Donor Warm Ischemia Time in DCD Liver Transplantation—Working Group Report From the ILTS DCD, Liver Preservation, and Machine Perfusion Consensus Conference

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Abstract. Donation after circulatory death (DCD) grafts are commonly used in liver transplantation. Attributable to the additional ischemic event during the donor warm ischemia time (DWIT), DCD grafts carry an increased risk for severe ischemia/reperfusion injury and postoperative complications, such as ischemic cholangiopathy. The actual ischemia during DWIT depends on the course of vital parameters after withdrawal of life support and varies widely between donors. The ischemic period (functional DWIT) starts when either Spo_2 or blood pressure drop below a certain point and lasts until the start of cold perfusion during organ retrieval. Over the years, multiple definitions and thresholds of functional DWIT duration have been used. The International Liver Transplantation Society organized a Consensus Conference on DCD, Liver Preservation, and Machine Perfusion on January 31, 2020 in Venice, Italy. The aim of this conference was to reach consensus about various aspects of DCD liver transplantation in context of currently available evidence. Here we present the recommendations with regards to the definitions used for DWIT and functional DWIT, the importance of vital parameters after withdrawal of life support, and acceptable thresholds of duration of functional DWIT to proceed with liver transplantation.

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INTRODUCTION

Donation after circulatory death (DCD) were the main source of donor livers until the Harvard neurologic definition and criteria for brain death were published in 1968.[1] Consequently, donors after brain death (DBD) became the source of organs for the majority of transplant recipients, as the criteria provided a medical and legal framework for brain death and consequently provided a more stable and controlled situation for organ procurement. However, the disparity between the donor numbers and the increasing demand for organs for transplantation have led to a number of strategies to increase the donor pool including the use of extended criteria donors, and among them the resurgence of DCD liver grafts.[2]

In the first reports, DCD liver transplantation has been associated with inferior long-term outcomes when compared to DBD, especially related to higher rates of primary nonfunction (PNF), ischemic cholangiopathy (IC), and hepatic artery thrombosis.[3-6] These inferior outcomes in DCD liver transplantation have been related to the additional warm ischemic insult during the donor warm ischemia time (DWIT).[6,7] In DCD, DWIT starts with the withdrawal of treatment in the donor, whereafter the vital parameters drop towards asystole and continues until the start of cold perfusion. After declaration of death, the organs are procured using a quick standardized technique. Later DCD reports have shown that donor selection, refined surgical techniques during the procurement and transplant, as well as patient selection are key factors in achieving good outcomes.[6,8-11] However, to fulfill this strict selection, a significant number of DCD livers are discarded every year worldwide.[12,13]

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Multiple retrospective single and multicenter studies have analyzed the impact of DWIT on the outcomes after liver transplantation; however, a unified definition for DWIT is still lacking. Different definitions and classifications have been incorporated by some authors to better understand the dynamics of DWIT that could help clinicians to increase utilization of DCD livers and minimize the risk of complications. There is a need for further prospective studies to analyze the impact of the different dynamics during DCD procurement. For that reason, the International Liver Transplantation Society (ILTS) organized a Consensus Conference on DCD, Liver Preservation, and Machine Perfusion on January 31, 2020 in Venice, Italy. The aim of this conference was to reach consensus about various aspects of DCD liver transplantation in context of currently available evidence. Here we present the recommendations with regards to the definitions used for DWIT, the importance of vital parameters after withdrawal of life support therapy (WLST), and acceptable thresholds of duration of DWIT to proceed with liver transplantation.

MATERIALS AND METHODS

An English literature search of PubMed (and MEDLINE via PubMed) online libraries and the Cochrane register was performed from January 2000 to October 2019. The following searches were performed: "liver transplantation" ([Mesh]) AND "donation after circulatory death" (or "DCD" or "donation after cardiac death" or "non-heart beating donation") AND "donor warm ischemia time" (or "DWIT" or "functional warm ischemia" or "donor warm ischemia." We also performed an online search for national and regional guideline statements regarding this subject. After summarizing the literature, a list of recommendations was formed by the working group. The initial literature review was summarized and guideline statements were written. The recommendations were classified in level of evidence and grade of recommendations according to the GRADE System.[14] The guideline statements were approved by all 7 members of the working group. There were 151 participants from 4 continents attending the consensus meeting in Venice on January 31, 2020. Eighteen delegates attended the working group discussion on DWIT. During the following plenary presentation and discussion by the working group leaders and the audience, the recommendations were finalized. This article was prepared by the working group and reviewed by the Special Interest Group topic coordinators to support the accuracy of the data and to exclude and possibly modify any of the recommendations. Our study is a review of the existing literature with consequent development of guidelines. This article does not describe any new human or animal studies. Therefore, no institutional review board approval was required.

DEVELOPING DEFINITIONS OF (FUNCTIONAL) DWIT

The DCD liver transplant literature is replete with various methods to define DWIT based upon length of time as well as indirect measures of tissue perfusion and oxygenation (Table 1). None to date have consistently demonstrated an association with common outcome measures, such as graft failure and IC. This section will describe published methods to define DCD DWIT, including their benefits and limitations.

Total and Functional DWIT

The earliest and easiest assessments to quantify DWIT came from measures of total DWIT (tDWIT), defined as time from donor WLST to initiation of cold perfusion.[21] tDWIT can be subcategorized into the agonal DWIT (donor WLST to circulatory arrest) and asystolic DWIT (circulatory arrest to start of cold perfusion).[16] Several definitions have to be taken into account around the death of the donor (Figure 1). At the end of the agonal phase, circulatory arrest is determined and the no touch period starts (the duration of the no touch period varies between countries from 2 to 20 min), and at the end of the no touch period, the declaration of death is confirmed. The benefit of these time-related measurements is that they require very little data capture by the organ recovery team. However, they do not provide any assessment of tissue perfusion or oxygenation during the agonal phase which varies quite widely among donors and is dependent on intrinsic factors

TABLE 1.
Published methods to assess DWIT

Method	Example	Comments
Time[15]	• Total DWIT • Subcategories of DWIT Agonal DWIT Asystolic DWIT	➢ Assess time only ➢ No indication of tissue perfusion/oxygenation
Threshold measures (functional DWIT)[16,17]	• SBP • DBP • MAP	➢ Peripheral measurement of perfusion and oxygenation may not reflect organ level perfusion
	• Spo_2 • Hypoxia score	➢ Combination of perfusion and oxygenation
Hemodynamic trajectories[18,19]	• Clustering	➢ Organizes trends in MAP and Spo_2 by patterns
	• Slope of SBP	➢ Assess how rapidly SBP is decreasing
Other[20]	• Shock index • Area under the SBP curve	➢ Have been assessed in kidney DCD

DBP, diastolic blood pressure; DCD, donation after circulatory death; DWIT, donor warm ischemia time; MAP, mean arterial pressure; SBP, systolic blood pressure; Spo_2, peripheral capillary oxygen saturation.

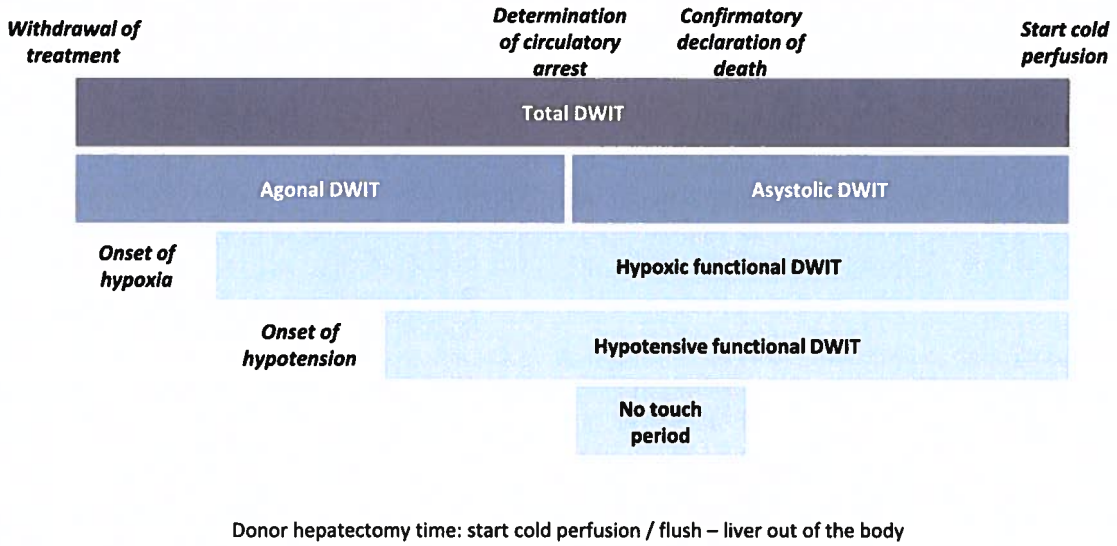

FIGURE 1. Overview of the components of donor warm ischemia time.

to the donor, methods used to assess vital parameters, and the method utilized to determine death (loss of mechanical or electrical activity).[17]

Given that cardiopulmonary activity remains stable for a certain period after WLST, it is assumed that organ quality may be minimally impacted until the decline to a certain threshold of perfusion and/or oxygenation. Once this threshold is reached, functional DWIT (fDWIT) starts and continues until the start of cold perfusion. Several investigators have assessed fDWIT starting with a threshold systolic blood pressure (SBP), diastolic blood pressure (DBP), or mean arterial pressure (MAP), while others have investigated threshold oxygenation (Spo_2) through the use of transcutaneous oxygen saturation, as displayed in Table 1. A combination of these is also possible. Quantifying the changes in perfusion or oxygenation requires consistent documentation, preferably every minute after WLST. Perhaps, because consistent minute-to-minute documentation has not been performed until recently by donor teams, only a few reports have attempted to assess vital parameter changes over time and their relation to graft failure or IC.

In the future, as larger numbers of patients accrue, we can expect to see additional methods to evaluate the quality of DWIT. As an example, Allen et al, in a large cohort of DCD kidney recipients, found that donor shock index and the area under the SBP curve were potentially related to graft failure and delayed graft function, respectively.[20] It is likely that integrative methods may allow for a more precise method of assessing the impact of DWIT. Peering into the future, one might imagine point-of-care serum testing of metabolites in the donor or in the perfusate of an ex situ organ that could allow more precise information regarding the impact of DWIT on organ quality. Normothermic machine perfusion (NRP) is one of the techniques offering this option, because it allows for a real-time assessment of the damage to the liver at the end of DWIT, using the kinetic analysis of transaminases and lactate levels during perfusion.[22] In addition, ex situ hypothermic or normothermic MP also has the potential to analyze graft metabolomics during perfusion.

Donor Hepatectomy Time

Despite cooling the abdominal cavity with ice when the donor liver is perfused with cold preservation solution, some authors maintain that the warm ischemic insult during organ procurement continues during the hepatectomy until the liver is ensconced in the ice box.[23,24] This period, known as donor hepatectomy time (DHT), is defined as the period that starts at the end of DWIT when the procurement surgeon does the cross clamp of the aorta and starts cold perfusion of the organs until the moment the liver is taken out of the body of the donor. If DHT is prolonged, there is likely to be insufficient cooling with subsequent rewarming of the graft, with the initiation of the cascade of ischemic injury to the donor liver, and this may account for the negative impact of DHT on graft survival, particularly in DCD donors.[25]

IMPORTANCE OF SPo_2 AND HEMODYNAMIC PARAMETERS

The first center experiences focused on the impact of tDWIT. The described results show a wide variation, with some studies reporting no relation between tDWIT and recipient outcomes, while others reported more graft loss and increased incidence of IC (Table 2, left side). tDWIT is a quantitative measurement of DWIT but lacks the quality measurement of fDWIT with the assessment of vital parameters. Therefore, if the data are available, we recommend using the fDWIT as the leading measurement of ischemic time in donors.

To assess the course of fDWIT: Firl et al described 3 patterns in the hemodynamic trajectory for both blood pressure (BP; MAP) and Spo_2 after WLST[17]:

- Gradual decline of vital parameters following withdrawal of life support;
- Initial stable vital parameters after withdrawal of life support followed by rapid decline;
- Rapid decline of vital parameters.

This study along with other human and animal studies showed that Spo_2 declines earlier and more rapidly

TABLE 2.

Thresholds for DWIT and DHT to proceed with liver transplantation and relation with post-transplant graft loss and IC

Study	Y	N	Data source	Total DWIT	Graft failure	IC	Functional or asystolic DWIT	Graft failure	IC
Mateo et al[4]	2006	367	UNOS registry	Total DWIT >30 min	Yes	NA	NA	NA	NA
Lee et al[26]	2006	874	UNOS registry	Total DWIT >15 min and >30 min	Yes	NA	NA	NA	NA
Chan et al[27]	2008	52	Single center	Total DWIT	NA	No	MAP <50 mm Hg	NA	No
							MAP <35 mm Hg	NA	No
							Spo_2 <70%	NA	No
Ho et al[18]	2008	39	Multicenter	Total DWIT	No	No	SBP <50 mm Hg >15 min	Yes	Yes
deVera et al[5]	2009	141	Single center	Total DWIT >20 min	Yes	No	NA	NA	NA
Mathur et al[28]	2010	1567	SRTR	Total DWIT >35 min	Yes	NA	NA	NA	NA
Hong et al[21]	2011	81	Single center	NA	NA	NA	MAP <60 mm Hg for >20 min	Yes	NA
							Spo_2 <70%	No	No
DeOliveira et al[8]	2011	167	Single center	NA	NA	NA	Spo_2 <70% or SBP <50 mm Hg	NA	NA
Taner et al[6]	2012	200	Single center	Total DWIT	NA	No	Asystolic DWIT (incremental increase based on time)	NA	Yes
							SBP <50 mm Hg	NA	No
							Spo_2 <30%	NA	No
Abt et al[19]	2013	110	Multicenter	Total DWIT	No	NA	Slope of SBP in first 10 min after extubation (SBP10) (>27.2 mm Hg/min)	Yes	NA
Doyle et al[29]	2015	49	Single center	Total DWIT	NA	No	Spo_2 <70%	NA	No
							SBP <50 mm Hg	NA	No
							Asystolic DWIT	NA	No
Firl et al[17]	2016	98	Single center	NA	NA	NA	Hemodynamic trajectory (cluster 1)	Yes	No
Chirichella et al[30]	2016	45	Single center	NA	NA	NA	Combination of Spo_2 <80% or DBP <60 mm Hg	NA	Yes
Kubal et al[31]	2016	30	Single center	Total DWIT	NA	Yes	Combination of Spo_2 <70% or MAP <50 mm Hg	NA	No
Kalisvaart et al[16]	2018	93	Single center	NA	NA	NA	Spo_2 <80% (>26 min hypoxic functional DWIT)	Yes	No
Coffey et al[32]	2017	249	Multicenter	Total DWIT	No	No	Spo_2 <60%	No	No
							MAP or SBP ≤50 mm Hg	No	No
Schlegel et al[33]	2018	1153	UK database	NA	NA	NA	SBP <50 mm Hg (incremental increase based on time)	Yes	NA

DWIT, donor warm ischemia time; MAP, mean arterial pressure; NA, not applicable; SBP, systolic blood pressure; Spo_2, peripheral capillary oxygen saturation.

than MAP after withdrawal of life support.[16,34,35] Rhee et al also showed in an animal model that cessation of the hepatic flow occurs well before electric standstill of the heart.[34] Multiple European and North American centers reported their experience in 12 studies but used different cutoffs for the definitions of hypoxic and hypotensive fDWIT, as shown in Table 2 (right side). The duration of the hypoxic fDWIT ranged from 12 to 29 min, using cutoffs for Spo_2 between 30% and 80%. In comparison, the observed hypotensive fDWIT ranged from 14 to 22 min. Also, in these studies, a wide range of cutoffs were used, with MAP, SBP, and DBP. Two studies found a correlation between the duration of hypoxic fDWIT and graft loss.[16,32] In 2 other studies, graft loss was observed in case of a long hypotensive fDWIT.[18,21] In addition, Abt et al found that a slow decline in SBP (<27.2 mm Hg/min) was associated with a worse 5-year graft survival.[19] Two studies used a combined definition, where either Spo_2 or BP fell below the designated cutoff.[30,31] In both studies, this form of fDWIT was related to an increased incidence of IC. Three studies did not find any relation between the duration of hypotensive or hypoxic DWIT.[6,27,29] In the study by Firl et al described earlier,[17] a slow, gradual decline in MAP after withdrawal of treatment was related to increased risk for graft loss. In addition, hypotensive fDWIT (SBP < 50 mm Hg) was found to be an independent factor for graft loss in the recently developed UK DCD Risk Score.[33]

In the clinical scenarios of septic, cardiogenic, or hemorrhagic shock, the liver suffers from similar hypoxia or hypotensive injury similar to that which occurs during DCD organ donation. Until recently, it was thought that ischemia or hypotensive events might be responsible for this form of hepatic injury, but new studies suggest that hypoxia is an important cause for hepatic injury, even without hemodynamic shock.[36] PNF, where the transplanted liver is exposed to a very severe form of hepatic ischemia/reperfusion injury, is a known problem when using DCD grafts.[37] However, IC has been seen as the Achilles heel in DCD liver transplantation as they are the major cause for graft loss on the longer term.[38] Taner et al found that only the duration of the asystolic phase was related to the development of IC.[39] This implicates that the biliary tree might be less affected by hypoxia or hypotension during the agonal phase, compared to the full no-flow ischemia during the asystolic phase.

The limited number of the retrospective studies on fDWIT and the multiple definitions used for fDWIT has not provided a clear view on the impact of vital parameters after WLST. Therefore, we propose a universal measurement of perfusion and oxygenation during the donation process for all DCD donation programs worldwide. This includes a precise minute-by-minute description of the vital parameters. This data can then be used to further investigate the course and impact of fDWIT. These measurements

should be of the highest level of accuracy, using an arterial line for BP and pulse oximetry on the forehead. Forehead Spo_2 monitoring has been shown to be more accurate than finger Spo_2 measurements.[40,41] All these modalities are subject to changes in local vasoconstriction as well as any material placed on the skin or nails. For Spo_2, it should be taken into account that pulse oximetry is not reliable below a value of 80% and in case of significant arterial hypotension.[42-44] Despite these potential confounding issues, the inclusion of a measure of perfusion and oxygenation adds a second dimension to the previously described chronological valuation.

Previous National and Consensus Recommendations

Several national and international societies have published practice guidelines for DCD donation and liver transplantation and suggested the following definitions for fDWIT and thresholds to proceed with transplantation:

- The American Society of Transplant Surgeons recommended in 2009 that tDWIT should be <30–45 min and fDWIT (MAP < 60 mm Hg) be a maximum of 20–30 min to achieve better outcomes.[45]
- The British Transplantation Society defined the start of fDWIT at the time point when Spo_2 drops below 70% or SBP <50 mm Hg.[46] Using these thresholds, it is recommended to not use the liver for transplantation if fDWIT is longer than 30 min.
- The Eurotransplant Manual of the Eurotransplant International Foundation defines fDWIT as the period between Spo_2 <80% or MAP <50 mm Hg and cross clamp.[47] No recommendation is given about the maximum acceptable duration of fDWIT.
- The Spanish National Transplant Organization (Organización Nacional de Transplantes) updated their guidelines in 2015 and defined fDWIT as the time point when SBP <60 mm Hg and a stand-down is recommended if DWIT extends 30 min.[48] Measurement of Spo_2 was taken out due to the potential low value of Spo_2 by pulse oximetry in context of a marked arterial hypotension.[44]

Proposed Definition for fDWIT

The workgroup proposes the universal definition of fDWIT to be from Spo_2 <80% and/or MAP <60 mm Hg until the initiation of perfusion. The workgroup thought it is necessary to include both vital parameters, as in some donors Spo_2 will decline faster than MAP and vice versa. The Spo_2 threshold was chosen because previous studies have shown that noninvasive measurements are inaccurate when Spo_2 drops below 80%. The relatively high MAP threshold was chosen because an MAP <60 mm Hg has been considered the threshold for impaired organ perfusion in previous sepsis studies.[49,50] It should be noted that the studies investigated vital parameters during the agonal phase are smaller retrospective studies with noninvasive measurements. The working group chose relatively strict definitions to guarantee that there would only be a limited amount of ischemia before Spo_2 <80% or MAP <60 mm Hg after WLST. Future studies are required to further investigate the course and impact of these vital parameters during DWIT.

Recommendations

Definition of DWIT

- The ILTS recommends that DWIT should be specified as:
  - tDWIT: Withdrawal of treatment—cold flush (NRP: initiation of perfusion)
  - fDWIT:
    - The start of fDWIT is defined as the timepoint where either/or:
      - Spo_2 <80%
      - MAP <60 mm Hg
    - End of fDWIT: start of cold flush (NRP: initiation of perfusion)
- The ILTS recommends that the DHT is specified as: time from flush to liver out of the body, for the standard super-rapid retrieval technique (Table 3).

(Level of Evidence B–C; Grade of Recommendation I Strong)

Measurement of Vital Parameters During DWIT

- The ILTS recommends that during DCD procurement, measurements of perfusion and oxygenation (BP [SBP/DBP/MAP], Spo_2, heart rate) should be monitored in a minute-by-minute fashion.

(Level of Evidence B; Grade of Recommendation I Strong)

- Quality of the measurements should be, when possible, on the most accurate level:
  - BP: measurement with arterial line;
  - Pulse oximetry on the forehead or finger.
- Potential suboptimal measurements should be taken into account:
  - BP: cuff measurements inaccurate, especially in hypotension and limited frequency assessment;
  - Spo_2: Pulse oximetry has shown to be inaccurate at a level <80% and in case of local vasoconstriction or hypotension.

(Level of Evidence B; Grade of Recommendation I Strong)

- The determination of death is upon the decision of the responsible physician or healthcare worker in the donor hospital, according to local policy/legislation. However, the method of determination of death should be recorded as:
  - Mechanical asystole (pulseless electric activity);
  - Electric asystole.

(Level of Evidence C; Grade of Recommendation I Strong)

ACCEPTABLE THRESHOLDS FOR DWIT TO PROCEED WITH TRANSPLANTATION

Recommendations

- There are no large multicenter studies with accurate measurements to date, so the ILTS recommends further

TABLE 3.

Conclusion of evidence and recommendations on the specific subjects according to the GRADE system[14]

Conclusion of evidence	Studies	Level of evidence	Grade of recommendation
Definitions of DWIT			
The ILTS recommends that DWIT should be specified as: • tDWIT: withdrawal of treatment—cold flush (NRP: initiation of perfusion) • fDWIT: o The start of fDWIT is defined as the timepoint where either/or: ▪ Spo_2 <80% ▪ MAP <60 mm Hg o End of fDWIT: start of cold flush (NRP: initiation of perfusion) The ILTS recommends that the donor hepatectomy time is specified as: ▪ Time from flush to liver out of the body, for the standard super-rapid retrieval technique	Chan et al, 2008[27] Ho et al, 2008[18] Hong et al, 2011[21] DeOliveira et al, 2011[8] Taner et al, 2012[6] Thuong et al, 2014[15] Doyle et al, 2015[29] Chirichella et al, 2016[30] Kubal et al, 2016[31] Firl et al, 2016[17] Jochmans et al, 2018[25] Kalisvaart et al, 2018[16] Coffey et al, 2018[32] Schlegel et al, 2018[33] Farid et al, 2019[23]	B–C	I Strong
Measurement of vital parameters during DWIT			
The ILTS recommends that during DCD procurement, measurements of perfusion and oxygenation (BP [SBP/DBP/MAP], Spo_2, heart rate) should be monitored in a minute-by-minute fashion.	Firl et al, 2016[17] Kalisvaart et al, 2018[16]	B	I Strong
Quality of the measurements should be, when possible, on the most accurate level: • BP: measurement with arterial line • Pulse oximetry on the forehead or finger Potential suboptimal measurements should be taken into account: • BP: cuff measurements inaccurate, especially in hypotension and limited frequency assessment • Spo_2: Pulse oximetry has shown to be inaccurate at a level <80% and in case of local vasoconstriction or hypotension	Van de Louw et al, 2001[42] Carter et al, 1998[43] Sinex, 1999[44]	B	I Strong
The determination of death is upon the decision of the responsible physician or healthcare worker in the donor hospital, according to local policy/legislation. However, the method of determination of death should be recorded as: • Mechanical asystole (pulseless electric activity) • Electric asystole	Thuong et al, 2014[15]	C	I Strong
Acceptable thresholds for DWIT to proceed with transplantation			
There are no large multicenter studies with accurate measurements to date, so the ILTS recommends further prospective data collection to acquire evidence and more solid recommendations (ie, Creation of an international registry)	Expert opinion	C	I Strong
In the rise of NRP and ex situ machine perfusion, these definitions may change in the upcoming years	Expert opinion	C	I Strong
fDWIT is of greater utility than tDWIT to assess the risk of graft loss	Mateo et al, 2006[4] Lee et al, 2006[26] de Vera et al, 2009[5] Mathur et al, 2010[28]	C	I Strong
If fDWIT exceeds 30 min, an increased risk for graft loss should be taken into account. Donor, graft, and recipient characteristics and preservation methods should be considered in the final decision.	Ho et al, 2008[18] Hong et al, 2011[21] Kalisvaart et al, 2018[16] Schlegel et al, 2018[33] Khorsandi et al, 2017[24] Taner et al, 2012[6]	C	I Strong
Circumstances of organ procurement			
The ILTS recommends that the withdrawal of treatment takes place in the operating room to minimize fDWIT, but this is dependent on local policy/legislation.	Cao et al, 2016[51]	C	I Strong
Surgeons with experience in DCD liver procurement are required both for assessment of the graft and to minimize duration of hepatectomy.	Expert opinion	C	I Strong

BP, blood pressure; DBP, diastolic blood pressure; DCD, donation after circulatory death; DWIT, donor warm ischemia time; fDWIT, functional donor warm ischemia time; ILTS, International Liver Transplantation Society; MAP, mean arterial pressure; NRP, normothermic machine perfusion; SBP, systolic blood pressure; Spo_2, peripheral capillary oxygen saturation; tDWIT, total donor warm ischemia time.

prospective data collection to acquire evidence and more solid recommendations (ie, creation of an international registry).

(Level of Evidence C; Grade of Recommendation I Strong)

- In the rise of NRP and ex-situ machine perfusion, these definitions may change in the upcoming years (Table 3).

(Level of Evidence C; Grade of Recommendation I Strong)

Thresholds for tDWIT

Over the years, multiple groups have tried to identify the threshold for a maximum duration of tDWIT in DCD liver transplantation and different cutoffs have been suggested, as shown in Table 2 (left side). However, in reality, it is likely that thresholds do not exist, but rather warm ischemic insults have an incremental effect. As such, cut-off values will depend on the level of risk that is deemed acceptable in each respective transplant patient and transplant center. Risk tolerance may vary substantially in different environments based on a multitude of factors. These could include donor availability, waitlist mortality, regulatory environment, cultural expectation, program experience, and ability to retransplant a patient should significant IC or PNF develop.

In 2006, Mateo et al performed the first retrospective study (with DWIT analysis) with UNOS data comparing 367 hepatic allografts from DCD donors to a control group comprising 33 111 DBD grafts, and reported a statistically significant stepwise increase in the relative risks of graft loss when tDWIT >30 min.[4] The second analysis with almost 900 DCD grafts reported an increased risk of graft failure when the DWIT was >15 min with stepwise increase if the DWIT >30 min.[26] They reported a significant 1.8-fold higher graft loss rate when the DWIT ≥35 min compared to those with DWIT <15 min. In 2009, in a single center retrospective analysis (n = 141), de Vera et al reported that a DWIT >20 min was associated with poorer graft survival, with a relative risk of 1.63.[5] The last UNOS analysis from 2010 showed a significant 1.8-fold higher graft loss rate when the DWIT ≥ 35 min compared to those with DWIT <15 min.[28]

Thresholds for fDWIT

Due to the multiple definitions used for fDWIT, a wide variation in acceptable thresholds has been reported (Table 2, right side). Using a multicenter retrospective analysis, Ho et al found that the time from SBP <50 mm Hg to cold perfusion >15 min was the best predictor of subsequent complications such as death, PNF, IC, and graft loss.[18] Profound hypoxia did not correlate with poor outcome in this study. On the contrary, Kalisvaart et al reported that a prolonged hypoxic fDWIT (Spo_2 <80%) of >26 min was associated with more severe hepatic ischemia/reperfusion injury and subsequent graft loss, while no correlation between hypotensive fDWIT (MAP <50 mm Hg) and graft loss was observed.[16] In the UK DCD Risk Score developed by Schlegel et al, fDWIT (SBP <50 mm Hg) was one of the strongest predictors of graft loss in a multivariable model that included retransplantation, recipient age, donor body mass index, donor age, cold ischemia time, and lab model for endstage liver disease.[33] fDWIT showed a progressive additional risk when >20 min and >30 min. Not all studies found a relation between fDWIT and recipient outcomes. DeOliveira et al published their outcomes from a UK single center in 2011.[8] They defined fDWIT as the time from systolic of ≤50mm Hg or oxygen saturations of ≤70%, with a cut-off of 30 min, and no difference in graft survival was detected. Chan et al studied 3 different thresholds for hypoxic (Spo_2 <70%) and hypotensive fDWIT (MAP <50 or <35 mm Hg), but they failed to demonstrate any impact of these variables as predictive of the development of IC in a multivariate analysis.[27] In 2015, a single center retrospective analysis by Doyle et al included in their analysis the period from Spo_2 <70% to flush and cross-clamp, time from SBP <50 mm Hg to flush and cross-clamp, and asystolic DWIT. However, no significant association was found between these variables and graft failure.[29] The maximum DWIT accepted in this analysis was 30 min; however, the authors suggested the need to decrease the cut-off to 20 min when other risk factors such as donor age >45 was present.

NRP and DHT

Both NRP and DHT have been discussed by another working group of the Venice consensus meeting in the guideline statement Regulations and Procurement Surgery in DCD Liver Transplantation by Amelia Hessheimer et al. In brief, the recommendations of this working group were as follows[52]:

- DHT should be kept as short as possible—at most 60 min from the start of cold preservation (Level of Evidence B).
- Livers from DCD donors functional warm ischemia time >30 min 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).

Proposed Thresholds for fDWIT

Using the proposed definition for fDWIT starting after Spo_2 <80% or MAP <60 mm Hg, we recommend that if fDWIT exceeds 30 min, an increased risk for graft loss should be taken into account. Donor, graft, and recipient characteristics and preservation methods should be considered in the final decision. The working group chose this threshold with the limited available data on duration of fDWIT. It is thought that with the relative strict fDWIT definitions of Spo_2 and MAP in combination with the 30 min threshold for fDWIT, DCD grafts can be safely used with limited warm ischemia. Further studies to different circumstances (high-risk grafts or machine perfusion) are required.

Recommendations

Thresholds for duration of DWIT to proceed with DCD liver transplantation:

- fDWIT is of greater utility than tDWIT, to assess the risk of graft loss.

(Level of Evidence C; Grade of Recommendation I Strong)

- If fDWIT exceeds 30 min, an increased risk for graft loss should be taken into account. Donor, graft, and recipient

characteristics and preservation methods should be considered in the final decision (Table 3).

(Level of Evidence C; Grade of Recommendation I Strong)

CIRCUMSTANCES OF ORGAN PROCUREMENT

The transport of the donor between the location of donor WLST and the location of organ procurement is part of the tDWIT and fDWIT. Depending on local authorities, WLST can take place in the operating room, anesthetic room, or ICU, with large variations in transplant time. Cao et al compared the outcome of recipients between recipients of DCD and DBD grafts in a meta-analysis.[51] They found that if WLST took place in the operating room, DCD recipients had comparable graft survival with DBD recipients. However, if WLST took place in ICU, recipients of these DCD grafts had an inferior graft survival. This suggests that the location of WLST can have a significant impact on recipient outcomes.

Recommendations

- The ILTS recommends that the withdrawal of treatment takes place in the operating room to minimize fDWIT, but this is dependent on local policy/legislation.

(Level of Evidence C; Grade of Recommendation I Strong)

- Surgeons with experience in DCD liver procurement are required both for assessment of the graft and to minimize duration of hepatectomy (Table 3).

(Level of Evidence C; Grade of Recommendation I Strong)

Composite Warm Ischemia

The difficulty in all these studies is that they do not always take into account other predictors of outcome, like donor and recipient risk factors, and in particular other warm ischemic insults that can have a cumulative effect. These periods include

- Previous ischemic injury to the donor liver in the donor where the liver might have already been exposed to some ischemia (vasopressors, hemodynamic instability, etc)
- The DHT, as discussed earlier[23-25]
- The time interval between the liver leaving the body and being fully immerged in the ice box
- Rewarming during bench work in the recipient center
- The anastomosis time or recipient warm ischemia time[53]

Although the impact of some of these periods have not been studied (yet), it is likely that all warm ischemia is detrimental and that these warm ischemic periods interact as shown by the fact that the negative impact of hepatectomy time on outcome is more pronounced in DCD donors than in DBD donors.[25] Therefore, one can argue to that future studies should assess the cumulative periods of warm (and cold) ischemia and not only DWIT. In example, a composite warm ischemia Score could be developed with all the different warm ischemia periods.

CONCLUSIONS

The statements of this ILTS Working group on DWIT in DCD liver transplantation are listed in Table 3. The aim of the ILTS Venice Conference was to develop new universally applicable clinical guidelines for DCD liver transplantation. The level of evidence of most of the recommendations was not high, but there was a strong consensus among the experts. Regarding donor warm ischemia time, the most important recommendations include a new definition of the threshold for the onset of fDWIT (starting with Spo_2 <80% and/or MAP <60 mm Hg) and with using this threshold we recommend that if fDWIT exceeds 30 min, an increased risk for graft loss should be taken into account. These new definition and threshold for functional donor warm ischemia time is an important step to expand and improve the safe utilization of DCD livers.

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