Regulations and Procurement Surgery in DCD Liver Transplantation: Expert Consensus Guidance From the International Liver Transplantation Society

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INTRODUCTION

In donation after circulatory death (DCD) liver transplantation, successful outcomes hinge on events occurring during organ recovery. While local and national regulations dictate processes by which DCD livers may be recovered, 2 standards have been established: (1) super rapid recovery (SRR) and (2) in situ normothermic regional perfusion (NRP).

The International Liver Transplantation Society (ILTS) organized a working group of 7 experts (6 surgeons and 1 nephrologist) in mid-2019. The working group was charged with the task of defining issues related to DCD regulations and procurement surgery, including relevant technical considerations, the impact of ethical and legal policies on DCD liver donation and procurement, and roles for postmortem NRP and DCD after euthanasia. Working group methodology has been described previously.1 Herein, we summarize pertinent literature as well as combined experience to provide useful guidance on DCD liver procurement, always keeping in mind the goal of optimizing liver utilization and outcomes.

PROCESSES FOR DCD LIVER PROCUREMENT: SUPER RAPID RECOVERY

SRR in DCD was established as the recovery method of choice to limit the detrimental effects of donor warm ischemia. Speed of recovery needs to be balanced with risk for injury. Ausania et al2 reviewed 7146 livers recovered from deceased donors in the United Kingdom, including 628 from DCD donors (9%). There were no differences in vascular injuries between donation after brain death (DBD) and DCD livers but more capsular injuries among the latter. More recently, Boteon et al3 analyzed experience with 370 DCD liver transplants performed in the United Kingdom and demonstrated that using SRR, 27% of livers experienced some form of injury during procurement, though no injuries resulted in liver discard.

Location of Withdrawal of Life Support Treatment

Depending on local or national regulations, withdrawal of life support treatment (WLST) in controlled DCD can be performed in either the intensive care unit (ICU) or...
operating room (OR). In a meta-analysis of 12 studies, DCD donors undergoing WLST in ICU had higher odds of liver graft loss versus DBD donors than those undergoing WLST in OR (ICU: 3 studies; odds ratio, 1.98; 95% CI, 1.13-3.47; \( P = 0.017 \); OR: 9 studies; odds ratio, 1.65; 95% CI, 1.16-2.36; \( P = 0.006 \)). While these results have subsequently been criticized due to inclusion of studies from multiple countries, donors performed over >30 years at centers with varying degrees of experience, and heterogeneous cold and warm ischemia times, the fact remains that WLST in OR can help reduce time and stress associated with donor transfer, preparation, and preservation, during which donor, graft, and even surgeon injury may occur.

ILTS Guidance

- In the absence of contraindications and in countries/settings where it is legally permitted, withdrawal of life support treatment may preferentially be performed in the operating room. (Level of evidence C)

Aortic Only Versus Dual-Vessel Preservation

Liver preservation techniques in deceased donor retrieval can be dual (aorta and portal vein) or single vessel (aorta only). Single-vessel preservation is achieved faster, which is why it is frequently used in DCD liver recovery. Published data comparing the 2 techniques can be found in studies evaluating DBD livers. D’Amico et al\(^6\) randomized 35 extended criteria DBD livers to dual- versus single-vessel liver preservation and concluded that dual-vessel preservation resulted in superior graft function and survival. More recently, Hameed et al reviewed recipient outcomes from the Australia and New Zealand Liver Transplant Registry 2007–2016, including graft and patient survival and causes of graft loss stratified according to preservation strategy (N = 957 for aorta only and 425 for dual-vessel preservation). Overall, there was a trend toward improved outcomes when dual-vessel preservation was used, which became significant when extended criteria donors were considered.\(^7\)

ILTS Guidance

- Dual preservation appears to offer improved results versus aorta only preservation using DBD livers, in particular those that are higher risk/extended criteria, in low-level clinical studies. Since establishing dual as opposed to aorta only preservation is not innocuous in the context of DCD and can prolong donor warm ischemia, it may be preferable to perform additional portal preservation subsequent to the onset of aortic preservation, either in situ in the donor or on the backtable. (Level of evidence C)

Donor Hepatectomy Time

Evaluation of data from the Eurotransplant region first brought attention to the fact that donor hepatectomy time (time between cold preservation and placing the organ in cold storage) can have a significant impact on posttransplant outcomes. In the Eurotransplant study, it was found that the effect of donor hepatectomy time on death-censored graft loss was more pronounced among recipients of DCD versus DBD livers (hazard ratio [HR], 1.14; 95% confidence interval [CI], 1.06-1.22 for DCD; HR, 1.03; 95% CI, 1.00-1.05 for DBD; \( P = 0.008 \)).\(^8\) In the United Kingdom, it was determined that donor hepatectomy time >60 minutes was a significant independent risk factor for graft loss.\(^9\) Results of a nationwide study on 376 DCD liver transplants from the Netherlands revealed that donor hepatectomy time was an independent risk factor for development of ischemic cholangiopathy (IC) within the first 2 years (adjusted HR, 1.18; 95% CI, 1.06-1.30; \( P = 0.002 \)).\(^10\) This finding was confirmed by Gilbo et al in a single-center analysis demonstrating donor hepatectomy time as a significant risk factor for IC (adjusted HR, 1.19; 95% CI, 1.04–1.35; \( P = 0.01 \)), but with equal susceptibility among DCD and DBD grafts. In the latter study, it was shown that a 10-minute increase in donor hepatectomy was comparable with 1-hour increase in cold ischemia.\(^11\)

ILTS Guidance

- There is sufficient evidence supporting the importance of short donor hepatectomy time during DCD liver retrieval. Donor hepatectomy time should be kept as short as possible—at most 60 minutes from the start of cold preservation. (Level of evidence B)

Processes for DCD Liver Procurement: Normothermic Regional Perfusion

While SRR was long considered the “gold standard” in DCD liver recovery, higher rates of biliary complications and graft loss relative to DBD prompted application of stricter donor and graft selection criteria in some settings and use of postmortem NRP in others. In DCD, NRP is used to temporarily restore flow of oxygenated blood and recondition organs before cold preservation.\(^12\) Multiple recent studies from Europe support the role of postmortem NRP in reducing biliary complications (including consistently reducing rates of IC to 0%–2%) and graft loss among DCD livers.\(^13-20\) No randomized clinical trial has been performed. Currently, NRP is permitted in DCD organ recovery in 5 European countries (Belgium, the Netherlands, Spain, Switzerland, and United Kingdom) and is mandatory in 3 (France, Italy, and Norway).\(^21\)

NRP Cannulation

Cannulation to establish the NRP circuit may be performed before WLST in countries or settings where it is ethically and legally permissible to do so and when prior consent has been obtained. In countries or settings where antemortem cannulation is not permitted, antemortem vessel localization with or without guidewire placement may be allowed. An analysis of DCD liver transplants performed in Spain from 2012 to 2016 demonstrated that when cannulation for NRP was performed with postmortem as opposed to antemortem, total and functional warm ischemic times were longer by about 9 and 7 minutes, respectively.\(^22\) In spite of longer warm ischemia, however, outcomes for DCD livers recovered with NRP with postmortem versus antemortem cannulation appear similar.\(^16,20\)

ILTS Guidance

- In DCD, antemortem and postmortem cannulation are associated with good outcomes. The timing of and approach to cannulation should adapt to local rules and legislation. (Level of evidence B)
Technical Issues and Organ Damage in DCD With NRP

Implementation of new technologies such as NRP is ideally supported by training programs to ensure that the entire team is familiar with the logistics of the procedure and is aware of potential pitfalls. The team structure should include at least 2 surgeons, a scrub practitioner, a perfusion specialist, and additional OR staff to manage logistics and processing of samples. Data published to date do not appear to suggest increased risk of organ damage or loss using this technique.13,16,18,19

ILTS Guidance
– Abdominal NRP appears to be safe and does not lead to organ loss. (Level of evidence B)

Warm Ischemia Times in DCD With NRP

The start of NRP or cold preservation (the latter in cases where recovery is performed with SR) marks the end of donor warm ischemia. When SRR is used, the common recommendation is to avoid transplantation of DCD livers with >30-minute functional warm ischemia (significant hypoperfusion) as they are more likely to fail, including due to development of IC within 6–12 months after transplantation.22–26 Development of IC is a devastating complication of DCD liver transplantation, leading to retransplantation or death in up to 70% of cases.25 Use of postmortem NRP, however, has a reconditioning effect in the liver and offers an opportunity for liver assessment before recovery.28 There are reports on successful transplantation of DCD livers with extended donor warm ischemia recovered with postmortem NRP, including livers arising from uncontrolled DCD donors with donor warm ischemia times >2 hours.17,18,29–31 For this reason, the transplantation of controlled DCD livers with >30 minutes of functional warm ischemia may be considered if and when evolution of relevant parameters during NRP is adequate (see the Liver Assessment During NRP section).32

ILTS Guidance
– Livers from DCD donors functional warm ischemia >30 minutes subsequently recovered with postmortem NRP may be considered for transplantation, as long as evolution of relevant parameters during NRP is adequate. (Level of evidence C)

Liver Assessment During NRP

The recommendation of the Spanish Organización Nacional de Trasplantes is that NRP be run 90–120 minutes.33 Similarly, in the United Kingdom, NRP is typically run 120 minutes.16,34 The minimum time necessary for the liver to recover from the warm ischemic insult, however, appears to be less, and there are groups that systematically perform 60 minutes of NRP with good results.13 Experimental studies have demonstrated that 30 minutes of NRP allows for complete recovery of hepatic energy substrates lost during cardiac arrest.35–39 In general, NRP is run between 1 and 4 hours to allow organ reconditioning and evaluation without provoking additional injury.20,32,40 Transaminase evolution during NRP may be used to evaluate extent of injury and likelihood of irreversible damage in controlled DCD livers, just as it is in the setting of uncontrolled DCD, where warm ischemic times are generally longer.18,29,41 There is variation in what are considered acceptable levels of transaminases during NRP, ranging from 4× the upper limit of normal to an assessment of trends. In general, values >500 IU/L are considered too high.13,16,20,32 An exception is Italy, where the mandatory “no touch” period of 20 minutes leads to greater ischemic injury. Transaminase values up to 1000–2000 IU/L during NRP are considered acceptable in some centers in Italy, though only preliminary results from mixed case series of uncontrolled and controlled DCD liver transplants have been published to date.17,18 Lactate clearance and falling perfusate glucose levels are other parameters that have been used to evaluate DCD liver function during NRP.16,17,19,42

ILTS Guidance
– Postmortem NRP should be run for at least 1 hour and at most 4 hours. (Level of evidence B-C)
– Liver enzymes are a useful component to liver assessment. The transaminase trend during NRP, which should ideally be stable, is more important in assessing liver viability than absolute values. (Level of evidence B-C)

PROCESSES FOR DCD LIVER PROCUREMENT: GENERAL CONSIDERATIONS

Fibrinolytic Therapy

Fibrinolytic agents such as tissue plasminogen activator (TPA) have been used in clinical DCD liver transplantation based on the assumption that they can reduce the appearance of IC by lysing fibrin microthrombi forming in peribiliary arterioles during low-flow and no-flow periods following WLST. Nonrandomized clinical trials using historical and in some cases older cohorts with significantly longer warm ischemia as controls have supported the use of exogenous fibrinolytic therapy:

– Hashimoto et al described 22 transplants performed with DCD grafts treated with TPA injected into the hepatic artery on the backtable. There was no control group; IC arose postoperatively in 2 cases (9%), including 1 in which heparin had been given before WLST. Of note, 64% of recipients had excessive postreperfusion bleeding.43

– Seal et al published a retrospective review of DCD liver transplants performed at 2 North American centers wherein a small dose of TPA was administered directly into the hepatic artery before completing the portal anastomosis in 85 of 113 DCD recipients. The authors described a lower rate of biliary strictures in the TPA-treated recipients (17% versus 33%, P = 0.07).44 Patients were not randomized, and authors compared recipients of livers treated with TPA with controls from an earlier era. One of the same 2 centers subsequently published a retrospective analysis of 138 DCD liver transplants performed in which the last 100 recipients received low-dose TPA and verapamil injected directly into the hepatic artery following graft reperfusion. Donors in both studies were heparinized before withdrawal, and rates of IC in both eras in the second study were low (3%–5%).45

– Kubal et al have described in 2 reports results of their center’s DCD optimization protocol, which includes treatment with TPA in the aortic flush and on the backtable as well as steps to minimize ischemic times, such as expedited

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recipient interventions and experienced surgeons for both donor and recipient hepatotectomy. Using this strategy, this group experienced significant reductions in DCD biliary complications, IC, and graft loss. It is unclear, however, whether these improved results are due to the use of TPA or the fact that all of their ischemic times (donor warm ischemia, hepatectomy time, cold ischemia, recipient warm ischemia) improved considerably in the second era. All donors were heparinized before WLST in both eras.46,47

A study from Pietersen et al compared recipients of livers treated with urokinase during backtable surgery (N = 63: 46 DBD and 17 DCD) with a group of controls from an earlier era (N = 122: 94 DBD and 28 DCD). The control group had lower body mass index but longer cold ischemic times, and rates of IC were the same in both groups: 11% and 39% among DBD and DCD recipients, respectively, in the control group, versus 10% and 41% among DBD and DCD recipients, respectively, in the urokinase group.48

Aside from the potential sources of bias related to donor and graft characteristics in the aforementioned studies, there is lack of clinical evidence of significant fibrin clot deposition following WLST. Verhoeven et al evaluated 282 sections from 94 biopsies from discarded human DCD liver grafts (N = 16) triple-stained to detect the presence of microthrombi. Microvascular clot with fibrin was only found in 1%–3% of the sections evaluated. Furthermore, when the authors evaluated both DCD and DBD grafts, microthrombi were found at rates of 3% and 11%, respectively, and there was no association between presence of microthrombi and subsequent development of IC.50 Other authors have similarly studied histopathological changes associated with appearance of IC after both DBD and DCD liver transplantation and have described low rates of microvascular thrombi and no significant association between presence of microthrombi and development of IC.50,51

Finally, administration of a fibrinolytic drug to a graft, which may have ongoing effects even after washout through binding of vascular endothelium,52 is an intervention that could pose risk for development of uncontrollable hemorrhage in the recipient. This issue is particularly relevant in the setting of DCD liver transplantation, where postreperfusion coagulopathy is not uncommon among recipients of marginal DCD livers.53,54

ILTS Guidance

- Based on lack of evidence in support of improved outcomes and risk for hemorrhagic complications, fibrinolytic agents should be avoided in DCD donors, grafts, and recipients. (Level of evidence B-C)

Timing of Heparinization

Heparin may or may not be administered before withdrawal of life support in DCD, in accordance with ethical and legal constructs in different hospitals, regions, and countries. There is basic and translation evidence supporting anti-inflammatory and cytoprotective roles for heparin in this setting.53,58 When antemortem cannulation is performed in preparation for postmortem NRP, systemic heparinization is necessary to avoid clotting of cannulae. In all other circumstances, clinical benefits that might be achieved with antemortem heparinization in DCD remain nebulous.

A 2016 meta-analysis evaluated the impact of strategies for withdrawal of care in DCD on posttransplant outcomes. It determined that antemortem heparin administration reduced odds of primary nonfunction from 11.24 (95% CI, 1.99-63.37; P = 0.006) to 3.48 (95% CI, 1.79-6.76; P < 0.001), though this was based on results of 9 retrospective studies, the majority of them from North America and including patients transplanted before 2010.4

Narvaez et al59 evaluated the SRTR database and compared DCD liver transplants performed with and without antemortem administration of heparin. Between 2003 and 2017, 5495 DCD livers were recovered in the United States: 4906 with antemortem heparin (89%) and 589 without (11%). There were no differences in discard rates depending on timing of heparin administration. Among 3745 DCD liver transplants, those performed without antemortem heparin (N = 407) had significantly older donors, longer cold ischemia times, and more retransplants and were primarily transplanted in an earlier era. Authors of the study observed more primary nonfunction and inferior ongoing graft survival among DCD livers recovered without antemortem heparin.

In Europe, antemortem administration of heparin is allowed and practiced in 7 countries (Austria; Belgium; France; Italy, though during the agonal period only; Norway; Spain; and Switzerland), while it is prohibited in Czech Republic, Ireland, the Netherlands, Sweden, and the United Kingdom.53 The UK experience in DCD liver transplantation, in particular, is considerable, and results reported in the United Kingdom are comparable with those in North America, where antemortem administration of heparin is frequent. This is even in spite of the fact that, on average, UK DCD liver donors are older and have longer ischemia times than in North America.24,60-62

ILTS Guidance

- Given its low risk profile and the potential for achieving cytoprotective effects, heparin should be given prior to WLST in DCD in absence of overt contraindications (e.g., intracranial hemorrhage) and in countries/settings where it is legally permissible to do. (Level of evidence B-C)

Cold Preservation Solution

Both University of Wisconsin (UW) and IGL-1 are colloid-containing solutions based on hydroxyethyl starch and polyethylene glycol-35,36 respectively. Evidence from the European Liver Transplant Registry evaluating >42 000 liver recipients transplanted over 10 years found that 3-year graft survival was equivalent (75%) using UW and IGL-1; slightly reduced (73%) using Celsior, a solution devoid of colloid; and significantly reduced (69%) with Custodiol HTK, another solution that is also colloid-free. Moreover, on multivariate analysis, it was demonstrated that use of HTK was an independent risk factor for increasing probability of graft loss by 10%.63 The observation of increased graft loss with HTK persisted even after removing living donor liver transplants, excluding German centers (where HTK is used at disproportionately higher rates), and after propensity score matching of liver transplant recipients to
control for baseline differences in relevant covariates.\textsuperscript{64,65} It, furthermore, confirms earlier findings from the United States. An analysis of >17 000 liver transplants performed in the United Network for Organ Sharing over a 4-year period demonstrated a significantly increased risk of graft loss in livers preserved with HTK versus those preserved with either UW or Celsior, in particular among those arising from DCD donors or with prolonged cold ischemia. A more recent study comparing liver transplant outcomes using HTK versus UW in the Eurotransplant region was recently published, but the analysis excluded all DCD livers.\textsuperscript{66} 

**ILTS Guidance**

- Registry data suggests that the use of HTK may be associated with higher liver graft loss, including using DCD livers and those with prolonged cold ischemia. Consideration should be given to avoiding use of HTK in DCD livers in cases where cold ischemia is estimated to be >8 hours. (Level of evidence B)

**DCD AFTER EUTHANASIA LIVER TRANSPLANTATION**

Organ donation after euthanasia (category V DCD) is currently permitted by law in Belgium and the Netherlands. Gilbo et al\textsuperscript{67} concluded from a single-center study that liver transplantation using grafts recovered after euthanasia resulted in comparable survival to Maastricht category III controlled DCD liver transplantation. In a recent study combining data from Belgium and the Netherlands, van Reeven et al compared results of 48 transplants using category V DCD livers versus those using 543 category III DCD livers. There were no differences in the study in 1-, 3-, and 5-year patient and graft survival rates between the 2 groups, nor did the rates of relevant postoperative complications vary.\textsuperscript{68}

**ILTS Guidance**

- Based on preliminary evidence, category V DCD liver transplantation appear to offer clinical results comparable to those of category III controlled DCD, and the use of livers arising through this process can be explored further in settings where appropriate legal and regulatory frameworks are in place. (Level of evidence C)

**CONCLUSIONS**

The statements of this ILTS Working Group of experts are summarized in Table 1, where they are classified according to the GRADE system.\textsuperscript{69} While the level of evidence supporting statements is low, there was relatively consistent agreement among experts. In the future, it is likely that clinical application of DCD liver transplantation will continue to expand alongside that of perfusion.

### TABLE 1.

Summary of ILTS guidance on regulations and procurement surgery in DCD liver transplantation

<table>
<thead>
<tr>
<th>Topic</th>
<th>ILTS guidance</th>
<th>Studies evaluated</th>
<th>Level of evidence\textsuperscript{a}</th>
<th>Grade\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Super rapid recovery</strong></td>
<td>Where it is legally permitted, WLST may be preferentially performed in the operating room.</td>
<td>4,5</td>
<td>C</td>
<td>I</td>
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<tr>
<td></td>
<td>Additional portal preservation may be performed subsequent to onset of aortic preservation in DCD liver recovery, either in situ in the donor or on the backtable.</td>
<td>6,7</td>
<td>C</td>
<td>IIa</td>
</tr>
<tr>
<td></td>
<td>Donor hepatectomy time should be kept as short as possible (at most 60 min from start of cold preservation).</td>
<td>8-11</td>
<td>B</td>
<td>I</td>
</tr>
<tr>
<td><strong>Normothermic regional perfusion</strong></td>
<td>The timing of cannulation (antemortem or postmortem) should adapt to local rules and legislation.</td>
<td>13–20,34,42,69–72</td>
<td>B</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td>Abdominal NRP appears to be safe and does not lead to organ loss.</td>
<td>13–20,34,42,69–72</td>
<td>B</td>
<td>I</td>
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<tr>
<td></td>
<td>Livers from DCD donors with functional warm ischemia &gt;30 min recovered with NRP may be considered for transplantation, as long as evolution of relevant parameters during NRP is adequate.</td>
<td>16,17,29–</td>
<td>C</td>
<td>IIa</td>
</tr>
<tr>
<td></td>
<td>Postmortem NRP should be run for at least 1 h and at most 4 h.</td>
<td>31,34,41,42,73–77</td>
<td>B-C</td>
<td>I</td>
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<tr>
<td></td>
<td>The transaminase trend during NRP, which should ideally be stable, is more important in assessing liver viability than absolute values.</td>
<td>13,16,20,32,34–40</td>
<td>B-C</td>
<td>I</td>
</tr>
<tr>
<td><strong>Adjuncts during DCD liver recovery</strong></td>
<td>Fibrinolytic agents should be avoided in DCD donors, grafts, and recipients.</td>
<td>43-54,58,78</td>
<td>B-C</td>
<td>III</td>
</tr>
<tr>
<td></td>
<td>Where it is legally permitted and in the absence of contraindications (eg, intracranial hemorrhage), heparin should be given before WLST.</td>
<td>4,5,55–62</td>
<td>B-C</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td>The cold preservation solution HTK should be avoided in DCD livers in cases where cold ischemia is estimated to be &gt;8 h.</td>
<td>63-66,79</td>
<td>B</td>
<td>III</td>
</tr>
<tr>
<td><strong>DCD after euthanasia</strong></td>
<td>Category V DCD liver transplantation appears to offer results comparable to those of category III controlled DCD, and the use of livers arising through this process can be explored further.</td>
<td>67,68</td>
<td>C</td>
<td>I</td>
</tr>
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</table>

\textsuperscript{a}Level of evidence: A—consistent high level of evidence from well-performed and high-quality studies or systematic reviews; B—moderate/low level of evidence from studies or systematic reviews with few important limitations; C—very low level of evidence from studies with serious flaws (only expert opinion or standards of care).

\textsuperscript{b}Grade: I—strong agreement to do; IIa—moderate agreement to do; IIb—weak agreement to do; III—agreement not to do.

DCD, donation after brain death; ILTS, International Liver Transplantation Society; NRP, normothermic regional perfusion; WLST, withdrawal of life support therapy.
technologies. SRR has long been the standard in DCD liver procurement, but it is likely that in the next several years, a clear role for NRP—be it as an adjunct or the cornerstone of this process—will be defined.

REFERENCES


