Impact of Donor Pre-Procurement Cardiac Arrest (PPCA) on Clinical Outcomes in Liver Transplantation

Background: Transplantation of liver grafts from deceased donors who experienced cardiac arrest prior to liver procurement is now common. This single-center study analyzed the impact of pre-donation arrest time on clinical outcomes in liver transplantation.

Material/Methods: Records of all orthotopic liver transplants performed at a single center over a 15-year period were reviewed. Donor records were reviewed and total arrest time was calculated as cumulative minutes. Post-transplant liver graft function was assessed using laboratory values. Graft survival was assessed with Cox regression analysis.

Results: Records for 1830 deceased donor transplants were reviewed, and 521 donors experienced pre-procurement cardiac arrest (28%). Median arrest time was 21 min (mean 25 min, range 1–120 min). After transplant, the peak alanine aminotransferase and bilirubin levels for liver grafts from donors with arrest were lower compared to those for donors without arrest (p<0.001). Early allograft dysfunction occurred in 25% (arrest) and 28% (no arrest) of patients (p=0.22). There were no differences in risk of early graft loss (3% vs. 3%, p=0.84), length of hospital stay (10 vs. 10 days, p=0.76), and 1-year graft survival (89% vs. 89%, p=0.94). Cox regression analysis comparing 4 groups (no arrest, <20 min, 20–40 min, and >40 min arrest) demonstrated no statistically significant difference in survival at 10 years. Subgroup analysis of 93 donation after cardiac death grafts showed no significant difference for these same outcomes.

Conclusions: These results support the use of select deceased liver donors who experience pre-donation cardiac arrest. Pre-donation arrest may be associated with less early allograft dysfunction, but had no impact on long-term clinical outcomes. The results for donation after cardiac death donors were similar.

MeSH Keywords: Donor Selection • Liver Transplantation • Outcome Assessment (Health Care)

Abbreviations: PPCA – pre-procurement cardiac arrest; DBD – donation after brain death; DCD – donation after cardiac arrest; UNOS – United Network for Organ Sharing; AST – aspartate aminotransferase; ALT – alanine aminotransferase; SPSS – Statistical Package for the Social Sciences

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Background

The use of extended criteria organ donors is now common in liver transplantation [1,2]. Extended criteria for liver donation have never been defined because of the complexity of matching donors and recipients, and the number of interacting factors considered in the matching process. One factor that has not been fully studied is donor pre-procurement cardiac arrest (PPCA). Historically, some centers considered any uncontrolled donor PPCA as an exclusionary criterion for liver donation. Now, use of these donors is routine [3,4]. Previous clinical investigation of PPCA assessed the presence of ischemic preconditioning induced by the hypotension associated with the arrest event [5–7]. Findings from these studies suggested similar clinical results for grafts from donors with PPCA. Subsequent studies supported these findings, although the study populations were small and did not represent a wide range of arrest times [8–10].

Another line of investigation in this field involves electively inducing short periods of ischemia under controlled settings at the time of procurement in donors previously declared brain dead. In these reports, ischemia is induced by clamping the portal vein and hepatic artery supplying the entire liver, or portion of liver being procured, for 5–10 min [11–18]. A meta-analysis of these small studies concluded that controlled ischemic preconditioning resulted in reduced liver injury following transplant and a large (but not statistically significant) reduction in 1-year mortality [19]. The present study was designed to analyze the clinical impact of uncontrolled PPCA on early and late post-transplant outcomes in a large population of liver transplant patients. Outcomes included early liver allograft function, and both early and late liver graft survival. Analysis included stratification by calculated length of arrest time. Data are included for both donation after brain death (DBD) and donation after cardiac death (DCD) cases.

Material and Methods

The electronic medical records for all orthotopic liver transplants performed at a single large U.S. center between 2001 and 2015 were reviewed (n=1830). Data were extracted from the transplant recipient registry at our center, electronic medical records, and donor information from the Indiana Donor Network (IDN). All liver transplant recipients were included as long as they were age 18 years and older and received a deceased donor allograft. Liver graft and post-transplant patient survival data were collected from the database, which is updated on a regular basis. This database also includes laboratory values measured for organ donors and in the first year post-transplant for all transplant recipients.

Donor PPCA time was calculated as the total of all documented arrest times prior to organ donation. This arrest time may have occurred in the field prior to hospital admission, or post-admission prior to stabilization for organ donation. The calculation of arrest time for patients found in asystole on first presentation started at the time cardiopulmonary resuscitation was initiated. Regarding resuscitation efforts, information about location, personnel, and quality of care could not be reliably characterized from the available records. Therefore, resuscitation administered by by-standers, pre-hospital personnel, and hospital staff were considered equivalent for this study. All organ donors recovered from the arrest event and were stabilized prior to proceeding with organ procurement. Surgeon criteria for accepting and implanting individual liver grafts were not documented. Donor cause of death was categorized based upon a review of the donor records. Exclusionary criteria for deceased donor liver grafts are multifactorial, but generally include total steatosis greater than 50%, necrosis greater than 20%, severe vascular disease of the hepatic artery, non-repairable trauma, certain donor neoplasms, and warm ischemia time greater than 30 min for donation after cardiac death. Of course, these factors depend both on donor and recipient age and other co-morbidities. The number of liver grafts rejected was not recorded, so the percentage of grafts transplanted could not be calculated.

All liver transplant recipients at this center were listed for transplant according to standard criteria. For patients receiving re-transplant within 30 days of the first transplant, the analysis included only data for the original transplant. Post-transplant liver graft function was assessed by the combination of liver function enzymes, international normalized ratio (INR), and early graft loss, as suggested by Olthoff et al. [20]. Specifically, early allograft dysfunction is defined as aspartate or alanine aminotransferase (AST, ALT) higher than 2000 u/L in the first 7 days post-transplant, day 7 total bilirubin level greater than 9.9, or day 7 international normalized ratio greater than 1.5. For the present study, serum ALT levels were used as a marker of liver injury because of its greater liver specificity when compared to AST [21]. Some researchers have suggested that serum ALT level on post-transplant day 3 is a better marker for liver ischemia injury than peak post-transplant ALT [22,23]. Both of these levels are reported in the present study. Any graft loss that occurred within 7 days of transplant was recorded as primary non-function as long as there was no clearly identifiable etiology. All liver transplant recipients were included in the final analysis of data, without any exclusions.

The protocol for induction and maintenance immunosuppression at our center has been described. Induction included rabbit antithymocyte globulin and steroids, followed by maintenance with Prograf monotherapy [24]. Deceased donor liver allografts were procured using previously described techniques [25]. Our
center uses a large percentage of extended criteria donors, which has been described [1,2]. Our protocol for DCD procurements has also been described [26]. Our center primarily uses a piggyback hepatectomy technique, which was used in 95% of cases, with no use of portal-caval shunt [27]. Venovenous bypass was not used in any case. Use of an antifibrinolytic agent (aprotinin or aminocaproic acid) is routine [28].

Standard statistical testing was utilized for continuous and categorical variables, as indicated. A Cox proportional hazards model was constructed for survival analysis. Co-variates were left in the final model if the p-value was ≤0.10. Statistical testing was performed on SPSS software (IBM SPSS Statistics Version 24, IBM Corporation, Armonk, New York, USA). Use of center data for retrospective analysis has been reviewed and approved by the Institutional Review Board (Indiana University School of Medicine, study number 1011003619R005). The study protocol for this research conformed to the Declaration of Helsinki.

Results

There were 1830 liver transplants included in this analysis: 1737 were DBD and 93 were DCD. There were 521 cases (28%) in which the liver donor experienced PPCA (mean 25 min, range 1–120 min). Among 1737 DBD cases, 475 had PPCA (27%). This is less than among DCD cases, in which 46 of 93 had PPCA (49%). Among the 521 donors with PPCA, the arrest time was less than 20 min for 205 (39%), 20–39 min for 204 (39%), and 40 min or more for 112 (22%). Reviewing the demographics of the organ donors, the PPCA donors were tended to be younger, non-white, and died primarily from hypoxic injury (generally related to drug overdose). There was no difference in sex or regional origin of the graft. Recipients were statistically similar, though the recipients of grafts from the PPCA donors were slightly older. Cold and warm ischemia times were both statistically lower for the PPCA grafts (Table 1).

Analysis of DCD cases demonstrates an expected increasing peak pre-procurement ALT level with increasing PPCA time (p<0.001). The peak donor bilirubin levels did not differ. Post-transplant, the PPCA grafts had a lower peak and post-operative day 3 ALT level (p=0.01, p=0.15). They also had a lower peak total bilirubin level (p=0.01). When combining the 3 PPCA groups and comparing them to the non-PPCA group, the incidence of early allograft dysfunction was lower for PPCA than for non-PPCA grafts (25% vs. 28%, p=0.22). There was no difference in hospital length of stay or in graft survival at 7 and 30 days post-transplant. One-year graft survival was also similar among all groups (Table 2).

Among the 93 DCD cases, there was a higher peak ALT level prior to donation, but not total bilirubin level, for PPCA patients (p=0.34, p=0.27). Post-transplant labs show no difference in peak and post-operative day 3 ALT, or in peak total bilirubin. There was no difference between the groups in early allograft dysfunction or length of hospital stay. There was a higher rate of early graft loss for the 2 PPCA groups (20–39 and 40 or more min) (5% and 10%, p=0.16), and a lower 1-year graft survival for the 10 donors with more than 40-min PPCA time (70%, p=0.61), but none of these outcomes reached statistical significance (Table 3).

Cox regression analysis was used to assess 10-year graft survival. The median death-censored follow-up time was 66 months. For DBD, the grafts from donors with no PPCA had slightly higher survival compared to all groups with PPCA, but this did not reach statistical significance (Figure 1A). For DCD, there was a markedly higher survival for donor grafts with no PPCA when compared to all PPCA patients grouped together; however, this difference was not statistically significant given the small numbers in this subgroup (Figure 1B).

Discussion

This study supports previous research suggesting that post-transplant ischemia and reperfusion injury may be ameliorated by a pre-procurement ischemic event (ischemic preconditioning). In this analysis of 1737 non-DCD liver donors, post-transplant ALT and total bilirubin levels were lower for all lengths of PPCA compared to liver grafts with no PPCA, but this did not affect clinical outcomes, including early allograft dysfunction, length of hospital stay, and early and late graft survival. The results were less clear for the subset of DCD transplants, although the smaller number in this group prevented a sufficiently-powered analysis. Use of liver grafts from carefully selected donors with PPCA appears to be a safe and appropriate means of expanding the liver donor pool.

In this cohort there were 112 donors with over 40 min of documented arrest time, and this group had outcomes better than, or similar to, donors who had no PPCA. In assessing these donors, care must be taken to account for a variety of other factors, including donor age, graft steatosis, predicted cold and warm ischemia time, and recipient age, as well as model for end-stage liver disease score and biopsy results. Clearly, not all donors who have recovered from cardiac arrest will be acceptable donors, but an important percentage should be pursued. On-site frozen-section biopsy is an important tool for use in assessing these grafts [29]. At our center, we transplant donor grafts with prolonged ischemia and elevated ALT levels as long as the biopsy demonstrates ischemic injury (necrosis) of less than 20%. An important clinical marker for liver function in the organ donor is the donor pH, as the liver has an important and active role in modulating body pH, along with the lungs...
and kidneys. A patient for whom the pH cannot be corrected and with no clear source for acidosis identified may have extensive hepatic necrosis or poor physiologic function that is not fully represented by biochemical measures of liver injury.

Subgroup analysis of DCD liver grafts from PPCA donors supports previous research published by the group from Birmingham (UK), which analyzed 26 PPCA-DCD grafts [10]. Of 93 DCD liver grafts in our study, 46 had PPCA (49%). Early graft function in this group was equivalent to donors with no PPCA. Donors with PPCA time up to 40 min experienced similar 1-year survival compared to non-PPCA donors. The PPCA-DCD group with more than 40 min of arrest time comprised only 10 patients. Of these, 1 graft was lost in the first week and 2 more were lost within the first year. These small numbers fail to adequately inform decision-making for this group. Alternatively, the fact that 7 of 10 DCD donors with PPCA time over 40 min achieved normal function at 1 year.

Table 1. Demographic data for 1830 liver transplant patients with comparison of patients in which the deceased donor did or did not experience out-of-hospital cardiac arrest prior to organ donation.

|                         | Overall | No donor out-of-hospital cardiac arrest | Donor out-of-hospital cardiac arrest time | p-Value |
|-------------------------|---------|------------------------------------------|-------------------------------------------|---------|
|                         |         | <20 minutes                               | 20–40 minutes                              | >40 minutes |   |
| Overall                 | 1830    | 1309 (72%)                                | 205 (11%)                                 | 204 (11%) | 112 (6%) |
| Donor                   |         |                                          |                                           |           |           |
| Gender: Male            | 58%     | 58%                                      | 57%                                       | 56%       | 55%       | 0.93     |
| Race: White             | 82%     | 90%                                      | 86%                                       | 85%       | 85%       | 0.03     |
| Age (years)             |         |                                          |                                           |           |           |           |
| Median (range)          | 41      | 42                                       | 36                                        | 38        | 40        | <0.001   |
| Donor cause of death    |         |                                          |                                           |           |           |           |
| Stroke                  | 39%     | 48%                                      | 19%                                       | 13%       | 15%       | <0.001   |
| Trauma                  | 36%     | 41%                                      | 39%                                       | 11%       | 11%       |           |
| Anoxia/other            | 25%     | 12%                                      | 42%                                       | 76%       | 75%       | <0.001   |
|                         | 5%      | 2%                                       | 2%                                        | 9%        | 9%        |           |
| Regional origin of graft|         |                                          |                                           |           |           |           |
| Local                   | 70%     | 71%                                      | 68%                                       | 66%       | 62%       | 0.22     |
| Recipient               |         |                                          |                                           |           |           |           |
| MELD (median)           | 18      | 18                                       | 20                                        | 19        | 20        | 0.21     |
| Gender: Male            | 68%     | 68%                                      | 69%                                       | 70%       | 67%       | 0.90     |
| Race: White             | 89%     | 89%                                      | 86%                                       | 89%       | 88%       | 0.13     |
| Age (years)             |         |                                          |                                           |           |           |           |
| Median                  | 55      | 54                                       | 57                                        | 56        | 57        | 0.03     |
| Body mass index         |         |                                          |                                           |           |           |           |
| Median                  | 28.1    | 28.1                                     | 28.9                                      | 29.0      | 27.7      | 0.76     |
| Retransplant            | 4%      | 4%                                       | 3%                                        | 4%        | 4%        | 0.22     |
| Transplant data         |         |                                          |                                           |           |           |           |
| Total ischemia time (median) |       |                                          |                                           |           |           |           |
| Cold (hours)            | 6.2     | 6.4                                      | 6.0                                       | 6.0       | 6.0       | <0.001   |
| Warm (minutes)          | 24      | 25                                       | 22                                        | 21        | 21        | <0.001   |
Table 2. For donation after brain death, a comparison of graft laboratory values and post-transplant function by donor pre-
procurement out-of-hospital cardiac arrest time.

| Donor cardiopulmonary arrest time | Overall | No donor cardiopulmonary arrest | <20 minutes | 20–39 minutes | ≥40 minutes | p-Value |
|-----------------------------------|---------|---------------------------------|-------------|--------------|-------------|--------|
| Number                            | 1737    | 1262 (73%)                      | 188 (11%)   | 185 (11%)    | 102 (6%)   |        |
| Donor laboratory value (median)    |         |                                 |             |              |             |        |
| Peak alanine aminotransferase      | 47      | 38                              | 86          | 142          | 211         | <0.001 |
| Peak total bilirubin               | 0.8     | 0.8                             | 0.9         | 0.8          | 0.7         | 0.14   |
| Recipient laboratory values (median) |         |                                 |             |              |             |        |
| Peak alanine aminotransferase      | 482     | 503                             | 412         | 388          | 395         | 0.01   |
| Day 3 alanine aminotransferase     | 248     | 283                             | 201         | 191          | 215         | 0.15   |
| Peak total bilirubin               | 5.0     | 5.3                             | 4.6         | 4.3          | 4.1         | 0.01   |
| Early allograft dysfunction*       | 27%     | 28%                             | 25%         | 27%          | 22%         | 0.45   |
| Length of hospital stay (days, median) | 10      | 10                              | 10          | 10           | 10          | 0.70   |
| 7-day graft loss                   | 3%      | 3%                              | 2%          | 2%           | 3%          | 0.82   |
| 30-day graft loss                  | 5%      | 6%                              | 5%          | 3%           | 6%          | 0.42   |
| 1-year graft survival              | 88%     | 88%                             | 86%         | 92%          | 88%         | 0.31   |

* Early allograft dysfunction defined as AST or ALT greater than 1000u/L in first 7 days, day 7 total bilirubin ≥10.0, or day 7 INR ≥1.6.

Table 3. For donation after cardiac death, a comparison of graft laboratory values and post-transplant function by donor pre-
procurement out-of-hospital cardiac arrest time.

| Donor cardiopulmonary arrest time | Overall | No donor cardiopulmonary arrest | <20 minutes | 20–39 minutes | ≥40 minutes | p-Value |
|-----------------------------------|---------|---------------------------------|-------------|--------------|-------------|--------|
| Number                            | 93      | 47 (51%)                        | 17 (18%)    | 19 (20%)     | 10 (11%)    |        |
| Donor laboratory value (median)    |         |                                 |             |              |             |        |
| Peak alanine aminotransferase      | 102     | 65                              | 131         | 121          | 195         | 0.34   |
| Peak total bilirubin               | 0.8     | 0.8                             | 0.6         | 0.8          | 1.2         | 0.27   |
| Recipient laboratory values (median) |         |                                 |             |              |             |        |
| Peak alanine aminotransferase      | 972     | 1114                            | 1151        | 677          | 1087        | 0.96   |
| Day 3 alanine aminotransferase     | 362     | 418                             | 361         | 233          | 538         | 0.66   |
| Peak total bilirubin               | 6.6     | 7.3                             | 7.6         | 6.4          | 4.6         | 0.48   |
| Early allograft dysfunction*       | 51%     | 55%                             | 53%         | 37%          | 50%         | 0.59   |
| Length of hospital stay (days, median) | 13      | 13                              | 13          | 14           | 9           | 0.68   |
| 7-day graft loss                   | 2%      | 0%                              | 0%          | 5%           | 10%         | 0.16   |
| 30-day graft loss                  | 2%      | 0%                              | 0%          | 5%           | 10%         | 0.16   |
| 1-year graft survival              | 84%     | 87%                             | 82%         | 84%          | 70%         | 0.61   |

* Early allograft dysfunction defined as AST or ALT greater than 1000u/L in first 7 days, day 7 total bilirubin ≥10.0, or day 7 INR ≥1.6.
(and 50% survival at 10 years) is an important indication of the value of these donors.

The limitations of this study are similar to those seen in other studies of this type. Donor liver grafts with PPCA that were transplanted were likely different from non-PPCA donors. In the demographic assessment, the PPCA donors were younger and had slightly less cold and warm ischemia time, which may have affected outcomes. Steatosis was not assessed in this analysis, but high-risk steatotic grafts with PPCA may have been categorically excluded. Unfortunately, in this cohort, the denominator (number of PPCA grafts rejected for transplant) was not available. In other words, grafts with PPCA likely had to be perfect in other all other ways to be used for transplant. Such an unknown factor would bias results. Also, in this analysis, PPCA could not be confirmed by objective testing. Pre-hospital care providers may have limited skills in detecting low blood pressure, and may inappropriately initiate chest compressions or the chest compressions may be inadequate to circulate blood sufficiently. An elevation of serum ALT after successful resuscitation acts as a marker for true ischemic injury to the liver, and also correlates with the severity of injury. Our group has previously shown a correlation between elevated liver function tests and clinical outcomes, with elevations up to 2000 u/L having similar long-term outcomes [30]. Such an elevation of serum ALT may be a better marker for ischemic preconditioning compared to minutes of cardiac arrest time.

**Conclusions**

This study provides additional information in the ongoing expansion of the acceptable pool of liver donors. Further research will focus on identifying donors with PPCA who were rejected for transplant, to determine the ability to use those organs as well. Also, analysis of the reperfusion biopsies from donors with PPCA may lead to identification of signs of early injury that are reversible. Similar research in this population can easily be extended to other solid organs.

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**Conflict of interest**

Dr. Mangus is on the speaker’s bureau for F. Kohler-Chemie for which he receives travel support and honoraria. The other authors have no conflict of interest to report.
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