportion of patients receiving acute circulatory support prior to heart transplantation over time. These patients exhibited longer lengths of stays and increased frequency of complications compared to those without acute circulatory support, but mortality in the more recent era was not significantly different between the two groups. Changes to the UNOS heart allocation protocol could accelerate this trend of increased use and should take the increased morbidity of these patients after transplantation into consideration.

**Introduction**

Congestive heart failure is a highly morbid, common disease affecting 5.7 million people and contributing to over 300,000 deaths each year in the United States1,2.For patients who are symptomatic despite maximal medical therapy, cardiac transplantation serves a crucial role in the treatment of end-stage heart failure. Appropriate patient selection balances time on the transplant waitlist with the desire to maximize survival and clinical outcomes after cardiac transplantation.

Heart transplantation outcomes have continuously improved from 1-year survival of less than 50% to greater than 90% in somecohorts3–5. Heart transplant volumes have plateaued, yet there has been a tremendous increase in the number of active transplant candidates from 1,203 in 2006 to 3,008 in 2013 6,7. 10% of patients on the heart transplant waitlist die every year due to the lack of available organs8,9.In part due to the mismatch between the number of donor organs and the number of transplant candidates, candidates in the most urgent classification, 1A, now make up the majority of eventual transplant recipients (67% of adult heart transplants in 2014)6.

There is concern that 1A classification currently groups together patients on the waitlist with disparate life expectancies. Among status 1Acandidates for heart transplantation, 6-month waitlist mortality ranges from 4.8% in those with durable mechanical circulatory support(e.g. a left ventricular assist device) complicated by infection to 35.7% in candidates supported by ECMO6,10–14.Roughly 40% patients are being bridged to cardiac transplantation with durable mechanical circulatory support, but less data is available on temporary circulatory support prior to cardiac transplantation.

Given this significant variation in prognosis for waitlist candidates at 1A status, the Thoracic Organ Transplantation Committee of Organ Procurement and Transplantation Network(OPTN) and United Network for Organ Sharing (UNOS) proposed changes in 2016 to the adult heart allocation system to further stratify high urgency patients6. By the proposed criteria, patients requiring support by ECMO or with temporary biventricular or right ventricular assist devices are given the highest priority, and the use of an intra-aortic balloon pump are among the criteria to be at the second highest priority, as these patients have the highest expected mortality on the waitlist.

There is some concern that this strategy could lead to worse outcomes post-transplant. For example, for patients undergoing ECMO support, the 6-month mortality after heart transplant is 24.0%6. The desire to balance the needs of critically ill patients with long-term outcomes after the receipt of a limited resource suggests the need for further study of patients who require acute circulatory support prior to transplantation. There is significant interest in the outcomes of these patients, but there are few studies detailing either their short or long-term outcomes. In this study, we use the largest national database of hospitalizations in the United States, the National Inpatient Sample (NIS), to assess the outcomes of patients who underwent acute circulatory support prior to heart transplantation and compare their outcomes to patients who did not require acute circulatory support.

We hypothesized that patients who underwent acute circulatory support prior to heart transplantation would exhibit significantly higher morbidity and mortality after cardiac transplantation than those patients who did not require acute circulatory support, and that those outcomes will vary by type of support (ECMO vs. PVAD vs. IABP). We also sought to describe trends in the prevalence of acute mechanical circulatory support prior to cardiac transplantation over time, as well as changes in outcomes.

**Methods**

**Data Source and Study Design**

The National Inpatient Sample (NIS), from the Healthcare Cost and Utilization Project, Agency for Healthcare Research and Quality, is the largest database of all-payer inpatient discharge information, sampling approximately 20% of all non-federal US hospitals and including approximately 9 million hospital admissions each year. It contains discharge data from over 5000 hospitals located across 45 states, of which approximately 1,200 hospitals are sampled each year to create a stratified sample of United States hospitals. Each NIS entry includes all diagnosis and procedure codes of activity during the patient’s hospitalization at the time of discharge, as well as patient demographics, hospital characteristics, and short-term complications of the hospitalization.

We identified all patients who underwent heart transplantation in the NIS from 1998 to 2014. This population was further divided by whether each patient underwent pre-transplant ECMO, PVAD, or IABP. Comorbidities including diabetes, ischemic heart disease, hypertension, renal dysfunction, obesity, peripheral vascular disease, and history of smoking were identified by International Classification of Diseases 9th edition (ICD-9) code (Supplementary Table A). In-hospital complications including acute renal failure, acute respiratory failure, redo sternotomy or reoperation, sepsis, bleeding complications, stroke, liver failure, and device failure were also identified by ICD-9 code (Supplementary Table B). To determine the effect of time on outcomes in this cohort, we divided the cohort into two eras: 1998 to 2006 and 2007 to 2014 (the modern era).

**Statistical Analysis**

Python 2.7 (Python Software Foundation, www.python.org) and R 2.13 (R Foundation, www.r-project.org) were used for statistical analysis. P-values were calculated by two-sided t-tests and Chi-squared tests, respectively, with significance thresholds of 0.05. Logistic regression was performed for the multivariate analysis.

**Results**

**Baseline Patient Characteristics**

Between 1998 and 2014, there were 6,892 patients who underwent cardiac transplantation in the NIS (Table 1). The patients were predominantly male (72.0%) and white (57.0%) and had a mean age of 46.5years (SD: 19.0). Most patients were hospitalized at large, urban, academic hospitals and the median day of heart transplant was hospital day 17 (interquartile range from day 2 to day 36). Consistent with the demographics of congestive heart failure overall, patients had a high proportion of ischemic heart disease (42.9%), hypertension (29.7%), diabetes (19.5%), and pre-existing renal dysfunction (33.2%).

Between 1998 and 2014, the use of acute circulatory support prior to cardiac transplantation increased significantly over time, from 5.9% of transplants from 1998-2006 to 8.2% from 2007-2014 (p <0.001, Figure 3).In this cohort, 456 transplant recipients required acute circulatory support prior to heart transplantation, of which 341patients had an IABP placed, 130patients were started on ECMO, and 21patients underwent PVAD placement. Twenty-seven patients had both IABP and ECMO, 9 patients had both IABP and subsequent PVAD, and 3 patients had both PVAD and ECMO. Patients requiring acute circulatory support were of similar age, sex, and average household income compared to patients who did not require acute circulatory support. For patients requiring acute circulatory support, there was a decreased rate of diabetes (15.1% vs. 19.9%, p = 0.02), hypertension (23.2% vs. 30.2%, p = 0.002), and preexisting renal dysfunction (26.1% vs. 33.7%, p = 0.001), but similar rates of ischemic heart disease, peripheral vascular disease, obesity, and history of smoking (p > 0.05).

**Post-transplant outcomes**

In this cohort of heart transplant patients identified in the National Inpatient Sample, in-hospital mortality decreased over time from 7.9% in 1998-2006 to 5.1% in 2007-2014. Patients who required acute circulatory support had worse outcomes post-transplant compared to patients who did not require mechanical circulatory support prior to transplantation (Table 2). Patients who required acute circulatory support had longer overall lengths of stay (70 vs. 41 days, p < 0.001) and increased in-hospital mortality (8.6% vs. 6.2%, p = 0.05). The difference in in-hospital mortality decreased for both patients who required acute circulatory support (p < 0.001 for trend), as well as patients who did not require acute circulatory support (p = 0.012 for trend), though the decline in mortality was more pronounced in patients who required acute circulatory support (Figure 1).

Comparing patients between the earlier era and the modern era, there was a 63% decrease in mortality for patients who received acute circulatory support and a 37% decrease in mortality for patients who did not. In the earlier era, patients who received circulatory support prior to transplant had an increased length of stay (70.8 vs. 43.4 days, p < 0.001) and had increased mortality (14.3% vs. 7.5%, p = 0.01). In the modern era, patients who received circulatory support prior to transplant still had an increased length of stay (68.9 vs. 39.2 days, p < 0.001), however the difference in mortality was not statistically significant (4.7% vs. 5.1%, p = 0.80).In a multivariate analysis of predictors of mortality, increased age and increasing number of comorbid conditions was associated with increased mortality (Table 3). Conversely, transplantation during the modern era, and diagnoses of hypertension, chronic kidney disease, or diabetes appeared protective. There was no independent risk modification based on type of acute circulatory support.

In-hospital complications were more common in patients who required acute circulatory support, with an increased risk of acute renal failure (55.5% vs. 36.0%, p < 0.001), acute liver failure (11.6% vs. 3.1%, p < 0.001), acute respiratory failure (27.4% vs. 10.2%, p < 0.001) as well as bleeding complications (31.8% vs. 18.3%, p < 0.001), surgical complications requiring reoperation (28.3% vs. 15.4%, p < 0.001), and sepsis (11.4% vs. 5.2%, p < 0.001). In multivariate analysis of predictors of renal failure, transplantation during the modern era, increasing age and increasing number of comorbid conditions were associated with an increased risk of renal failure (Table 4). Female gender, diabetes, obesity, hypertension, smoking, chronic kidney disease, and ischemic heart disease were protective. In comparing the three acute circulatory support modalities, pre-transplant ECMO (RR 1.0972, p = 0.02) and IABP (RR 1.1045, p < 0.001) placement conferred a statistically significant risk of renal failure. PVAD placement conferred a similar risk by odds ratio but was likely underpowered to show effect (RR 1.1089, p = 0.292).

The frequency of strokes in both groups increased over time in general, with the rate of stroke increasing from 0.5% to 7% in those requiring acute circulatory support, and from 1.6% to 3% in those without acute circulatory support (Table 2). In multivariate analysis, female gender and increasing number of comorbid conditions were associated with increased risk of stroke (Table 5). Conversely, increasing age, diabetes, obesity, hypertension, and chronic kidney disease were associated with a decreased risk of stroke. The modern era was associated with increased risk of stroke (RR 1.008, p = 0.056), however the effect was not statistically significant. There was no independent risk based on the type of acute circulatory support received.

**Discussion**

In this cohort of heart transplant patients identified in the National Inpatient Sample, in-hospital mortality decreased over time, and this trend in decreasing mortality persisted despite an increasingly elderly patient population, patients with more comorbidities, and increased use of acute circulatory support prior to heart transplantation.

This trend held true for both patients who received acute circulatory support before transplant and patients who did not. In fact, the most significant improvement in mortality was in the cohort who received circulatory support, with a 63% reduction in mortality during the hospitalization. Although not statistically significant, in the modern era there was a modest trend towards decreased mortality in the acute circulatory support cohort.

During this time period, the use of acute circulatory support prior to transplant increased, more than doubling from 2002 to 2014. While mortality rates became similar between the two cohorts, the rate of post-transplant complications remained significantly higher in those patients who received acute circulatory support prior to transplantation, and the rates of important complications such as stroke and renal failure increased over time.

The question of when and whether patients are "too sick" for heart transplantation is not explicitly described in the UNOS heart allocation proposal. Based on the proposed changes, there could be an acceleration of the number of patients who receive acute circulatory support prior to transplant. This could shift the overall transplant candidate population towards sicker patients prior to transplantation and lead to longer wait times for other patients on the transplant list, while also increasing post-transplant morbidity and mortality, and overall cost to the healthcare system.

The question of when patients are “too sick” also depends on the state of the art in transplantation, and has changed over time. If, as we found, the in-hospital mortality rates of transplant patients who require acute circulatory support converges with the mortality rate of patients who do not require acute circulatory support, advances in circulatory support might allow more patients to overcome critical cardiac failure and become transplant candidates.

Yet even if mortality remains similar between patients who receive acute circulatory support prior to transplant and those who do not, our finding of increased complication rates in patients receiving acute circulatory support gives one pause. As the field of mechanical circulatory support advances, the focus on improving outcomes needs to broaden beyond mortality to other acute complications, which negatively impact quality of life and cost. Thus we need ways to reduce complication rates, whether by improved management of these patients or improved technology. The new UNOS allocation scheme does suggest the use of serial hemodynamic evaluations to determine whether a patient can remain a candidate for cardiac transplantation while on acute circulatory support, and these and other measures could further refine our evaluation of patients’ candidacy while on the waitlist, potentially improving morbidity rates post transplantation in patients receiving acute circulatory support.

There are a few limitations to our study based on the design of the NIS. We are not able to explicitly determine to priority of the patients in our cohort nor the time on the transplant waiting list. Given the use of acute circulatory support, we can assume that patients were status 1A prior to transplantation. As a retrospective cohort, we are not able to ascertain why acute circulatory support was initiated and the discussion around which modality of circulatory support was chosen. The lack of hemodynamic measures in the NIS means we cannot assess changes in patient’s clinical condition prior to transplant. Additionally, the NIS also only lists same hospitalization complications and mortality and does not have information of post-hospital follow-up. Given the increased length of stay and the high rates of complications while hospitalized, including increased acute renal failure, liver failure, respiratory failure, cardiac complications, and bleeding complications, it is likely these patients would have a more challenging post-hospitalization course.

We also paradoxically found that pre-morbid conditions such as diabetes, hypertension, and chronic kidney disease were protective against post-transplant mortality and renal failure in multivariate analysis. These findings likely represent contemporary changes in management and the limitations of the dataset, which does not contain hemodynamic data or contemporaneous data on end-organ function at time of implant. In the modern era, hemodialysis was more common post-transplant regardless of whether patients who received pre-transplant acute circulatory support, potentially suggesting changing availability and threshold to initiate hemodialysis over time rather than an increasing prevalence of kidney failure in transplant patients over time. While the number of comorbid conditions was associated with worse outcomes, certain pre-existing diagnoses were protective in the model. This could be a result of variability in the coding ICD9 codes. Going forward, it would be important to obtain hemodynamic data to better risk-stratify patients for better outcomes after transplantation.

In conclusion, we found that overall morbidity and mortality after heart transplantation was increased in patients who received acute circulatory support, and though mortality rates were not significantly different in more recent years, the rates of complications increased over time in patients receiving acute circulatory support. If the use of acute circulatory support prior to heart transplantation continues to increase over time, further refinement of patient management and selection in those patients is required in order to improve outcomes.

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**Figure and Table Captions**

Figure 1: Time trend of mortality rate by presence of acute circulatory support prior to transplantation

Figure 2: Time trend of renal failure rate by presence of acute circulatory support prior to transplantation

Figure 3: Time trend of stroke rate by presence of acute circulatory support prior to transplantation

Table 1: Baseline characteristics of patients who underwent cardiac transplant from 1998 to 2011, stratified by use of acute mechanical support prior to transplantation

Table 2: Mortality, length of stay, complications in patients who underwent cardiac transplant from 1998 to 2014, by transplantation era

Table 3: Multivariate analysis of risk factors for mortality

Table 4: Multivariate analysis of risk factors for renal failure

Table 5: Multivariate analysis of risk factors for stroke

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Supplement A: ICD-9 codes of comorbid conditions

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| **Comorbidities** | **ICD-9 codes** |
| Diabetes Mellitus | 250.00-250.93, 249.00-249.91 |
| Ischemic Heart Disease | 410.0-410.9, 411.0-411.8, 412, 413.0-413.9, 414.0-414.9, V45.8, V45.82 |
| Hypertension | 401.0-401.9, 402.0, 402.00-402.91, 403.0, 403.00-403.91, 404.0 404.00-404.93, 405.0, 405.01-405.91, 437.2 |
| Pre-existing renal dysfunction | 585.3, 585.4, 585.5, 585.6, 585.9, V42.0, V45.1, V45.11, V45.12, V56.0, V56.1, V56.2, V56.3, V56.31, V56.32, V56.8 |
| Peripheral vascular disease | 440.0-440.9, 443.1, 443.8,443.81, 443.82, 443.89, 443.9, 447.1, V43.4 |
| History of smoking | 305.1, V15.82 |
| BMI > 30 kg/m2 | 278.0, 278.01, 278.02 |

Supplement B: ICD-9 codes of complications

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| **Complication** | **ICD-9 codes** |
| Post Transplant Circulatory Support1 | 37.61, 37.68, 39.61 |
| Acute Renal Failure | 584.5, 584.6, 584.7, 584.8, 584.9 |
| Acute Liver Failure | 570 |
| Acute Respiratory Failure | 518.81 |
| Cardiac Complications | 997.1, 429.4, 432.0, 432.3, 426.0 |
| Sepsis | 995.91, 995.92 |
| Stroke | 433.0-433.9, 434.0-434.9 |
| Surgical Complication Requiring Reoperation | 340.3, 341, 347.9, 380.3 |
| Bleeding Complication | 530.21 ,456.0 ,530.7 ,530.82 ,578.0 ,578.1 ,578.9 ,456.20 ,531.00 ,531.01 ,531.20 ,531.21 ,531.40 ,531.41 ,531.60 ,531.61 ,532.00 ,532.01 ,532.20 ,532.21 ,532.40 ,532.41 ,532.60 ,532.61 ,533.00 ,533.01 ,533.20 ,533.21 ,533.40 ,533.41 ,533.60 ,533.61 ,534.00 ,534.01 ,534.20 ,534.21 ,534.40 ,534.41 ,534.60 ,534.61 ,535.01 ,535.11 ,535.21 ,535.31 ,535.41 ,535.51 ,535.61 ,535.71 ,537.83 ,562.02 ,562.03 ,562.12 ,562.13 ,569.3 ,569.85 ,537.84 ,569.86 |
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1Day of procedure past day of transplant