Abstract

There are increasing numbers of patients on liver transplant waiting lists, and there is a continuing organ shortage crisis. Therefore, more centers and organ procurement organizations are developing protocols for donation after cardiac death. However, the effect of donation after cardiac death allografts on overall patient survival remains controversial, with some centers reporting equivalent patient posttransplant survival but many others indicating increased rates of complications, retransplant, utilization of resources, and death. Several potential risk factors that predict graft loss and recipient complications have been identified. To improve patient outcomes and reduce dropouts, experimental strategies that target both donors and recipients at various phases of the transplant process have focused on attenuating ischemia-reperfusion injury and have achieved encouraging results. In the present article, our goal is to provide an overview of the current status of, and recent advances in, liver transplant from donation after cardiac death, to better understand the risks and potential benefits of donation after cardiac death liver transplant.

Key words: End-stage liver disease, Donation after cardiac death, Complication

Introduction

Liver transplant remains the standard treatment for patients with end-stage liver disease. During recent years, there have been major improvements in organ transplant outcomes because of improved surgical techniques, organ preservation, immunosuppression, and antimicrobial therapies. This success has increased the demand for organ transplant and disparity between the number of patients awaiting transplant and number of organs available. As of November 6, 2014, there were 124,013 people who needed a lifesaving organ transplant (total number of waiting list candidates), including 79,475 people who were active waiting list candidates. However, just 19,426 transplants were performed this year. This discrepancy between supply and demand has resulted in marked morbidity and mortality for patients awaiting liver transplant, and has inspired the search for alternatives to offer liver transplant to more patients.

During the past decade, methods to expand the donor organ pool have been developed, including living-donor liver transplant, split-liver transplant, and the use of expanded criteria for selecting donors, including the use of donation after cardiac death (DCD) donors. Donation after brain death (DBD) is the predominant source of organs for transplant, but brain death accounts for only a small percentage of all-cause mortality, whereas cardiovascular death is a leading cause of mortality. Therefore, DCD represents an attractive strategy to remedy organ shortages and decrease transplant waiting list mortality. Indeed, the number of DCD liver transplants has increased rapidly during the past decade. In the United Kingdom, DCD activity contributed to 35% deceased-donor transplants in 2009 and 2010. The United Network for Organ Sharing (UNOS) data show similar trends, with...
DCD accounting for 10% overall transplant activity. In some European countries, DCD currently represents 20% of the liver donor pool (Figure 1).11

![Liver Transplant From Donation After Cardiac Death (DCD) Donors in Different European Countries in 2009](image)

Figure 1. Liver Transplant From Donation After Cardiac Death (DCD) Donors in Different European Countries in 2009

Due to the increased use of allografts from DCD donors, it is important to evaluate DCD liver transplants and the effect of recipient and donor factors on graft survival. In contrast with DBD organs, DCD livers are obtained from non-heart-beating donors, resulting in a requisite time interval without perfusion compounded by a variable period of hypoxemia following excision. The delay between circulatory arrest and organ preservation also can cause acute ischemic injury in DCD organs, which is likely responsible for the typical complications of DCD liver transplant. However, the effect of DCD allografts on overall patient survival has been controversial, with some centers reporting equivalent patient posttransplant survival but many others demonstrating increased rates of complications, retransplant, and death.12,13 Additionally, the clinical effect of DCD liver transplant continues to be debated.

It is now well established that DCD transplant is associated with markedly greater posttransplant costs compared with transplants with DBD organs. Furthermore, to improve patient outcomes and reduce dropouts, research continues about how best to increase the value of DCD grafts. Most of this work has focused on organ preservation using machine-assisted perfusion. Additional techniques have involved pharmacologic manipulation of the donor, graft, and recipient. In the present article, our aim is to analyze the current literature about outcomes and complications of DCD liver transplant and to investigate interventional and experimental strategies to overcome issues associated with DCD liver transplant.

Current Practice and Outcome of Donation After Cardiac Death Liver Transplant

To assess the outcomes of patients receiving DCD liver allografts, we analyzed the available previously published literature, including several single-center studies (Table 1)6,12-19 and large studies (Table 2)7,20-25 of national databases, to compare the outcomes of recipients who received DCD versus DBD donor livers and to better understand the risk factors for graft survival, loss, and failure.

Single-center studies of donation after cardiac death liver transplants

We observed that single-center studies have documented large differences in survival between DCD and DBD allografts (Table 1), with some studies reporting that patient and graft survival rates were significantly lower in the DCD compared with DBD group. Foley and coworkers14 reviewed DCD procedures at the University of Wisconsin and found decreased 1- and 3-year patient survival (DCD, 80% and 68%; DBD, 91% and 84%; P = .002) and graft survival rates (DCD, 67% and 56%; DBD, 86% and 80%; P = .0001) with DCD than DBD recipients. Subsequent to this study, the same group evaluated the long-term outcomes of liver transplant from DCD donors in 2011 and had similar conclusions,13 describing patient survival as significantly lower in the DCD than DBD group at 1, 5, 10, and 15 years (DCD: 84%, 68%, 54%, and 54%; DBD: 91%, 81%, 67%, and 58%; P < .01). Graft survival was significantly lower in the DCD than DBD group at 1, 5, 10, and 15 years (DCD: 69%, 56%, 43%, and 43%; DBD: 86%, 76%, 60%, and 51%; P < .001). The decreased patient and graft survival rates following transplant from DCD donors were confirmed by
Pine and associates.\textsuperscript{15} However, other reports have yielded inconsistent results; de Vera and coworkers\textsuperscript{16} and Skaro and coworkers\textsuperscript{17} reported that patient survival was similar for DCD and DBD recipients but that graft survival was significantly lower in DCD than DBD recipients. In addition, relevant to this investigation, several single-institution studies have failed to identify differences in graft and patient survival rates between DCD and DBD livers. Dubbeld and associates\textsuperscript{18} reported that 1- and 3-year patient survival rates were similar for DCD (85\% and 80\%) and DBD (86.3\% and 80.8\%) transplants ($P = .763$), as were graft survival rates (DCD: 74\% and 68\%; DBD: 80.4\% and 74.5\%; $P < .212$). In agreement with this finding, the experimental data of Grewal and coworkers\textsuperscript{19} and Taner and associates\textsuperscript{12} also indicated that the 1-, 3-, and 5-year patient survival and graft survival rates were not significantly different between the DCD and DBD groups. It seems plausible that these inconsistent results in the single-center analyses were due to limitations related to sample size. It also is possible that some centers used techniques and strategies that resulted in better DCD liver transplant outcomes. Therefore, much can be learned from the techniques used at these centers to improve outcomes. However, it also is true that these studies are difficult to generalize because individualized center practices and allocation-related issues can affect donor selection. Taking the study by Taner and associates\textsuperscript{12} as an example, the comparable results that they observed for DCD and DBD livers resulted from the application of stringent acceptance criteria for DCD liver transplant. Accordingly, the DCD donors were younger (age, 40 vs 47 y), had shorter cold ischemia time (CIT) (6 vs 7 h), were less likely to be shared (44\% vs 78\%), and more often had died from trauma (24\% vs 55\%). Supporting this explanation, the DCD donors who were aged $\leq$ 45 years, had warm ischemia time (WIT) $\leq$ 15 min, and had CIT $\leq$ 10 h yielded livers that performed similarly to the livers of their DBD counterparts, according to national data.\textsuperscript{20}

### Table 1. Single-Center Experiences and Outcomes Using Allografts from Donation After Brain Death or Donation After Cardiac Death

<table>
<thead>
<tr>
<th>Study</th>
<th>Liver Transplant (no.)</th>
<th>1 y (%)</th>
<th>3 y (%)</th>
<th>5 y (%)</th>
<th>$P$</th>
<th>1 y (%)</th>
<th>3 y (%)</th>
<th>5 y (%)</th>
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<td>553</td>
<td>80</td>
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<td>68</td>
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<td>86</td>
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<td>78.7</td>
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<td>100</td>
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</tr>
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<td>1328</td>
<td>91.5</td>
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<td>77.2</td>
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</tr>
<tr>
<td>de Vera et al.\textsuperscript{16}</td>
<td>141</td>
<td>282</td>
<td>79</td>
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<td>92.6</td>
<td>89.8</td>
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<td>76.6</td>
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<tr>
<td>Foley et al.\textsuperscript{13}</td>
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<td>74.0</td>
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<td>61.3</td>
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<td>Skaro et al.\textsuperscript{17}</td>
<td>32</td>
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<td>74.0</td>
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<td>80.7</td>
<td>.17</td>
<td>61.3</td>
<td>85.2</td>
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</table>

Abbreviations: DBD, donation after brain death; DCD, donation after cardiac death; NS, not significant

### Table 2. National Data Analyses and Outcomes Using Allografts from Donation After Brain Death or Donation After Cardiac Death

<table>
<thead>
<tr>
<th>Study</th>
<th>Liver Transplant (no.)</th>
<th>1 y (%)</th>
<th>3 y (%)</th>
<th>5 y (%)</th>
<th>$P$</th>
<th>1 y (%)</th>
<th>3 y (%)</th>
<th>5 y (%)</th>
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<td>33111</td>
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<td>Merion et al.\textsuperscript{7}</td>
<td>472</td>
<td>23598</td>
<td>70.1</td>
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<td>&lt; .001</td>
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<td>Lee et al.\textsuperscript{20}</td>
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<td>43734</td>
<td>82.3</td>
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<td>Selck et al.\textsuperscript{24}</td>
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<td>21089</td>
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<td>&lt; .001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jay et al.\textsuperscript{25}</td>
<td>1113</td>
<td>42254</td>
<td>82</td>
<td>86</td>
<td>71</td>
<td>77</td>
<td>&lt; .001</td>
<td></td>
<td></td>
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<td>Harring et al.\textsuperscript{22}</td>
<td>2351</td>
<td>85148</td>
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<td>74.8</td>
<td>78.3</td>
<td>68.9</td>
<td>72.5</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

Abbreviations: DBD, donation after brain death; DCD, donation after cardiac death; NS, not significant
Large studies based on the Scientific Registry of Transplant Recipients and United Network for Organ Sharing/Organ Procurement and Transplantation Network databases

As the number of DCD patients has increased, the outcomes of liver transplant patients from DCD donors have differed from those described in single-center reports. As indicated in Table 2, all 7 large studies, using data from the Scientific Registry of Transplant Recipients (SRTR) and UNOS/Organ Procurement and Transplantation Network (OPTN) databases, reported that patient and graft survival from DCD donors were significantly inferior to those of DBD donors. Merion and coworkers7 studied 472 DCD patients from the UNOS database between 2000 and 2004 and found that DCD livers had an adjusted odds ratio for graft failure of 1.85. Similarly, Mateo and associates21 analyzed the UNOS data from 1996 to 2003, focusing on DCD livers, and came to a similar conclusion regarding inferior graft survival in recipients of DCD than DBD livers. In agreement with these findings, Lee and associates20 performed a retrospective review of the UNOS/OPTN database and analyzed 874 DCD and 43,734 DBD liver transplants. They observed that patient survival was significantly worse in the DCD than DBD group at 1, 3, and 5 years (DCD: 82.3%, 75.9%, and 65.3%; DBD: 85.4%, 77.5%, and 71.5%; P = .010). Graft survival also was significantly lower in the DCD than DBD group at 1, 3, and 5 years (DCD: 72.1%, 61.8%, and 38.8%; DBD: 80.7%, 71.9%, and 65.6%; P < .001). These findings were in accordance with those from a study by Harring and coworkers,22 which also demonstrated worse patient and allograft survival for DCD liver recipients.

As indicated earlier, multiple centers have published single-center results. Some publications have indicated equivalent survival results when favorable donors (with respect to age and WIT) and transplant parameters (with respect to CIT) are carefully considered in the DCD selection criteria.20,21 Additionally, it was reported previously that other factors, such as postoperative medical treatment in the center also might have contributed to the center effect.18 With this consideration, the UNOS/OPTN database is useful based on the breadth of knowledge and large amount of data available. By examining national data, center biases can be eliminated and trends can be examined easily. Based on this information, we agree with the conclusions of the authors that DCD liver transplant has inferior outcomes to DBD liver transplant, and careful selection of DCD donors and minimizing ischemic times might be key factors in optimizing the results of DCD liver transplant.

Risk factors for graft survival

As illustrated above, long-term patient and graft survival rates after DCD liver transplant remain significantly lower but acceptable compared with those of DBD liver transplants. To further improve clinical decision making during liver transplant, several investigators have identified predictors of graft failure and patient mortality after liver transplant with DCD allografts. Accumulating evidence has identified several recipient, donor, and transplant factors as predictors of graft failure following DCD transplant (Table 3).12,21,26,27 Mateo and coworkers21 reported that among the recipient risk factors, a history of previous liver transplant (relative risk [RR] = 1.84 for revision vs primary; P < .001), being hospitalized or in an intensive care unit (ICU) (RR = 1.19 for hospital or ICU vs others; P < .001), being on life support (RR = 1.54 for being with vs without life support), having a serum creatinine level > 2.0 mg/dL (RR = 1.23 for > 2.0 vs ≤ 2.0 mg/dL; P < .001), a history of dialysis (RR = 1.26 for dialysis vs no dialysis; P < .001), and age > 60 years (RR = 1.17 for > vs < 60 y; P < .001) had deleterious effects on graft survival after adjusting for all other factors. Relevant to this investigation, Hong and associates27 defined a prognostic scoring system for risk stratification of patients undergoing orthotopic liver transplant using grafts from DCD donors. They identified 6 independent risk factors for graft failure, including 3 recipient risk factors, 2 donor factors, and an operative factor (Table 3). Harring and coworkers22 observed that improved DCD liver transplant outcomes were associated with recipients who were aged < 50 years and had an international normalized ratio < 2 or albumin level > 3.5 g/dL. Therefore, several potential risk factors that predict graft loss have been identified. By considering these risk factors, we can minimize organ waste from discards and recipient complications.

Complications of Livers From Donation After Cardiac Death Donors

Despite the observed increase in DCD liver utilization, many centers remain reluctant to use these organs
aggressively. An important concern regarding the use of DCD livers is the development of biliary complications. In contrast with DBD donors, a controlled DCD donor is not brain dead but is in a nonrecoverable, critical state. Life support is withdrawn, typically in or near the operating room, and circulatory arrest occurs. The patient is declared dead, and a predefined safety interval is allowed to elapse, typically 5 minutes, before organ procurement is initiated. As circulatory collapse occurs, the organs have increased hypoxia and thrombus formation compared with organs of DBD donors. The varied duration of cellular and tissue hypoxia leads to anaerobic metabolism and lactic acidosis. If perfusion is delayed, in situ thrombosis prevents organ perfusion and promotes necrosis, with a paradoxically low level of transaminases after transplant. Following this type of damage, it can take a protracted period of time for the transplanted organ to begin to function normally. In addition, another important mechanism leading to further aggravated cellular injury occurs during the restoration of blood flow. Several single-institution and national cohort studies have demonstrated that DCD liver transplant is associated with higher risks of PNF, biliary complications, ischemic cholangiopathy (IC) and retransplant (Table 4). Foley and coworkers reported that rates of overall biliary complications (DCD, 47%; DBD, 26%; \( P < .01 \)) and IC (DCD, 34%; DBD, 1%; \( P < .01 \)) were significantly higher in the DCD group. Research conducted by Chan and associates indicated no incidence of PNF from DCD allografts. Hepatic artery complications and anastomotic bile duct complications were comparable in the 2 groups. However, there was increased risk of the development of IC in the DCD group (13.5% vs 1.1%; \( P < .001 \)). Relevant to this investigation, Skaro and associates reviewed the outcomes of 32 DCD and 237 DBD liver transplant recipients at their institution (Northwestern Memorial Hospital) between December 2003 and May 2008. The results indicated that recipients of DCD livers had 2.1-fold greater risk of graft failure, 2.5-fold greater risk of relisting (40.6% vs 16.0%; \( P = .003 \)), and 3.2-fold greater risk of retransplant (21.9% vs 6.8%; \( P = .01 \)) compared with the risks of those events in DBD recipients. The development of biliary complications was more prevalent among DCD recipients (53.1%) than DBD recipients (21.5%) \( (P < .001) \). The IC was identified in 12 DCD recipients (37.5%) but only 4 DBD recipients (1.7%) \( (P < .001) \). They also observed that most relisting (69.2%) and

### Table 3. Summary Data About Risk Factors For Graft Survival

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Recipient Characteristics</th>
<th>Risk Factors</th>
<th>Donor Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mathur et al.26</td>
<td>2009</td>
<td>Age ≥ 55 y</td>
<td>Male sex</td>
<td>Age ≥ 50 y</td>
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<td>Hong et al.27</td>
<td>2011</td>
<td>Diagnosis of HCV with malignancy, non-HCV with malignancy, or HCV only</td>
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<td>Hepatitis B core antibody positivity; Mean arterial pressure &lt; 60 mm Hg for &gt; 20 min after withdrawal of life support</td>
</tr>
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<td>Mateo et al.21</td>
<td>2005</td>
<td>Previous OLT</td>
<td>Being on life support</td>
<td>Donor age</td>
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<td>Hong et al.27</td>
<td>2011</td>
<td>Diagnosis of HCV with malignancy, non-HCV with malignancy, or HCV only</td>
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<td>Mean arterial pressure &lt; 60 mm Hg for &gt; 20 min after withdrawal of life support</td>
</tr>
<tr>
<td>Mateo et al.21</td>
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<td>Taner et al.12</td>
<td>2012</td>
<td>History of previous transplant</td>
<td>Life support status at transplant</td>
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</table>
retransplant (71.4%) in the DCD group could be attributed to biliary complications.

Similarly, Jay and associates\(^29\) conducted a meta-analysis to increase understanding of the risks of biliary complications, particularly IC, after DCD compared with DBD liver transplant. This meta-analysis included 489 DCD and 4455 DBD transplants. The authors observed that the overall rate of biliary complications was 29% (range, 11%-53%) for DCD recipients and 17% (range, 9%-22%) for DBD recipients. The DCD recipients had 2.4-fold increased odds of biliary complications (95% confidence interval [CI] = 1.8%-3.4%). These studies demonstrated an IC rate of 16% (range, 8%-38%) for DCD recipients compared with 3% (range, 0%-8%) for DBD recipients. The DCD recipients had 10.8-fold increased odds of IC (95% CI = 4.8-24.2).

The IC is the leading cause of DCD graft loss and is the complication that has most prevented the widespread acceptance of DCD graft use by transplant centers. Despite much research, the pathogenesis of IC remains unclear. Thus, identification of the factors participating in the development of IC is crucially important to promote the use of these grafts. Previous publications have sought to identify risk factors for the development of IC in DCD grafts (Table 5).\(^12,13,28,31\) In addition, a higher incidence of intrahepatic bile duct strictures (IHBS) of 16% following DCD liver transplant, compared with 3% in DBD recipients, was recently reported.\(^29\) The DCD recipients had 10.8-fold increased odds of presenting with IHBS. Various risk factors for IHBS also have been identified, including donor WIT, donor age > 40 years, and CIT > 8 hours.\(^13,28\) However, single-center analyses have provided conflicting findings about complications in DCD recipients. In some studies, the frequencies of PNF,\(^14,19,28\) hepatic artery thrombosis,\(^14,16,19,28,32\) and acute rejection\(^15,19,32\) after DCD liver transplant did not seem significantly higher than those after DBD liver transplant. Taking a study by DeOliveira and colleagues\(^33\) as an example, primary IC occurred only in 4 recipients (2.5%) from the DCD group (n = 167) and was absent in the DBD group (n = 333). The distribution of biliary complications was similar between the DCD (n = 30 [19.7%]) and DBD (n = 41 [12.5%]; \(P = .09\)) groups. Moreover, biliary complications did not negatively affect patient survival in either DCD or DBD group (\(P = .947; P = .996\)). These excellent results, in contrast with those of most other series, possibly can be attributed to the exclusive use of controlled DCD organs with short WIT and a conservative selection policy. In addition, the

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**Table 4. Complications After Liver Transplant in Recipients From Donation After Brain Death or Donation After Cardiac Death Donors**

<table>
<thead>
<tr>
<th>Study</th>
<th>Liver Transplant (no.)</th>
<th>Primary Biliary Complication (%)</th>
<th>Ischemic Cholangiopathy (%)</th>
<th>Retransplant (%)</th>
<th>Hepatic Artery Thrombosis (%)</th>
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<td>4455</td>
<td>.844</td>
<td>16.6</td>
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<td>Skaro et al.(^17)</td>
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<td>3.1</td>
<td>0.4</td>
<td>.22</td>
<td>53.1</td>
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</table>

**Abbreviations:** DBD, donation after brain death; DCD, donation after cardiac death; NP, not provided; NS, not significant
discrepancy might have depended on the broad variation in procurement practices between various centers, affecting the outcomes and complication rates.\textsuperscript{24,34} Therefore, it is necessary to develop a standardized protocol for the procurement of these organs, because doing this would decrease the factors that affect outcomes negatively.

**Experimental Strategies to Improve Outcomes After Donation After Cardiac Death Liver Transplant**

Due to the inevitable WIT occurring during the declaration of death and organ retrieval process, DCD recipients have experienced significantly worse patient and graft survival rates after transplant than DBD recipients. To improve DCD liver transplant outcomes, several levels of intervention have been offered as potential areas of research into the reconditioning of DCD liver grafts. Interventions, both prior to and following death, could increase the likelihood that organs will be suitable for transplant. Accumulating evidence has suggested that pharmacologic protection and machine perfusion of the liver are promising protective strategies against ischemia-reperfusion injury and especially applicable to high-risk organs. These strategies attempt to rehabilitate marginal grafts, improve the viability and number of organs for transplant, and increase the likelihood of organs being suitable, thereby expanding the donor pool.

**Pharmacologic modulation**

Multifactorial modulation of DCD donors using pharmacologic agents was reported in a recent animal study.\textsuperscript{35} Investigators used combined pharmacologic modulation in situ and during the recipient surgery. Infusion of anticoagulant drugs prior to death decreased the risk of thrombosis after circulatory arrest and the resulting negative effects on organ function.\textsuperscript{36} The risk of hepatic artery thrombosis likely could be reduced by heparin administration immediately prior to therapy withdrawal in the donor.\textsuperscript{11} However, the administration of drugs is regarded as ethically unacceptable in some countries (including the United Kingdom) because of the lack of any benefit to the donor. In addition, numerous animal studies have indicated a variety of substances that have yielded positive results, but these agents have not been applied successfully thus far in humans. Cytoprotective drugs, including fibrinolytic agents (streptokinase),\textsuperscript{37} vasodilators (phentolamine, epoprostenol, dopamine),\textsuperscript{35,38} antibiotics, hormones (glucagon, growth factors),\textsuperscript{39} and antioxidants (superoxide dismutase, edaravone),\textsuperscript{40,41} also have been added to the flush and/or preservation solution and appear to be necessary because the organs tend to develop vasospasm, thrombus formation in the microcirculation, and colonic bacterial contamination secondary to the translocation of organs during WIT.\textsuperscript{42,43} Although it appears that scientists have made headway in addressing key issues associated with DCD liver transplant, these points have yet to be proven in long-term follow-up studies or applied to clinical practice.

**Liver preservation techniques**

Maintaining organ viability during preservation is essential for successful liver transplant.\textsuperscript{44} The current standard for organ preservation (simple cold storage) has proved to be insufficient to preserve these organs. Research into machine perfusion systems (including in situ and ex situ) is consequently an active field in donor organ recovery and preservation.\textsuperscript{45-48}

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<tr>
<th>Study</th>
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| Chan et al.\textsuperscript{28} | 2007 | Donor weight > 100 kg  
Total ischemia time ≥ 9 h  
Donors aged > 50 y (predicted the development of IC) |
| Taner et al.\textsuperscript{12} | 2012 | Asystole-to-cross clamp duration  
African American recipient race (significant factors for predicting the development of IC) (P < .05) |
| Foley et al.\textsuperscript{13} | 2011 | Donor age > 40 y (significant risk factors for the development of overall biliary complications) (P < .01)  
CIT > 8 h (P < .05)  
Donor age > 40 y (P < .01) (significantly increased the risk of IC) |
| Karp et al.\textsuperscript{31} | 2011 | CIT (strong predictor of PNF or IC) (P < .021) |

**Abbreviations:** CIT, cold ischemia time; IC, ischemic cholangiopathy; PNF, primary nonfunction
situ perfusion using autologous blood and an extracorporeal membrane oxygenation device has become the main approach for uncontrolled DCD donors in the Barcelona and Madrid units and recently has been instituted in Paris. Similarly, it is employed by some United States transplant units (Michigan; Madison, Wisconsin) for controlled DCD donors. Compared with ex situ machine perfusion, in situ perfusion is preferable because it obviates the need for exhaustive techniques to reconnect the organs to the machine, increasing simplicity. Additionally, it is an indispensable technique that can provide the opportunity to meet legal and logistic requirements for organ recovery without excessive WIT, and depending on the legal opportunities, it can be initiated prior to obtaining consent for organ donation. It usually is performed in the emergency room after failed resuscitation.

Alternatively, normothermic ex vivo liver perfusion seems to offer another option (Figure 2). Here, a machine perfusion system is used to pump oxygenated blood through a circuit that includes the liver, with appropriate pressures for the arteries and veins. With this approach, the liver can be tested to evaluate function; therefore, the liver can be transplanted subsequently with greater confidence of a successful outcome. The Oxford group has developed and used this type of perfusion rig for porcine DCD livers, which were successfully transplanted despite exposure to long and otherwise fatal WIT periods.

From another perspective, the 2 principle techniques for machine perfusion can be described as hypothermic and normothermic. The results of hypothermic perfusion appear to be different from those of normothermic models. Several studies have suggested postconditioning in the setting of experimental liver and kidney transplant, with hypothermic postconditioning yielding better outcomes. The role of aeration of the cold-stored liver also was clarified. A study by Schlegel and associates provided evidence that machine perfusion in the complete absence of oxygen failed to prevent reperfusion injury and, instead, provoked mitochondrial and nuclear injury with the release of high mobility group box 1 protein. Oxygen, provided either by surface diffusion (surface oxygenation) or intravascular diffusion (oxygen persufflation), is needed in DCD grafts, and it helps to improve the energy status of organs and promote early recovery. Although machine perfusion has been increasingly discussed as a promising tool to optimize livers before transplant, the mechanisms underlying protection by liver perfusion techniques have not been fully addressed. Research undertaken by Schlegel and associates reported that there appeared to be at least 2 mechanisms of protection by hypothermic machine perfusion. First, oxygenation under hypothermic conditions protected against mitochondrial and nuclear injury via down-regulation of mitochondrial activity before reperfusion. Second, under low pressure conditions, cold perfusion itself prevented endothelial damage, independent of oxygen. Similarly, Xu and coworkers employed pig models of DCD livers to study the repair mechanism of normothermic machine perfusion. Their data demonstrated that normothermic machine perfusion effectively restored the tissue adenosine triphosphate (ATP) content (Figure 3) and improved mitochondrial integrity, which might contribute to the improvement of DCD liver viability and function.

**Assessment of liver viability prior to implant**

Due to the serious consequences of transplanting a DCD liver with potentially severe ischemia-reperfusion injury (PNF, retransplant, or recipient death), it would be ideal if the viability of such livers could be predicted before, rather than after, transplant. Currently, various biomarkers have been described to quantify ischemic injury prior to organ retrieval or transplant, with the objective of assessing...
the suitability of grafts for transplant. Perk and coworkers confirmed that the metabolic index of ischemic injury was a feasible marker to evaluate perfused ischemic rat livers; using only 3 perfusate metabolites (glucose, urea, and lactate), the developed multi-way partial least squares discriminant analysis (MPLSDA) model distinguished between fresh and ischemic livers with 90% specificity. In addition, bile production was a good viability indicator, in addition to measurements associated with other liver functions (detoxification, metabolism, or synthesis). Moreover, the ATP content and redox active iron status of the liver during hypothermic machine perfusion also could be used to assess liver viability, and normothermic (37°C) machine perfusion is particularly amenable to test viability when the liver is in a normal metabolic state.

Another approach to viability testing is to evaluate the vascular resistance and enzyme release in the perfusate of hypothermic machine perfusion livers. Alanine aminotransferase (ALT) is an enzyme found in high concentrations in hepatocytes, and it is considered clinically to indicate liver failure. Uygun and associates observed that rat liver recipient survival could be predicted based on the level of ALT during perfusion. Moreover, biomarkers of liver cell damage, such as transaminases, lactate dehydrogenase, and liver fatty acid binding protein, correlated well with WIT and concomitant hepatocyte damage in pig DCD liver transplant models. In addition, other biomarkers, including xanthine, hypoxanthine, hyaluronic acid, and reduced glutathione have been suggested for the assessment of graft viability. Therefore, evaluating these biomarkers in DCD liver grafts prior to implant would be helpful. However, some technical limitations (such as the inability to identify these biomarkers in peripheral body fluids), technical demands, and time constraints in the clinical setting preclude these biomarkers from being incorporated into current practice.

**Important Issues**

**Increased numbers of donation after cardiac death transplants at the expense of donation after brain death organs**

During the past few years, there has been an increase in the number of DCD donors, which has largely followed the promotion of multiorgan donation. However, the initial optimism of DCD as a viable and alternative organ source has diminished with the realization that the increased number of DCD organs might have occurred at the expense of DBD organs. During the past few years, a gradually increasing proportion of transplanted livers from deceased donors have been procured from DCD donors. However, this tendency has not been accompanied by an absolute increase in the total number of livers transplanted in countries that have implemented DCD transplant (Table 6 and Figure 4). There are several possible explanations for this phenomenon. First, there has been a general decline in brain-dead donors, in part due to improvements in neurosurgery and seat belt legislation. Second, there might be excessive enthusiasm and erroneous perceptions of ICU teams that DCD is as good as DBD. Third, DCD might offer the opportunity to avoid prolonging ICU treatment until brain death occurs while obviating an unnecessary waiting period for relatives and the unnecessary use of ICU resources. Therefore, the question of whether increased DCD activity has occurred at the expense of DBD activity remains unresolved. If it is true that a potential increase in DCD donors has occurred at the expense of DBD donors, this substitution would
have detrimental effects on liver donation and the overall results of liver transplant. However, this phenomenon can be reversed, as shown by the Dutch transplant community, which previously underwent a marked increase in DCD. They subsequently launched a publicity initiative directed toward ICU personnel and transplant coordinators, and consequently reduced DCD numbers and restored the number of DBD donors.

Figure 4. Relation Between Donation After Brain Death (DBD) and Donation After Cardiac Death (DCD) Transplants in the United Kingdom

An increase in the number of DCD transplants was accompanied by a decrease in the number of DBD transplants. This may have occurred, in part, because of substitution (early conversion of potential DBD into DCD transplant) (Courtesy of Mark Jones from UK Transplant and Darius Mirza, Birmingham, United Kingdom, with permission received).

Donation after cardiac death costs and resource utilization

As indicated earlier, DCD liver transplant has been associated with higher risks of complications, including PNF, IC, overall biliary complications, and IHBS. These complications cause increased utilization of resources, including retransplant, repeated and prolonged hospital admissions, and endoscopic retrograde cholangiopancreatography or percutaneous transhepatic cholangiography. Relevant to this investigation, Jay and coworkers estimated direct medical care costs based on inpatient and outpatient care for 28 DCD and 198 DBD liver recipients. They found that the mean 1-year posttransplant costs were higher for DCD recipients (124.9% DBD costs; \( P = .04; 95\% \text{ CI} = 102\%-151\% \)). Furthermore, the increased DCD costs persisted (125.2% DBD costs; \( P = .009; 95\% \text{ CI} = 106\%-144\% \)) after adjustment for recipient characteristics (age, sex, race, body mass index, Model For End-Stage Liver Disease [MELD] score, hepatitis C, hepatocellular carcinoma, and medical status). With the exception of graft type (DCD), no donor factors were significantly associated with cost. Upon further investigation of the experimental data, the authors demonstrated that DCD recipients experienced higher retransplant rates associated with the greatly increased frequency of biliary complications (DCD, 58%; DBD, 21%; \( P < .001 \)), especially IC (DCD, 44%; DBD, 1.6%; \( P < .001 \)) in DCD recipients. The incidence of IC was associated with a 53% increase (\( P = .001 \)) in 1-year posttransplant costs, and retransplant was associated with a 107% increase (\( P < .001 \)) in 1-year posttransplant costs. These data were consistent with those of De Vera and associates, who examined 141 DCD and 282 DBD transplants and observed that the costs of DCD were 20% higher for the index admission. In addition, van der Hilst and coworkers reported that the cost per life-year for DBD was €88,913 compared with €112,376 for DCD, and this difference was statistically significant. The authors attributed this higher cost to an increased need for dialysis and longer length of hospital stay. However, patients who received DCD liver transplants and did not develop complications reported an excellent quality of life. For patients with severe complications after DCD liver transplant, their situation still was better than dying after refusing a DCD offer or continuing to wait for a DBD liver, because patient choices frequently are not between standard livers and marginal livers (including DCD) but rather, between marginal livers and no livers. The benefit of earlier access to liver transplant provided by a DCD graft could outweigh the risks of prolonged waiting for a standard graft.
a system of limited health care resources, it becomes necessary to evaluate the cost effectiveness of clinical practice. Although these analyses demonstrated a significant increase in initial costs for DCD liver transplant, they did not include long-term clinical follow-up to evaluate graft function and did not calculate total costs over time.

Relevant to this investigation, Snyder and colleagues provided a new and informative perspective on the overall societal cost effectiveness of expanding the donor pool to include DCD kidney transplant. Using a 10-year horizon, they found that the waiting list strategy using DBD-only donors resulted in costs of $351,000 to achieve 5.4 quality-adjusted life years (QALYs) ($65,000/QALY). A waiting list strategy that included both DBD and DCD donors resulted in costs of $336,000 to achieve 6.0 QALYs ($56,000/QALY). Therefore, the DBD plus DCD donor waiting list strategy was superior to the DBD-only strategy. In addition, to identify the group of patients who would benefit from DCD liver transplant, Jay and associates studied the comparative effectiveness of DCD liver transplant. Their data demonstrated that for patients with a MELD score < 15, DCD transplant was associated with both higher costs and reduced effectiveness. In the same study, for patients with a MELD score between 15 and 20, the benefit was borderline; however, for patients with a MELD score > 20, there was a clear increase in effectiveness after DCD transplant, confirming the results of previous studies.

Considering these findings, the regulatory oversight of DCD liver transplant should be modified to encourage the utilization of higher-risk DCD grafts in recipients for whom these risks are mitigated by poor waiting list outcomes.

Conclusions

In summary, the analysis presented here of several single-center studies and large studies using the national UNOS/OPTN database demonstrates that DCD recipients experience inferior graft survival and higher rates of PNF, biliary complications, IC, and retransplant. These outcomes are associated with markedly increased costs for DCD recipients. Despite these disadvantages, the results of liver transplant after DCD should not preclude the use of these livers because there is a critical organ shortage and many patients are dying on the waiting list. Attention should be directed toward further reducing WIT, CIT, and possibly donor age. Similarly, with careful donor/recipient selection and appropriate and sufficient postoperative care, acceptable results can be achieved. Furthermore, new techniques should be developed to minimize the effect of the hypoxia and microthrombi that occur during the DCD process, which could help reduce the incidence of complications and poor graft function.

To address the increased costs of DCD transplant, health care authorities must undertake measures, such as differentiated reimbursement in accordance with the donor source, to better accommodate the increased costs of DCD grafts. More importantly, further attempts should be made by regulatory authorities and transplant societies to standardize procurement protocols and techniques, with the goal of reducing the inherent problems associated with DCD liver grafts. Increased attention and initiatives to promote DCD as a strategy to enlarge the donor pool (not at the cost of DBD) remain crucially important. Overall, the future of DCD liver transplant from DCD donors is promising, but much work remains before it achieves a similar outcome profile to transplant from DBD donors.

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