Donation after Circulatory Death (DCD) Liver Transplantation

A Practical Guide

Kristopher P. Croome
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C. Burcin Taner
Editors

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To my amazing wife Sarah; you are my rock, my inspiration, and my partner in all that I do. Also to my children Xander and Charlotte, you bring light and joy to each and every day. Finally to all of my mentors; I am forever grateful for all the opportunities and guidance you have given me.

Kristopher P. Croome

To all the young and older patients awaiting the gift of life and to the donors who have made transplantation possible.

To my parents and sisters and to my sons Andrea and Matteo.

Paolo Muiesan

To my partner in life and wife Nilufer Ertekin-Taner for constantly trying to make me a better person.

To my daughters Su and Ada for constantly trying to make me a better dad.

To patients who trust us to make scientific progress towards a better future.

C. Burcin Taner

Preface

The transplant community continues to pursue novel strategies to help alleviate the worldwide disparity between the number of patients awaiting liver transplantation and the availability of donor organs.

Donation after circulatory death (DCD) donors represents a large area of potential growth in organ availability. Initial enthusiasm for liver transplantation using DCD donors in the early 2000s was tempered by early reports of high rates of biliary complications and inferior graft survival. With all new innovations, there is undoubtedly an initial learning curve and over time the collective outcomes with DCD liver transplant have improved both in North America and in Europe. Moreover, in several European countries, DCD donors now make up as much as 30% of all deceased donors.

In the present book, we aim to present the first comprehensive review of all facets of liver transplantation using DCD donors. Each of the 19 chapters has been written by leading experts in the field, representing some of the most experienced DCD liver transplant programs in the world. While several topics have overlapping coverage in different chapters, we feel this provides utility in that the reader is able to see the perspective of multiple experts on crucial topics. As editors of this book, we aimed to leverage the collective expertise of the wide-breadth of authors, by providing them the opportunity to express their expert opinion. It is our hope that this book will be a valuable resource for all those involved in liver transplantation using DCD donors.

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The History of DCD Liver Transplant

1

Adam S. A. Gracon and David P. Foley

Introduction

Based on the data of US Department of Health and Human Services' Organ Procurement and Transplantation Network (OPTN) as of September 2019, the number of organ procurements from donation after cardiac death (DCD) donors has increased significantly from 57 in 1994 to 2132 in 2018. In 2018, at least 5 DCD donor recoveries were performed in 98% of the donor service areas (DSAs), and at least 50 recoveries were performed in 20% of the DSAs. In all, a total of 19,885 DCD donor recoveries have occurred since the OPTN began DCD data collection in 1993. This is illustrated in Fig. 1.1. DCD now represents nearly 20% of all deceased donors. Similarly, the number of DCD liver donors has also increased significantly. In 1993 when data collection began, only 16 DCD liver transplants using these organs were performed in the United States. As of 2018, this number had increased to 764 with a total of 8300 DCD liver transplants performed since 1993. With this increase, DCD donors contribute livers for nearly 10% of liver transplants performed in the United States annually. DCD has proven to be a mechanism to increase the donor liver organ pool with acceptable outcomes [1]. However, when compared to donation after brain death (DBD) liver transplants, DCD liver transplantation is associated with increased risk.

The inception of modern organ transplantation was solidified in the 1950s and 1960s with technically successful allotransplantation of the kidney, liver, lung, pancreas, and heart [2–8]. Although further advances required technical refinement, improved understanding of immunology, and evolving immunosuppressive

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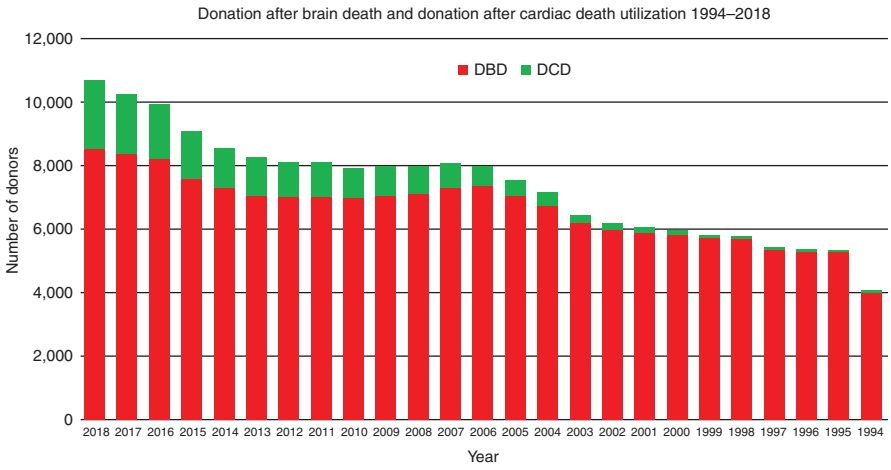

Fig. 1.1 Proportion of donation after brain death (DBD) and donation after cardiac death (DCD) donors annually in the United States from 1994 to 2018 based on the US Department of Health and Human Services' Organ Procurement and Transplantation Network (OPTN) data as of September 2019

regimens, the successful use of organs obtained in the setting of DCD was critical to early achievements in liver transplantation. Formerly referred to as non-heart-beating donation, or donation after cardiac death, DCD involves the cessation of circulatory and respiratory function prior to organ recovery. DCD donors were the primary source of deceased donor organs prior to the development of universally accepted brain death criteria. After the establishment of brain death criteria, DCD donors were all but abandoned as a source of liver allografts in favor of donation after brain death (DBD). DBD provided a means to recover organs in a controlled procedure during which time there was circulatory and respiratory function to keep the donor organs well perfused and oxygenated. Additionally, having well-accepted brain death criteria avoided many of the moral and ethical concerns that had been raised with DCD. It wasn't until the early 1990s when a significant expansion in the transplant waitlist instigated a resurgence in DCD as an approach to expanding the organ donor pool [9]. With continued evidence of acceptable recipient outcomes, DCD has now become a steadily growing source of transplant organs in the United States and in Europe.

The First DCD Liver Transplants

In 1963, Starzl et al. documented three liver transplants, representing the first liver allotransplants ever described in humans [2]. In addition, these first three cases also represented the first DCD donor livers recovered and utilized for transplantation. The first donor was a 3-year-old undergoing an attempted removal of a third ventricular brain tumor. During surgery, he sustained a cardiac arrest. Open cardiac

massage was performed for 45 minutes prior to death, after which an additional 15 minutes transpired prior to initiation of extracorporeal perfusion [2]. The liver was successfully recovered and transplanted into a 3-year-old male with congenital biliary atresia. Unfortunately, the recipient died as a result of acute blood loss in the operating room, 4 hours after reperfusion of the allograft.

The second donor was a 55-year-old man who was hospitalized for treatment of the sequelae of cerebral astrocytoma. Given his terminal illness, he was approached as a potential donor. His clinical course was monitored closely, including careful attention to blood pressure and urine output, which the transplant team used as a surrogate for good tissue perfusion. After suffering a respiratory arrest, that patient was placed on extracorporeal machine perfusion. His blood pressure prior to the time of arrest was 100 mmHg, and extracorporeal perfusion was initiated within 5 minutes of the pronouncement of death. The liver was successfully recovered and transplanted into a 48-year-old man with cirrhosis and a primary hepatoma. The recipient survived 22 days, but subsequently died as a result of massive pulmonary embolism.

The third donor was a 69-year-old who suffered an intracranial hemorrhage. Similar to the second donor, this donor's clinical course was monitored closely with regard to blood pressure and urine output with preserved blood pressure preceding a respiratory arrest. Extracorporeal machine perfusion was initiated within 6 minutes of his death. After successful recovery of the liver, a 67-year-old male with obstructive jaundice in the setting of intrahepatic carcinoma was transplanted. He survived 7.5 days with death resulting from progressive pulmonary dysfunction, suspected pulmonary embolism, and gastrointestinal hemorrhage.

With these early results, questions arose regarding the feasibility of successfully achieving long-term outcomes in liver transplantation. However, these questions abated when Starzl reported the first liver transplant with survival past the early postoperative period in 1968 [10]. In this case, an 18-month-old child survived for 13 months prior to dying as a result of metastatic hepatocellular carcinoma. Six additional patients were included in the same series who also had significant improvements in survival that were measured in months as opposed to days as had previously been reported [2, 10]. In all of these cases, organs were recovered from DCD donors.

During the same time that Starzl reported liver transplant survival beyond 1 year, Dr. Christiaan Barnard performed the first heart transplant in South Africa in 1967 [6]. In this case, the donor had suffered a traumatic brain injury and was deemed "brain dead" by a hospital neurosurgeon. Because death of the brain was a legally acceptable evidence of death in South Africa, the donor was taken to the operating room on ventilator support for organ procurement to occur. Interestingly, Barnard waited for the heart to stop beating prior to initiating procurement, at which point circulatory bypass was initiated and the patient was cooled [6, 11]. The heart was successfully transplanted, and this was considered the first successful heart transplant. At this point, the medical community recognized the strong potential of solid organ transplantation. The technical feasibility of transplantation for the treatment of end-stage organ disease had been clearly demonstrated. However, the availability

of viable donor organs became a persistent obstacle to widespread adoption. It was during this period of time that the concept of brain death was already an emerging topic of interest, but its relevance was propelled as concerns were raised regarding donor timing and criteria for death. Significant ethical and moral questions began to arise with no clear consensus.

Refining Criteria for Determination of Death: Transitioning to Donation After Brain Death

In 1968, an ad hoc committee from Harvard Medical School was formed with the purpose of examining the definition of brain death. Their report entitled "A Definition of Irreversible Coma" was published in the *Journal of the American Medical Association*. The primary purpose of this report was to "define irreversible coma as a criterion for death" [12]. Two critical reasons were provided to support the importance of this definition. First, significant improvement in the care of critically ill or injured patients had occurred resulting in many patients with permanent absence of neurologic function, despite the maintenance of circulatory function. It was acknowledged that this resulted in a significant burden on the patient's family, the hospitals, and the availability of hospital beds in the setting where a patient had no hope for neurologic recovery. Second, refining the definition of death would allow for the avoidance of controversy related to the recovery of organs for transplantation.

With the controversy that existed at that time, this report represented an important advance in both the care of the critically ill and solid organ transplantation. The committee's report gained broad support from religious, medical, and legal communities and was subsequently approved by the American Medical Association and American Bar Association [13, 14]. With clarification of criteria for determining death, physicians had an established framework for determining death prior to cessation of vital signs. This in turn could allow for procurement of organs prior to the cessation of heart function.

It was during this same year that the Uniform Anatomical Gift Act was approved at the National Conference of the Commissioners on Uniform State Laws. At this conference, a group composed of law professors, lawyers, and judges representing every state met to establish uniformity in state law [14, 15]. At the time the Act was approved, significant variability in state law existed regarding organ and tissue donation. This included some states with laws dating to the seventeenth century, other states with laws preventing the donation of certain organs, and states with no statutes related to donation at all. Given the legal complexities of human donation and lack of uniformity among states, the goal of this Act was to provide an acceptable legal environment that could facilitate donation of human tissue and organs [15]. Importantly, the Act established a legal consensus that states could use to establish new statutes.

These two advances in the medicolegal environment of transplantation were accompanied by the Uniform Brain Death Act in 1978, as well as its replacement,

the Uniform Determination of Death Act in 1980. These legal changes combined with a growing scientific understanding of the impact of warm ischemia on allograft outcomes resulted in most transplant centers focusing primarily on DBD and abandoning efforts in DCD. The incorporation of DBD allowed for a significant expansion in the donor pool and was accompanied by further advances in surgical technique and immunosuppressive strategies that led to improved outcomes. This allowed for even more expansion of the discipline and cemented transplantation as a viable treatment option for end-stage solid organ disease. However, with an increased number of transplants, even more candidates were being identified, and it became apparent at a very early stage that the supply of donor organs available was far short of the increasing demand [16].

Resurgence of DCD

By the early 1990s, more than 15,000 organ transplants were being performed annually in the United States. However, at the same time, there were more than 30,000 patients waitlisted for transplant [13]. Additionally, the disparity between available donor organs and the number of recipients on the waitlist was increasing. From 1988 to 1991, the number of transplant candidates on the waitlist rose by 55%. However, over this same time period, the number of donors increased by only 16% [9]. In response to the growing need for available donor organs evidenced by increasing numbers of candidates dying on the transplant waitlist, alternative sources of organs began to be explored. This included re-examining and re-expanding the use of DCD donors as a viable approach to expanding the donor pool.

Efforts in this pursuit were begun in the late 1980s and early 1990s and were largely driven by a small number of academic medical centers. Some of these centers, such as the University of Wisconsin, never abandoned the use of DCD for renal allografts, but instead continued optimizing their use in conjunction with the introduction of DBD. In fact, the University of Wisconsin has included the use of DCD as part of their transplant program since its inception in 1966, expanding to include extrarenal organs in 1993 [17, 18]. Other centers, including the University of Pittsburgh Medical Center (UPMC), re-engaged in the use of DCD donor organs as a mechanism for further expansion of the donor pool. In the case of UPMC, preliminary estimates from their local organ procurement organization (OPO) were that utilizing DCD had the potential to increase the donor pool by 20–25% [9]. After nearly 4 years of development, UPMC finalized the first published DCD policy in the United States in May 1992. In total, more than 100 individuals participated in development of the policy, which involved a wide variety of stakeholders including physicians, other healthcare providers, ethicists, legal experts, clergy, social workers, the local organ procurement organization, and civic leaders [19]. This policy outlined several critical principles that established a framework for the use of DCD organs that could be utilized by transplant centers nationwide. Many of these principles continue to guide the approach to DCD recoveries today including patient autonomy, healthcare provider roles in the care of the patient, and clearly

emphasizing the importance of separation of the surgical recovery team from the primary team caring for the donor [20]. The efforts focused on further expansion of DCD by the University of Wisconsin and UPMC. However, other centers were still reluctant to implement similar policies due to controversy based on perceived ethical or moral conflicts [21].

In an effort to foster the public's understanding and acceptance of organ procurement, the medical community continued focusing on three established fundamental principles of organ procurement. These include requiring the patient or family consent prior to organ procurement, prohibition of actively hastening a donor's death, and dead donor rule [22]. The dead donor rule refers to a requisite that donor death occurs prior to organ procurement and similarly that the process of organ procurement cannot cause death. This terminology was first used by John Robertson in 1988, and although the nomenclature is not codified in law, it represents one of the primary tenets of organ donation related to DCD since it began in the 1960s [22]. These efforts that included the development of institutional policies and protocols at participating transplant centers ultimately led to endorsements by the Institute of Medicine (IOM) and Joint Commission for the Accreditation of Hospitals Organization in the late 1990s and early 2000s [17, 23–25].

With further expansion in the use of DCD organs, a national conference on DCD was convened in 2005 in Philadelphia to facilitate alignment among all stakeholders on critical issues related to their use [26]. Included was broad representation of the medical community including medical and surgical transplant physicians, as well as critical care physicians, neuroscientists, and bioethicists. The primary goal of the conference was rooted in addressing the critical components of DCD donation through dedicated workgroups. This included donor-specific topics such as clarifying candidacy. Consensus was made to focus on those donors with irreversible or end-stage disease processes where withdrawal of life-sustaining treatment was already being considered by the patient's treatment team. Importantly, the discussion of candidacy also incorporated approaches to identifying which candidates can be expected to progress to death within a timeframe that would allow organ donation to proceed. Included was the use of early prediction tools such as the University of Wisconsin's DCD assessment algorithm. The DCD prediction tool incorporated donor-specific variables such as ventilatory settings, oxygenation status, age, BMI, and vasopressor requirements to establish a scoring system where donors are stratified into high, moderate, and low risk for progression to death [26]. This would allow transplant centers to pursue recovering those organs in donors with a high likelihood of progressing to death. Another donor-specific point of discussion at the conference was the determination of death by cardiopulmonary criterion, where the necessity of both cessation of function and irreversibility was highlighted. Recognizing the possibility of donor autoresuscitation, the duration of a dedicated period of observed circulatory cessation to determine death was a topic of debate. The group of attendees agreed that a period of observation time was necessary to confirm that no autoresuscitation of the heart and circulation had occurred prior to the declaration of death. However, no evidence-based recommendation could be made for one

definitive time period. The group also agreed that the IOM recommendation of 5 minutes and the Society of Critical Care Medicine recommendation of at least 2 minutes, but no more than 5 minutes, were acceptable observation time periods for future DCD protocols.

Given the absence of universal protocols in the management of patients who are destined to become DCD donors, conference workgroups also targeted the establishment of protocols for DCD organ recovery and transplantation. This included premortem administration of medications such as heparin and vasodilators as well as procedures including cannulation of arteries for infusion of preservation solution after death has been declared. Ultimately, local OPO protocols were in favor of informed consent being critical for any premortem interventions that would be used while abiding by the principle that any intervention on the donor should not hasten death.

With a recognition that DCD organs carried additional risk when compared to DBD organs, approaches to mitigating risk also began to be delineated by conference workgroups. Included were proposals for acceptable donor warm ischemia time (WIT), posited to be a risk factor in recipient outcomes. At this early stage, recommendations for desirable WIT included less than 60 minutes for kidneys, 30 minutes for livers, and 60 minutes for pancreas. However, it was noted that additional data were needed, and recommendations were made for changes in data collection that would allow further study. Lastly, the conference attendees focused on the future use of DCD organs. Dedicated workgroups were tasked with addressing the expansion of OPOs participating in DCD recoveries, overall DCD organ allocation, and public perception of DCD [26]. This conference underscored that the early success of DCD organ transplant had rendered it an important component of transplantation and provided a consensus-guided framework for continued expansion.

Early Outcomes with DCD Liver Transplant

With increasing experience in DCD liver transplantation in the 1990s, single-center series began to be reported. In 1995, UPMC published the first small series reporting results of liver transplants involving 17 DCD donors [27]. This included ten uncontrolled DCD donors where procurement occurred after a period of CPR and seven controlled DCD donors where procurement occurred after withdrawal of care in the operating room. In the case of the uncontrolled DCD donors, six were transplanted with 50% of recipients requiring early retransplant for either primary nonfunction or vascular complications. In contrast, six of the controlled DCD donor livers that were used demonstrated excellent initial function. However, two patients developed early hepatic artery thrombosis within the first month, and a third patient died at 2 months with a functioning graft. The other three patients were alive at 27 months of follow-up. The authors of this series suggested that controlled DCD may provide adequate liver allograft function but uncontrolled DCD was suboptimal given the rate of complications [27]. In the same year, D'Alessandro et al. at the

University of Wisconsin published a second small series of 16 DCD donors with a total of 39 organs transplanted, including 5 liver transplants [28]. One of the five recipients required retransplantation for primary non-function related to technical complications. Of the remaining four recipients, three had a functional graft after at least 12 months of follow-up. Again, this supported the findings from UPMC suggesting that DCD liver transplantation provided acceptable allograft function. Importantly, over the short study period, the group in Wisconsin were also able to demonstrate an increase in transplanted renal and extrarenal organs of nearly 10% using DCD donors [28].

With these studies demonstrating proof of concept for DCD liver transplantation, their use expanded allowing for further investigation and delineation of comparative outcomes as well as risks. A larger study of 36 DCD liver transplants performed between 1993 and 2002 was published in 2005 by Foley and colleagues from the University of Wisconsin [29]. These outcomes were compared to 553 liver transplants from DBD donors. Overall patient survival rates at 1 year (DCD, 80%, versus DBD, 91%) and 3 years (DCD, 68%, versus DBD, 84%) were significantly lower in the DCD group ($P = 0.002$). Similarly, graft survival rates at 1 year (DCD, 67%, versus DBD, 86%) and 3 years (DCD, 56%, versus DBD, 80%) were also lower in the DCD group ($P = 0.0001$). Post-transplant complications were also compared between DBD and DCD recipients. The overall rate of biliary strictures was found to be greater in DCD at 1 year (33% versus 10%) and 3 years (37% versus 12%; $P = 0.0001$). Similarly, the incidence of both hepatic artery stenosis (16.6% versus 5.4%; $P = 0.001$) and hepatic abscess or biloma formation (16.7% versus 8.3%; $P = 0.04$) were greater among DCD liver recipients [29]. The group however did not find an increased incidence of primary non-function, hepatic artery thrombosis, or portal vein complications in DCD livers when compared to DBD [29]. Although these early reports highlighted an increased risk of complications when using DCD liver allografts, they also suggested that patient outcomes were sufficient to warrant expanded use.

Additional studies published during this period further highlighted increased risk associated with the use of DCD liver allografts. In comparing biliary complications between DCD and DBD recipients, Abt et al. demonstrated that major biliary complications occurred in 33.3% of DCD recipients compared to 19.2% among DBD recipients ($P < 0.01$) [30]. Similarly, Maheshwari et al. demonstrated a high rate of biliary complications in DCD. Here, it was shown that 60% of DCD recipients developed biliary complications. In further delineating characteristics of these complications, 10% involved a major bile leak in two patients, 25% involved anastomotic strictures, 35% involved hilar strictures, 45% involved extrahepatic donor duct strictures, and 50% involved intrahepatic strictures [31]. However, it was not entirely clear as to which patients with intrahepatic bile duct strictures could avoid the need for retransplantation.

Focusing on classification, as well as prognosis, Lee et al. examined 44 DCD liver allograft recipients who developed intrahepatic biliary strictures postoperatively [32]. Four patterns of strictures were classified into groups based on cholangiography. These included unilateral focal, confluence, bilateral multifocal, and

diffuse necrosis. This analysis revealed that the characteristics of ischemic strictures had a significant impact on patient outcomes. In the setting of unilateral focal and confluence lesions, patients had a good prognosis with biliary interventions alone. In contrary, patients with bilateral multifocal and diffuse necrosis-type lesions had high rates of biliary interventions with some improvement, but the majority progressed to retransplant or death more frequently [32]. It was at this point that the transplant community recognized that not all intrahepatic strictures required retransplantation. In fact, many could be managed through percutaneous transhepatic approaches or endoscopically, whereas severe cases of multifocal strictures and diffuse biliary necrosis require timely retransplantation.

Addressing Increased Risk with DCD Liver Transplantation

An appreciation for the disproportionate rate of biliary complications in DCD liver recipients instigated further investigation to identify contributory factors [33]. It also resulted in new approaches to mitigation. During the past 15 years, more attention has focused on the mechanisms behind the development of cholangiopathy in DCD liver transplants. Although several potential mechanisms for ischemic cholangiopathy have been proposed, one unproven hypothesis states that thrombus formation in the peri-biliary arterial plexus leads to bile duct ischemia and ultimately irreversible biliary strictures. As a result, an early approach to prevention included the use of tissue plasminogen activator (TPA). As demonstrated by Hashimoto et al., initial reports suggested benefit in the use of TPA [34]. Here it was shown that approximately 10% of DCD liver recipients developed ischemic biliary strictures when TPA was introduced into the donor hepatic artery prior to transplantation. When compared to published rates, this represented significant improvement.

Another strategy for the prevention of biliary complications emerged with the analysis of DCD liver transplant recipients receiving induction immunosuppression. Halldorson et al. demonstrated that the use of anti-thymocyte globulin resulted in significantly reduced rates of ischemic cholangiopathy when compared to basiliximab induction (12.5% vs. 35.2; $p = 0.011$), as well as improved graft survival [35]. More recently, ex vivo liver perfusion has emerged as a novel strategy to improve outcomes after transplant. Ex vivo normothermic liver perfusion can also be used to evaluate DCD liver function prior to transplantation and to potentially reduce post-transplant complications [36]. This exciting research in ex vivo liver perfusion may lead to identifying predictive factors of graft failure and improved selection of DCD liver grafts for transplant [37, 38]. Similarly, extracorporeal perfusion support at the time of donor procurement and normothermic regional perfusion, similar to that used by Starzl, have demonstrated initial success [39, 40].

Finally, with further characterization of donor and recipient factors that contribute to DCD liver transplant outcomes, prediction scoring systems have been developed more recently to aid in optimizing donor-recipient matching. This includes the

recently published UK DCD risk score, which incorporates donor factors such as age and BMI as well as recipient factors including age, model for end-stage liver disease (MELD) score, and whether they have had a previous transplant. Additionally, the score incorporates procurement-specific factors including functional donor warm ischemia time and cold ischemia time [41]. Although it is unlikely these scoring systems incorporate all relevant factors associated with worse outcomes in DCD liver transplant, they do serve as a framework to help guide decision-making when evaluating potential donors and recipients.

Conclusions

As illustrated in Fig. 1.2, the field of liver transplantation using livers from DCD donors has incorporated multiple notable events shaping its evolution over the past 50 years. While early on there was concern regarding the feasibility of DCD liver transplantation and the ethical boundaries of DCD organ recovery, the focus now has evolved to mitigating risk factors for cholangiopathy and graft loss. By identifying optimal donor and recipient matching and utilizing adjunctive ex vivo therapies to decrease organ injury, increased utilization and improved outcomes will be achievable. Additionally, ongoing improvement in technical and logistic components of DCD recovery including standardization will help further expand DCD throughout all DSAs. This will be of particular importance as liver allocation policies move toward broader distribution of organs, which will necessitate local surgeons be capable of performing reliable and reproducible recovery operations that recipient surgeons can depend on. It is hopeful that more research in these areas will lead to a potential expansion of the DCD donor liver pool and thus an increase in the number of lifesaving liver transplants.

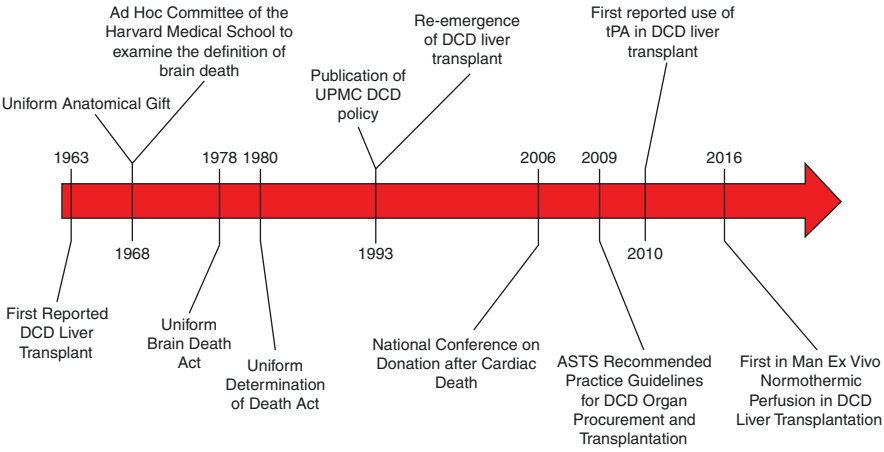

Fig. 1.2 Timeline of notable events in the history of donation after cardiac death liver transplantation

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Ethics and Law of DCD Transplant

2

Annalisa Dolcet, Kristopher P. Croome, and Nigel Heaton

Throughout the world, the practice of organ donation for transplantation is governed by the dead donor rule, that is, non-paired vital organs can be retrieved only from patients who are dead. Prior to the development of the Harvard criteria for brain death in 1968, all deceased organ donors were declared deceased using circulatory arrest criteria and thus represented the first donation after circulatory death (DCD) organ transplants performed [1]. In the United States, most states have adopted the Uniform Determination of Death Act (UDODA) or a very close variant. According to the UDODA, an individual who has sustained either (1) irreversible cessation of circulatory or respiratory functions or (2) irreversible cessation of all functions of the entire brain, including the brainstem, is dead [2].

Following the acceptance of declaration of death according to neurological criteria as a legal entity, most countries including the United States preferentially utilized donation after brain death (DBD) donors until the 1990s. At that time, the ongoing shortage of donor organs led to renewed pursuit of potential donors following declaration of death from cardiorespiratory arrest. Potential controversies surrounding this form of organ donation caused the Department of Human Health Services (DHHS) to ask the Institute of Medicine to evaluate the medical and ethical issues surrounding DCD transplantation. In 1997, the Institute of Medicinve concluded that organs recovered from asystolic donors were a medically effective and ethically acceptable way of bridging the gap between demand and supply of human organs [3].

With DCD, the mode of death and donation is very different from DBD and raises a number of ethical considerations which include: the timing of the decision with regard to the withdrawal of treatment in patients who may be potential donors,

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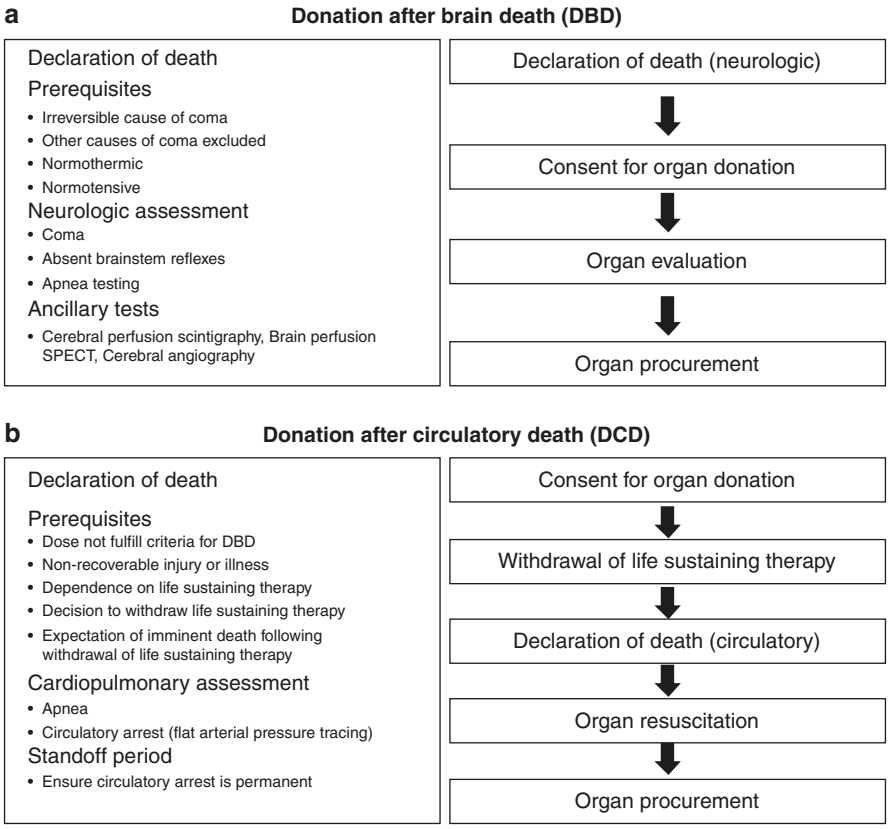

Fig. 2.1 (**a**, **b**) Deceased donation pathways

donor treatment prior to death to protect potential donor organs, site for withdrawal of treatment (based on access to theater), declaration of death, and stand-off time prior to starting retrieval and organ allocation/sharing and recipient outcomes (Fig. 2.1). Discussing the ethical issues of DCD is particularly important given the variations in aspects of clinical practice and DCD policies in different countries, not just worldwide but even within Europe. Common standards and operating policies have yet to be defined internationally to ensure the integrity of and public confidence in organ donation and transplantation.

The following are some of the key ethical principles that must be considered in all decisions surrounding DCD organ donation:

- *Altruism*: the voluntary stated wish of the individual to make the "gift" of donation of his/her organs upon death without expectation of reward
- *Autonomy*: the right of the individual to determine his/her own fate, including that of his/her organs after death

- *Dignity*: the unique and precious status of the human being and the ethical requirement to treat it respectfully without inflicting harm in both life and death
- *Non-maleficence*: the ethical principle that healthcare professionals should not cause harm or distress to their patients
- *Futility*: the contentious principle that it is unethical to perform interventions which cannot benefit the individual receiving them; the controversy focusing upon what does or does not constitute benefit

In addition, the following concepts must be considered with regard to how DCD organs are utilized or allocated:

- *Equity*: the concept of fairness or justice with respect to the way the organs donated are allocated and utilized.
- *Efficiency*: this ensures minimal waste of organs.
- *Utility*: distribution of organs maximizes benefit to recipients, "the greatest good for the most people".

Classification of DCD Donors

Initially, to describe donation from patients who died of cardiorespiratory arrest, the term *non-heart-beating donor* (NHBD) was used in Europe and was adopted at the First International Workshop on Nonheart-Beating Donors in Maastricht in 1995. At that time, donors after circulatory death were divided into four categories known as the Maastricht classification [4] (Table 2.1).

Attempts to improve the Maastricht classification have focused on adding more categories. A subsequent form of classification proposed by the Spanish national consensus to adjust the Maastricht classification included a number of subcategories [5] (Table 2.2). Further modifications to the classification were proposed by Detry et al. after the Eurotransplant organization including eight different countries formally recognized the possibility of organ donation after euthanasia in the Netherlands, Belgium, and Luxemburg [6]. In this classification, a fifth category, which consists of euthanasia or medically assisted cardiocirculatory death, was included (Table 2.3). Finally, following the DCD Conference in Paris in 2013, it was agreed to modify the original Maastricht classification and update according to new developments but attempt to keep its relative simplicity and straightforwardness (Table 2.4) [7].

Table 2.1 Maastricht classification of donors after circulatory death 1995

Category	Description	Procurement
I	Dead on arrival	Uncontrolled
II	Unsuccessful resuscitation	Uncontrolled
III	Awaiting cardiac arrest	Controlled
IV	Cardiac arrest while brain dead	Uncontrolled

Table 2.2 Modified Maastricht classification for donors after circulatory death (Madrid 2011)

Uncontrolled DCD	I	Dead in the out-of-hospital setting	Includes victims of a sudden death, whether traumatic or not, occurring out of the hospital and who, for obvious reasons, have not been resuscitated
	II	Unsuccessful resuscitation	Includes patients who suffer a CA and in whom CPR has been applied and resulted unsuccessful
			II. a. Out-of-hospital CA occurs in the out-of-hospital setting and is attended by an extra-hospital emergency service which transfers the patient to the hospital with cardiac compression and ventilatory support
			II. b. In-hospital CA occurs within the hospital, being attended by healthcare personnel with immediate initiation of CPR
Controlled DCD	III	Awaiting cardiac arrest	Includes patients in whom withdrawal of life-sustaining therapies is applied∗, as agreed upon within the healthcare team and with the relatives or representatives of the patient
	IV	Cardiac arrest while brain dead	Includes patients who suffer a CA in the process of the determination of death by neurological criteria or after such determination has been performed, but before the transfer to the operating theatre. It is likely that restoration of cardiac activity is first attempted, with a switch to the protocol of donation after circulatory death, if this fails

Table 2.3 Modified Maastricht classification for donors after circulatory death (Detry, 2012)

Uncontrolled DCD	I	Dead in the out-of-hospital setting	IA. Cardiocirculatory death outside hospital with no witness. Totally uncontrolled
			IB. Cardiocirculatory death outside hospital with witnesses and rapid resuscitation attempt. Uncontrolled
	II	Unsuccessful resuscitation	IIA. Unexpected cardiocirculatory death in ICU. Uncontrolled
			IIB. Unexpected cardiocirculatory death in hospital (ER or ward), with witnesses and rapid resuscitation attempt. Uncontrolled
Controlled DCD	III	Awaiting cardiac arrest	IIIA. Expected cardiocirculatory death in ICU. Controlled
			IIIB. Expected cardiocirculatory death in OR (withdrawal phase>30 min). Controlled
			IIIC. Expected cardiocirculatory death in OR (withdrawal phase<30 min). (highly) controlled
	IV	Cardiac arrest while brain dead	IVA. Unexpected cardiocirculatory arrest in a brain-dead donor (in ICU). Uncontrolled
			IVB. Expected cardiocirculatory arrest in a brain-dead donor (in OR or ICU). (highly) controlled
	V	Euthanasia	VA. Medically assisted cardiocirculatory death in ICU or ward. Controlled
			VB. Medically assisted cardiocirculatory death in OR. Highly controlled

Table 2.4 Modified Maastricht classification for donors after circulatory death (Paris 2013)

Category I Uncontrolled	Found dead IA. Out-of-hospital IB. In-hospital	Sudden unexpected CA without any attempt of resuscitation by a life medical team; WIT to be considered according to national life recommendations in place; reference to in- or out-of-hospital (IH-OH) life setting
Category II Uncontrolled	Witnessed cardiac arrest IIA. Out-of-hospital IIB. In-hospital	Sudden unexpected irreversible CA with unsuccessful resuscitation by a life medical team; reference to in- or out-of-hospital (IH-OH) life setting
Category III Controlled	Withdrawal of life-sustaining therapy	Planned withdrawal of life-sustaining therapy[a]; expected CA
Category IV Uncontrolled Controlled	Cardiac arrest while brain dead	Sudden CA after brain death diagnosis during donor life management but prior to planned organ recovery

Avoiding Conflicts of Interest

DCD donors are unique in that prior to declaration of irreversible cessation of circulatory or respiratory function, they are still a living patient. In this setting, there are many interventions that may improve the successful donation of organs but may not directly benefit or may even hasten the death of the potential donor. In order to avoid actual or perceived conflict of interest, the transplant team members should not be involved in decisions related to patient prognosis, withdrawal of ventilatory or organ-perfusion support, or determination of death [8].

Potential of DCD

As a result of public campaigns and information to gain support and understanding, the contribution of DCD to overall deceased donor numbers has increased but still varies internationally. Differences in medical practices, public attitudes, legislature, and resources all influence DCD practice worldwide. In some countries such as the United Kingdom, the Netherlands, and Spain, DCD accounts for a substantial proportion of overall deceased organ donors, whereas in other countries it is unusual because of legal restrictions (e.g. Italy where the death of a patient is declared only after a 20-minute flat ECG that proves asystole). In Holland, Australia, and the United Kingdom, the numbers of controlled DCD donors have been increasing substantially over the last decade and now represent more than one-third of all deceased organ donors (Fig. 2.2) [9].

In the United Kingdom, intensivists are comfortable with making decisions regarding the futility of continued interventions and support, accounting for as many as 60% of deaths in the UK ICUs after a decision to limit or withdraw treatments that are judged to be of no overall benefit to the patient [10].

This creates the potential for controlled DCD in contrast to countries such as Spain and other Southern European countries where decisions to limit life-sustaining

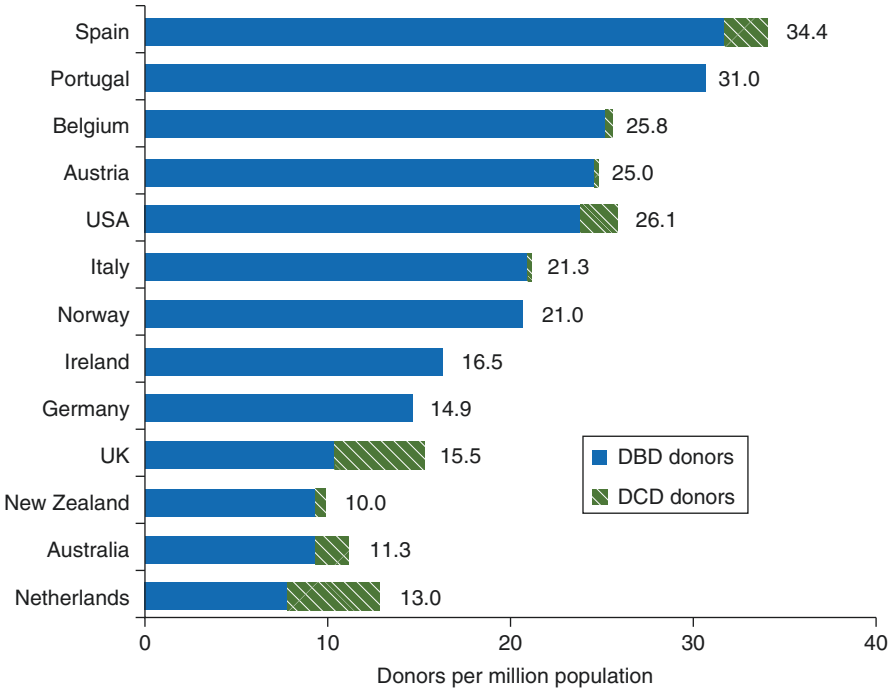

Fig. 2.2 Donors per million population in different countries. (Reprinted from Murphy and Smith [9]. With permission from Elsevier)

treatments (particularly with regard to admission to ICU) are less common and the potential for controlled DCD is lower. The reasons for these differences are complex, besides social acceptance of treatment withdrawal and medical care issues, and many focus on the striking international variation in the ICU bed capacity. For instance, there are 27 ICU beds per million population (pmp) in the United Kingdom compared with 76 in Australia and 87.5 ICU beds pmp in Spain; it seems inevitable that intensivists in the United Kingdom may both avoid admitting patients to ICU with a hopeless prognosis (including those with acute catastrophic brain injury) and also consider withdrawing treatments that are no longer beneficial sooner than colleagues in other countries with greater critical care capacity [11].

Difference in Treatment Withdrawal

Decision-Making

All DCD guidelines recommend that the decision to withdraw cardiorespiratory support should always be independent and made before any consideration of organ donation. Most also advise separation of these discussions in time and that the approach should be made by staff experienced in organ donation and with

appropriate training in managing grieving families. No member of the transplant or donor coordination team should be involved in decision-making around withdrawal of treatment. Specialist Nurses-Organ Donation should not provide medical care for the potential donor while they are still alive.

Timing of Treatment Withdrawal

Treatment withdrawal is delayed until a retrieval team has travelled to the donor hospital and completed their necessary preparations in theatre. It is vital that those responsible for organ allocation and retrieval do all they can to minimize unnecessary delay, recognizing the needs of the donor and their family at this time. This is particularly important in circumstances when it is proposed to delay withdrawal until the recipients of particularly vulnerable organs (e.g. liver, pancreas, and lung) have been identified and admitted to the transplant center.

Manner of Treatment Withdrawal

There is a significant variation in how treatment withdrawal is managed in adult critical care units, particularly with regard to airway management and the use of medication to provide comfort. Although guidelines have been published regarding the withdrawal of treatment, these documents do not provide a specific protocol for how end-of-life care should be managed. Many DCD guidelines recommend that treatment withdrawal should follow the standard protocols of the intensive care unit, to ensure that ICU practitioners do not have a conflict of interest in treatment withdrawal decisions and practice. The interests of a patient as a donor are better served by sedation and extubation, as this makes donation more likely and, importantly, does no harm to the patient. However, while it is widely held that terminal extubation promotes the possibility of DCD, evidence to support this view is limited and not supported by data from the "UK Potential Donor Audit." In any event, there is currently no consensus within adult ICU practice in the United Kingdom on how the airway should be managed during treatment withdrawal for DCD or on the use of adjuvant sedation, anxiolysis, and analgesia. It is therefore usually left to individual ICUs to formulate their own protocols. Our experience is that planned extubation should be included in withdrawal protocols. Although the need to develop and adhere to such protocols applies to all end-of-life care decisions, it is of particular importance that all units with DCD programs have such protocols and that clinicians work within them in a consistent and transparent manner.

Location of Treatment Withdrawal

To standardize the approach to DCD organ donation, local written policies are key to avoiding misunderstandings. Withdrawal of treatment within the operating

theatre reduces the potential warm ischemic time (WIT) after the diagnosis of death. Units planning for withdrawal in the operating theatre must have systems in place to ensure that a patient's right to comfort, dignity, and privacy is guaranteed and that this care is delivered by appropriately trained and experienced healthcare professionals such as members of the ICU or theater team. The transfer of the care of a dying patient to theatre staff, who may not be trained and inexperienced in end-of-life management, is unacceptable and unethical. Similarly, it is important that unlimited access for close family, friends, and those meeting the religious or spiritual needs of the patient are ensured within this environment. It is also important that the medical professional responsible for confirming death is suitably experienced and readily available and that a plan for the subsequent care of the patient should be in place should death not occur. In Australia, withdrawal of cardiorespiratory support is almost always undertaken in ICU as it is considered that death in the operating theatre is a rare and difficult event for staff. Such an approach ensures that if cessation of the circulation does not occur in a time frame compatible with donation, further disruption to the family and patient is avoided and distress minimized. Members of the transplant team, including donor transplant coordinators, must not be involved in any aspect of the end-of-life care.

Premortem Interventions

Potential DCD donors invariably lack capacity at the time of their final illness, although there are occasions where patients with neurological illness such as motor neurone disease, high cervical cord injury, and end-stage respiratory failure have consented themselves for donation. In circumstances where patients lack capacity for decision-making, ICU clinicians in the United Kingdom have an obligation to limit treatments to those which offer some overall benefit to their patient. In the past, such assessments have focused heavily upon what might be considered to be in the medical best interests of an individual, an approach that might appear to render interventions to promote deceased donation for the benefit of a third-party transplant recipient unethical and even unlawful. However, it is now recognized that what is of "overall benefit" to an individual within the context of their end-of-life care is much broader than this and should include an assessment of factors such as their emotional, cultural, family, and religious interests and also the patient's medical condition. These interests, including those relating to organ donation, are usually determined by discussions with the patient's family and by consulting the organ donor register in countries that have one. Once it is established that an individual wished to be an organ donor, then certain interventions can be considered to be in their best interests if they facilitate donation and do not cause distress or harm.

Interventions that may or may not represent potential harm should be assessed on an individual basis. What might be the correct course of action for one individual might not be for another. Using this approach, obtaining blood samples, maintaining life-sustaining treatment, and altering the time and place of treatment withdrawal may all be considered to be in a patient's best interests if they had given an

expressed desire to be an organ donor and they represent no harm, whereas interventions such as systemic heparinization (which might promote the expansion of an intracerebral hematoma), cardiopulmonary resuscitation, and femoral cannulation that might inflict pain or distress to a patient or the close family or accelerate death are unlikely to be considered in the patient's best interests in most societies. However, interpretation of these aspects of "care" vary across the world (the utilization of premortem heparin is acceptable in the United States but not in the United Kingdom), and hence the view of what is ethical is not consistent and varies between countries, hospitals, and clinicians.

Absence of Circulation Before the Diagnosis of Death

One of the most debated areas in the practice of DCD is at what point death can be declared after loss of the circulation and respiration. DCD requires that death is declared at the earliest possible time after circulatory arrest that is medically, ethically, and professionally acceptable to minimize warm ischemic time while ensuring that the dead donor rule is not breached, that is, the patient is not unintentionally killed as a result of donating their organs. Perhaps surprisingly, there has until recently been very little professional guidance on how and when to declare death after loss of the circulation and respiration. This is despite the fact that globally, circulatory criteria are the most commonly used and accepted criteria for determination of death. However, the introduction of DCD programs and reports of autoresuscitation (spontaneous return of the circulation after circulatory arrest) have brought these criteria into sharp focus and resulted in the publication of many national guidelines.

Much controversy surrounds the precise time that needs to elapse after the onset of circulatory arrest before "irreversible" death can be declared. There is a significant variation around the world, with some believing that the criteria for the determination of death are being manipulated to facilitate transplantation while apparently not breaching the dead donor rule. Others have suggested that the dead donor rule has resulted in the definition of death being revised inappropriately and should therefore be abandoned, permitting the removal of vital organs while a donor was still alive. They argue that with proper safeguards, no patient will die from organ donation who would not otherwise die as a result of the withdrawal of life support [12].

Most countries allow death to be confirmed (and therefore organ retrieval to begin) after 5 minutes of continuous cardiorespiratory arrest (stand-off time). Five minutes of continuous asystole is sufficient to ensure that both consciousness and respiration have ceased and that the possibility of spontaneous resumption of the circulation has passed. However, the brain may at this time remain to some degree responsive to the artificial restoration of its blood supply, be this as a result of continued CPR and the introduction of extra-corporeal circulatory support or as a result of post-mortem interventions that inadvertently provoke the return of ventricular function. It follows that at this time, that is, after 5 min of continuous asystole,

irreversibility depends in part upon prohibiting restoration of the cerebral circulation rather than an absolute inability to restore cerebral function. This contrasts with circumstances in which neurological criteria for the determination of death are applied. In these circumstances, the pathology leading to the irreversible loss of consciousness and respiration has been established for several hours before the diagnosis is made.

The challenges in this area are considerable. Irreversibility in such circumstances might be considered to be weaker than when death is confirmed by neurological criteria because here it depends upon intent and pathophysiology. Others suggest that the loss of circulation should be described as permanent rather than irreversible, and propose that for the purposes of DCD, death should only be recognized when the risk of autoresuscitation has passed, when CPR will not be attempted, and when there is an absolute prohibition on interventions that may restore the cerebral circulation being undertaken after the declaration of death. A recent systematic review of autoresuscitation showed that this has only been reported in the context of abandoned CPR and not when invasive treatment is withdrawn [13].

There seems to be a growing consensus that a minimum of 5 minutes of continuously observed and appropriately monitored absence of the circulation, apnea, and coma will define the point at which death can be diagnosed. The development of such consensus will increase confidence in the way death is determined and prevent a repetition of practices in DCD that have previously aroused much concern and criticism, such as retrieval of a heart from a neonatal DCD donor after only 75 seconds of loss of the circulation [14]. However variations in practice exist around the world with a stand-off time of up to 20 minutes being used [15]. However, with extended stand-off time, the subsequent graft function may be compromised resulting in non-use or graft dysfunction in the recipient. Further discussions regarding the ethics of stand-off times are needed to develop internationally recognized criteria that the general public can have confidence in.

Interventions After Death

As noted above, warm ischemic injury is a major limiting factor for DCD, and it is legitimate for retrieval teams to consider the benefits of reversal of such processes before cold perfusion and how this might be achieved. It is mandatory for critical care teams to evaluate such proposals within the pathophysiological context of the criteria used to diagnose death. This is particularly relevent to uncontrolled DCD that allows CPR to continue after the declaration of death [16]. A recent study has revealed that 3 patients in a series of 48 had a return of spontaneous circulation when a mechanical device was used during transfer of potential DCD donors from the community to the transplant center, one of whom went on to make a good neurological recovery [17].

There is now a growing consensus that no intervention that might potentially restore cerebral circulation at a time when nervous tissue might be responsive to such restoration should be allowed under any circumstances, given the time-sensitive way in which death is diagnosed in the setting of DCD.

Protocols for uncontrolled DCD raise further specific ethical issues regarding post-mortem interventions, including how much information families receive and the acceptability of applying invasive measures to preserve organs before obtaining consent from the family or establishing the patient's wishes, particularly with uncontrolled DCD. The legal framework for donation in Spain, which is one of presumed consent, is interpreted in practice to support such interventions, while in the United Kingdom, the Human Tissue Act specifically allows the placement of femoral perfusion cannulae ahead of the family approach.

Reinforcing Donation Supply: DBD Versus DCD

In the United Kingdom, currently an average of 3.6 organs is transplanted per DBD donor compared with 2.1 organs per DCD donor [18]. While the number of organs transplanted from DCD donors may increase in the future, they are unlikely to fully match those transplanted after DBD, either in terms of the number of organs transplanted or their quality. Therefore, the focus of DCD programs should be to provide the option of deceased donation for patients who will never meet the neurological criteria for the diagnosis of death, rather than an option for clinical staff and families to support donation without the need for lengthy neurological evaluations and subsequent donor optimization. However, many involved in transplantation express the view that DCD programs do indeed detract from DBD and thereby jeopardize cardiothoracic and to a lesser extent liver and kidney transplant programs and point to the falling number of DBD donors in countries with active controlled DCD programs.

Detailed analysis in the United Kingdom does not support this view, with the registry data indicating that the incidence of DBD was declining for several years before the expansion of the DCD program (Fig. 2.3) [18]. However, in other countries such as the Netherlands, DCD does appear to have partially replaced DBD. The decrease in the incidence of death diagnosed by neurological criteria, and therefore the potential for DBD, over the last 6 years, is primarily a consequence of improved road safety and changes in the neurosurgical care management and improved outcomes of acute traumatic brain injury and intracranial hemorrhage.

It is important to ensure that DBD are identified and their potential for donation is maximized. Of note, it is disconcerning to observe that 10% of DCD donors in the United Kingdom appear to fulfill the pre-conditions for brainstem death testing but were not tested. The reasons for this need to be understood and addressed. Audit and performance management review can lead to further improvement in the cycle of identifying potential donors and approaching families appropriately to increase organ donation and graft utilization.

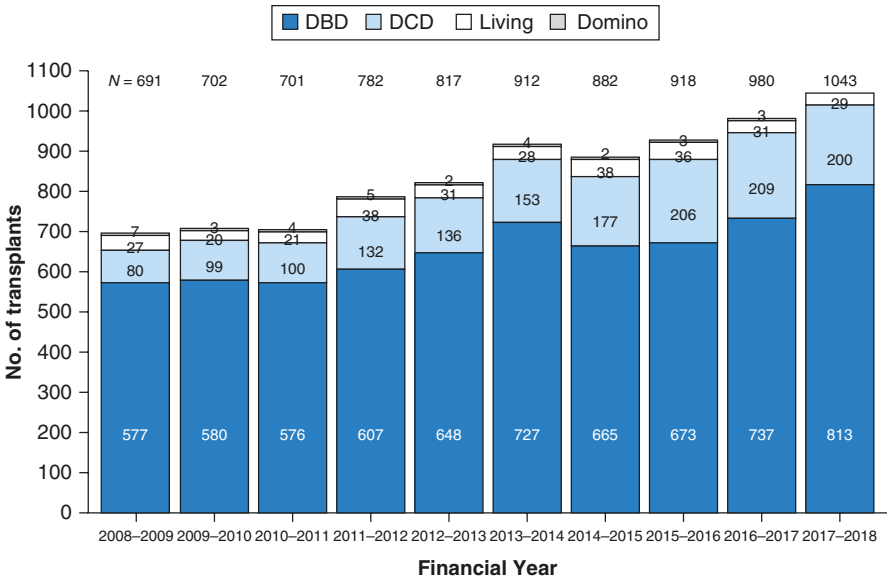

Fig. 2.3 Total number of liver transplants by donor type, 1 April 2008–31 March 2018, Annual Report NHSBT. (Adapted from Ref. [18])

Professional training and education programs reinforce the importance of testing potentially brain-dead patients irrespective of whether they are to become donors, particularly because it allows clinicians to give the patient's family a definitive diagnosis of death rather than a prognosis that death will follow the withdrawal of treatment.

Donation After Euthanasia

Euthanasia is a controversial topic with complex ethical arguments well beyond the scope of this book. In many countries, euthanasia is not a legal practice, and therefore any discussion surrounding organ transplantation and euthanasia in places where it is not legally performed is irrelevant. In both Belgium and the Netherlands, euthanasia is legally allowed, and organ donation from DCD donors following euthanasia has been performed [19–21]. In both countries, combining euthanasia and subsequent organ donation is feasible on legal and medical grounds and is increasingly gaining social and ethical acceptance [22, 23]. In Belgium, if the patient is ill, but is not expected to die within the near future, a third physician, with specific expertise regarding the condition from which the patient suffers, needs to consult the patient, and a period of at least 1 month between the request for euthanasia and the euthanasia procedure itself has to be respected [22, 23]. In the Netherlands, the patient should be hopelessly and unbearably suffering, and other

reasonable solutions should be non-available. In this process, a second independent physician should be consulted. The euthanasia procedure should be carried out "carefully," according to the latest standards [22, 23].

Heart Transplantation from Donation After Circulatory Death Donors

Although this book is focused on liver transplantation from DCD donors, it is likely that moving forward, liver procurement teams will be faced with concomitant heart procurements taking place from DCD donors. There is currently a clinical trial underway investigating heart transplantation from DCD donors utilizing the OCS Heart System (TransMedics) [24].

Early transplant programs utilized organs from DCD donors, including the first heart transplants performed by Christiaan Barnard [25]; however, this practice was largely abandoned following the acceptance of brain-death criteria. As of late the ethics surrounding heart transplantation from DCD donors has been thoroughly debated [26]. In 2012, the American Thoracic Society, the International Society for Heart and Lung Transplantation, and the United Network for Organ Sharing (among others) published an official statement in support of DCD [27]. Moreover, DCD heart transplant programs already exist in the United Kingdom, Belgium, and Australia.

Previous Legal Controversy

As is stated above, it is imperative that procurement team members are not involved in decisions regarding patient care in potential DCD donors prior to their death. A procuring surgeon in California, USA, was previously charged with three felony counts for allegedly becoming involved in administration of narcotic and anxiolytic medication during an attempted DCD procurement [28]. Although the surgeon was ultimately acquitted, this case highlights the importance of even perceived attempts to influence patient care in potential DCD donors [29].

Executed Prisoners and DCD Transplant

In China, numerous previous international human rights violations related to organ procurement practices have been described [30, 31]. Historically over 90% of the organs transplanted in China were from prisoners. Since China does not have a law recognizing brain death, cardiac death is the standard determination of death for organ donors in China [32]. Chinese sources claim that all hospitals have terminated using organs from executed prisoners and the civilian organ donation has been the sole source for an organ transplant in China since January 2015 [32].

Country-Specific Laws

As has previously been stated, significant variability exists in DCD organ donation practices across the world [33]. Table 2.5 [33, 34] provides a list of countries that have published data on DCD organ procurement activity. Figure 2.4 provides data on total DCD donors by country from 2017; however, this data is not specific to DCD liver transplantation [35]. In seven European countries (Finland, Germany, Greece, Bosnia-Herzegovina, Hungary, Lithuania, Turkey), there is currently no DCD activity, mainly because of legal restriction. The following section provides country-specific information on both laws and practices surrounding DCD organ donation.

Australia

DCD donors in Australia are performed in a controlled fashion (Maastricht category III). A national protocol for donation after circulatory death donors in Australia has previously been published [36]. In Australia, the mandatory "no-touch" time is 2–5 minutes.

Table 2.5 DCD programs and transplant activity 2008–2016 [33, 34]

Continent	Country	Year started (uDCD/cDCD)	"No-touch" time	DCD liver transplants performed 2008–2016[1, 2]
Europe	Austria	1990s	10	5
	Belgium	2006/2005	5	440
	Czech Republic	2002/2015	5	1
	France	2007/2015	5	48
	Ireland	NA/2011	10	0
	Israel	2014/NA	5	0
	Italy	2007/2015	20	14
	Latvia	1973/NA	5	0
	Lithuania	2016/NA	5	0
	The Netherlands	1980s	5	336
	Norway	NA/2010	5	4
	Poland	2015/NA	5	0
	Portugal	2016/NA	10	0
	Russia	1967/NA	30	0
	Spain	1980s/2009	5	339
	Switzerland	1985/1985	5	45
	United Kingdom	2013/1985	5	1268
North America	Canada	2006	5	NA
	USA	1992	2 to 5	2885
Asia	China	NA	NA	NA
	Japan	NA	NA	NA
Oceania	Australia	2004	2 to 5	NA
	New Zealand	2008	5	NA

uDCD uncontrolled DCD; *cDCD* controlled DCD

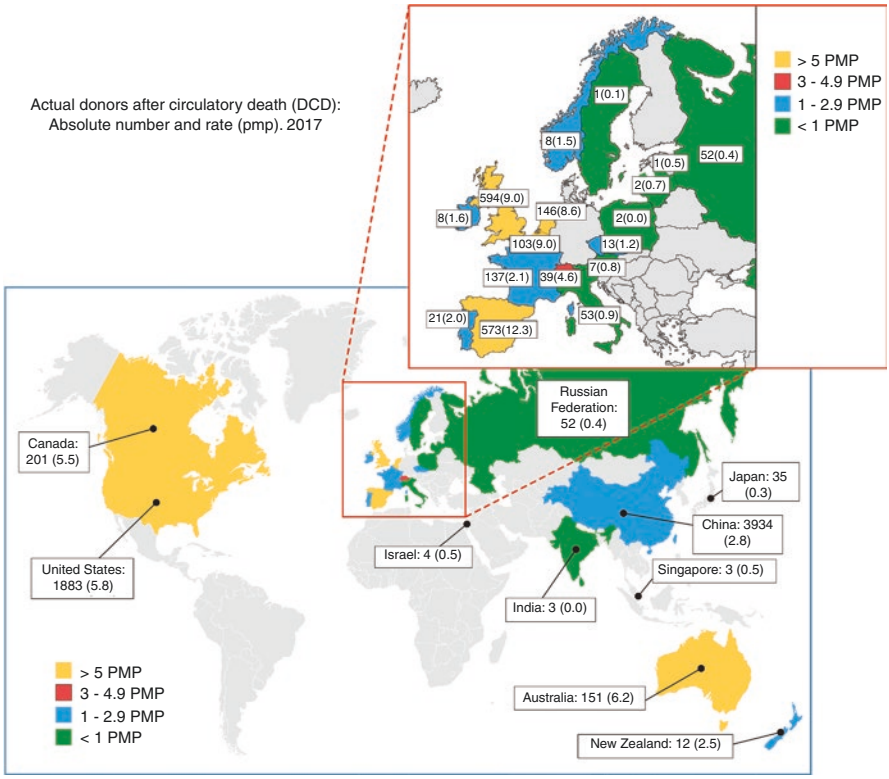

Fig. 2.4 Global DCD donors in 2017 (includes all non-liver DCD organ donors). (Data of the WHO-ONT Global Observatory on Donation and Transplantation. All Rights Reserved © 2017 Global Observatory on Donation and Transplantation)

Belgium

Both controlled (Maastricht III) and uncontrolled (Maastricht II) DCD donors are pursued in Belgium. Donation following euthanasia is legal in Belgium. Antemortem systemic heparinization is allowed in Belgium. In Belgium, the mandatory "no-touch" time is 5 minutes.

Canada

A Canadian national forum was held in February 2005 to discuss and develop recommendations on the principles, procedures, and practice related to DCD, including ethical and legal considerations [37]. DCD organs have been actively pursued in Canada since 2006. DCD donors in Canada are performed in a controlled fashion (Maastricht category III). Premortem administration of heparin is allowed in Canada, and mandatory "no-touch" time is 5 minutes.

China

The current cultural traditions of China have precluded a public consensus on brain death. Chinese culture and law recognize the circulatory death criteria, but concepts such as vegetative state and brain death remain vague for many Chinese citizens [32]. In China, there is presently no law recognizing brain death. Since cardiac death is the standard determination of death, all deceased donors in China are DCD donors. These donors would likely be considered as Maastricht IV (death by cardiac arrest after brain death) [38].

China has long been criticized for commercial and unethical use of organs from executed prisoners among the international community [39]. China has received a significant amount of international pressure with regard to their organ donation practices. In 2010 a citizen-based voluntary organ donor system was initiated. With the success of implementing the voluntary citizen-based organ donation program, all hospitals have terminated using organs from executed prisoners, and the civilian organ donation has been the sole source for an organ transplant in China since January 2015 [40].

France

Historically DCD donors were not pursued in France. Procurement from DCD donors was re-examined in France in 2003–2004, taking into account the feasibility, results, and ethical and legal consequences. The terms of the law were changed to authorize donation after circulatory death, but only for a limited number of pilot centers with a single national medical protocol issued by the Agence de la biomédecine [41]. Initially, the End of Life Law, which had only just been passed in 2005, ruled out Maastricht category III donors at the start of the program. In 2010, the parliamentary information mission on the revision of the bioethics law invited the Intensive Care Societies to debate and make recommendations for controlled donation after circulatory death.

Italy

In Italy, a "no-touch" time of 20 minutes is required following cardiac arrest as certified using continuous ECG prior to commencement of organ procurement. This long "no-touch" period has long prevented the development of any DCD LT program in Italy [42]. The first Italian series of DCD LT was initiated in September 2015 using normothermic machine perfusion (NRP). Systemic heparinization is only allowed during the agonal period. In Italy, a presumed consent law (opt-out) has been approved but not enforced, primarily because of lack of data about public opinion.

Japan

For many years, the concept of brain -death was not recognized culturally or legally in Japan. For this reason, the majority of liver transplants performed in Japan have

been from living donors. In 1997, Japan's Organ Transplant Law (OTL) was enacted, which legalized organ donation from brain-dead donors in Japan [43]. Despite the legalization of donation from brain- dead donors, the small numbers of deceased donors in Japan continue to be predominantly DCD donors, given the lack of cultural acceptance of brain -death.

The Netherlands

The Netherlands was one of the first European countries to transplant organs (kidneys) from DCD donors, starting in the early 1980s [44, 45]. The Netherlands has also been transplanting livers from DCD donors since 1999 [45]. The majority of DCD donors in the Netherlands are controlled DCD (Maastricht category III). Donation following euthanasia is legal in the Netherlands. Both controlled (Maastricht III) and uncontrolled (Maastricht II) DCD donors are pursued in the Netherlands. In the Netherlands, the mandatory "no-touch" time is 5 minutes.

New Zealand

Following approval from the multi-region ethics committee in 2007, the Organ Donation New Zealand (ODNZ) commenced introducing DCD in donor hospital throughout New Zealand. DCD donors in New Zealand are performed in a controlled fashion (Maastricht category III).

Spain

Spain has been one of the pioneering countries for utilization of uncontrolled DCD donors. Currently both uncontrolled and controlled DCD donors are performed in Spain (Maastricht categories I, II, and III). The country is well known for their high rates of organ donation as well as opt-out donor system. Controlled DCD organ donation was initiated in Spain in 2009 [46]. Antemortem systemic heparinization and cannulation are allowed in Spain. The mandatory "no-touch" time in Spain is 5 minutes.

Switzerland

In Switzerland, DCD was introduced in 1985, but it was stopped after the introduction of the national transplant law in 2007 due to legal uncertainty [47–49]. The law had apparent inconsistences with the Swiss Academy of Medical Sciences (SAMS). Subsequently the Federal Office of Public Health (FOPH) made clear that DCD was authorized by law and that the SAMS guidelines ought to be adjusted to allow

preparatory medical measures with regard to DCD [48, 49]. After the analysis of the legal situation and the adaption of the SAMS guidelines, the Zurich University Hospital was the first to reintroduce a DCD program in late 2011 (Maastricht category III; procurement of lungs, livers, pancreas, and kidneys) [50]. The mandatory "no-touch" time in Switzerland is 5 minutes.

United Kingdom

The United Kingdom has seen a significant increase in the number of organ donors from 2003 to present. This rise in organ donors has been almost solely because of a rise in DCD. This has been almost solely a result of an increase in donation after circulatory death (DCD) from 1.1 to 7.9 donors per million population (pmp) between 2003 and 2012 [51]. The United Kingdom now performs one of the highest numbers of DCD transplants in the world. The majority of DCD donors in the United Kingdom are performed in a controlled fashion (Maastricht category III). The mandatory "no-touch" time is 5 minutes in the United Kingdom. DCD practice in the United Kingdom does not allow antemortem systemic heparinization to be given.

United States

Prior to the development of the Harvard criteria for brain death in 1968, all deceased organ donors in the United States were declared deceased using circulatory arrest criteria. Following the development and acceptance of brain death, virtually all deceased donors in the United States were DBDs. DCD organ transplantation was reintroduced by the University of Pittsburgh in 1992 [52]. Both the University of Pittsburgh and the University of Wisconsin described their pioneering work with controlled DCD kidney and liver transplantation in 1995 [53, 54]. Since that time, the number of DCD organs in the United States has continued to increase. DCD donors in the United States are almost exclusively performed in a controlled fashion (Maastricht category III). Antemortem systemic heparinization is performed for the majority of DCD donors in the United States. "No-touch" time in the Unites States is between 2 and 5 minutes. The Society of Critical Care Medicine recommends at least 2 minutes of observation and the Institute of Medicine recommends 5 minutes [55]. A previous report by Light et al. described an uncontrolled DCD program in Washington, D.C., that recovered 26 kidneys, of which 21 were transplanted [56]. This program has since been discontinued. More recently an uncontrolled DCD protocol was investigated at two academic centers in Pittsburgh [57]. While four organs were recovered as part of that program (three kidneys and one liver), none of the organs were ultimately used for transplantation.

Conclusion

The ethical framework for the transplant surgeon and the extended multidisciplinary team, when utilizing DCD, is important and poorly understood. The onus is on the accepting surgeon to utilize DCD grafts and to achieve "acceptable outcomes". How are these grafts utilized? There is evidence of bias in allocation with reports, for example, of DCD liver grafts being used disproportionately in patients with Hepatocellular carcinoma (HCC), women, and low Model for end-stage liver disease (MELD) recipients [34]. The decision not to use a graft may be straightforward; however, the tipping point for use is determined by surgeon experience, recipient urgency and anticipated surgical difficulty, whether the graft was an import, and the potential cold ischemic time and the likelihood of rescue in the event of primary graft nonfunction. Are these decision improved by consulting within a multidisciplinary team? How do surgeons "safely build experience" with DCD within the surgical team? It may be considered that decisions regarding use may be more transparent, but consistency of decision-making will also depend on team size and composition and is likely to err on the side of conservative behavior when confronted by marginal grafts. What constitutes ethical behavior in deciding to utilize a graft and risk poor outcome in the recipient? This may only become "obvious" in retrospect when the outcome is known. Therefore it is important to have mandatory audit recording outcomes such as marginal graft utilization, graft outcome, the incidence of ischemic cholangiopathy, and waiting list mortality.

Selection and consent of appropriate recipients may also raise ethical issues. The selection of potential recipients as suitable by the multidisciplinary team for DCD grafts could permit the use of a young or old DCD liver graft with very different risk profiles. The consent of the recipient for the use of the liver and the risk profile should be explicit; otherwise, the ethical behavior of the surgeon will be questioned. The formulation of algorithms for characterizing risk/benefit of the specific donor-recipient pairings would be valuable and help the patient understand risk and provide a benchmark to surgical team to assess their performance.

Informing the recipient of the risk of not being transplanted if the DCD liver is turned down should also be explicit. In the United Kingdom, not accessing the DCD donor pool reduces the likelihood of transplantation by 11% [18]. Thus understanding decision-making and graft use is complex and challenging, and there is little data on surgeon and team performance.

Centre-specific outcome monitoring should include organ utilization, waiting list mortality, and graft and patient outcomes. Organ allocation schemes appear to be a greater challenge for DCD compared with DBD because of the risk involved in their use and the potential for prolonging cold ischemia if organs are "exported." Machine perfusion will offer an alternative way forward. For patients who develop ischemic cholangiopathy after DCD transplant who require retransplantation, there is evidence that they are less likely to be retransplanted in a timely manner and often receive another marginal graft. This is because the mode of graft failure is different

with recurrent cholangitis leading to malnutrition and physical frailty and is not recognized by the majority of allocation schemes as a high priority [58]. Recognition of this pattern should lead to a facilitation of retransplantation to avoid the disadvantage of receiving second marginal grafts.

Utilizing organs from DCD donors has now become commonplace in the West in contrast to the East where living donation remains the main form of donation. The ethical problems associated with their use are very different. DCD grafts should be considered as marginal grafts except in highly selected donors (less than 40 years, no steatosis, warm ischemia <30 minutes, cold ischemia >8 hours). The risk of graft dysfunction/nonfunction is borne by the recipient in contrast to living donation where the primary risk is for the donor.

The advent of machine perfusion either in situ or ex situ using hypothermic or normothermic perfusion offers a way forward. The ability to ameliorate ischemia-reperfusion injury reduces the risk of early graft failure and cholangiopathy. Normothermic perfusion allows for monitoring organ function prior to transplantation which would lessen some of the ethical issues clinicians face when considering using these grafts. Increased utilization would also help the transplant community in terms of how DCD transplantation is viewed. The low utilization rates that are currently experienced are expensive in financial and personnel terms. It risks the burnout of retrieval teams who work hard often for no tangible output. Hopefully the advent of new technologies to improve or restore potential graft function prior to transplantation will usher in an era of increasing rates of donor utilization with excellent clinical outcomes. Machine perfusion should help and improve utilization of DCD grafts. A number of randomized controlled trials have been completed, and further studies are planned to assess their impact on DCD liver transplant. This represents an ethical approach to the evaluation and introduction of new technology in transplantation. Robust data will provide a robust framework for future clinical practice. The standardization of DCD across the world should decrease the ethical issues faced by transplant teams today. Ethical challenges will continue to exercise the transplant community in DCD transplantation, and continuing audit and the publication of robust outcome measures will reassure donor families and the general public where support is critical to the future provision of organ donation.

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3 Donor Procurement Operation in Donation After Circulatory Death Donors

David D. Lee and Martin D. Jendrisak

Outcomes for liver transplantation with the use of donation after circulatory death (DCD) donors have largely been influenced by the donor operation. Coordination with the staff from the organ procurement organization (OPO) as well as the hospital staff is critical for a successful outcome. As often the first contact with organ transplantation for many of the hospital staff, donor surgeons should view themselves as ambassadors of transplantation. The transplant surgical team can best support the donation process by [1] arriving to the donor hospital ahead of the scheduled time, [2] making introduction and reviewing the surgical recovery process with the OR staff, [3] communicating special needs for procurement, and [4] maintaining professional conduct in the OR and talking supportively about organ and tissue donation. The transplant centers rely heavily on a good partnership between the OPO and the donor hospitals – a Centers for Medicare and Medicaid Services (CMS) contractual requirement to permit clinical evaluation by the OPO for donation potential. The OPO provides donation education to the hospital, assists with hospital in crafting their DCD policy modelled after American Society of Transplant Surgeons (ASTS) guidelines, and provides family support to donor families. Adjunct to this partnership, it would be recommended that all parties (OPO staff, operating room nurses, technicians and assistants, respiratory therapists, ICU nurses, observers, and if possible withdrawing physicians) meet to discuss the details of the donation process in the manner of a "huddle." The goals of this huddle are as follows:

1. To provide an opportunity for introductions. As ambassadors of transplantation, the donor surgeon is responsible for articulating the uniqueness of DCD in perspective with more controlled donor operations involving brain-dead donors (DBD).

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2. To provide an opportunity to humanize the gift of life through organ donation. Thank all participants in the process on behalf of the transplant center but also importantly the recipients of the organs. Highlight the donor and donor family wishes to proceed with organ donation despite not meeting brain death criteria – an amazing gift in the setting of a very difficult time for the donor family.
3. As speed of cold perfusion of organs is critically important in the DCD organ recovery operation and hospital polices as well as staff interpretation of hospital policies may be in disagreement; it is important to clarify key questions to the donation process with all parties involved(these would include, but not exclusively):
   (a) Where is the withdrawal going to happen? In the OR vs. PACU vs. ICU? What is the distance from ICU to OR?
   (b) Will the donor be placed on a stretcher vs. ICU bed vs. OR table?
   (c) When will heparin be given?
   (d) How long is the hospital policy's "hands-off/mandatory wait time" period?
   (e) Will the donor be allowed to be transported during the "hands-off/mandatory wait time" period?
   (f) Who will assist during the transport of the donor, and will it be necessary to clear the rails from the stretcher or hospital bed or removing the IV pole attached to bed or stretcher?
   (g) How are vitals going to be monitored, and how is asystole or electromechanical dissociation (PEA) going to be defined and identified? How will asystole or PEA be confirmed?
   (h) How is communication going to take place between the donor surgical team and the OPO staff monitoring the withdrawal?
   (i) Who will communicate when incision can be made? Assigning, a priori, one responsible OPO staff member allows for clarity of the donation process.
   (j) When can the patient be prepped and draped?
   (k) Who will be responsible for assisting the family, if they are present, during the withdrawal?

Having buy-in from the hospital staff as well as the OPO members is critical for a smooth and successful donor operation. Speed and timing has long been considered a key component to the donor operation. Casavilla et al. provided us the earliest description of the "super-rapid" technique for organ retrieval [1]. Subsequently, many reports revealed that extended donor warm ischemia time (DWIT) presented a critical risk factor for post-liver transplant graft failure and poor outcomes – most critically the ischemic-type biliary strictures (ITBS) [2–5]. Using a more granular approach to the time intervals during the withdrawal, the Mayo Clinic Florida group identified the asystole-to-cross-clamp time interval as critical to avoiding ITBS, and they recommend avoiding donors in whom this time interval exceeds 10 minutes [6, 7]. With this in mind, this highlights ever more the need for clear and close coordination with the donor procedure leading up to the incision as well as from incision to cross-clamp. A DCD time sheet can be seen in Appendix 3.1.

In 1995, the first description of the "super-rapid technique" is as follows:

> After a midline incision from the xiphoid process to the symphysis pubis, the distal aorta was cannulated, and perfusion of the organs with cold preservation solution started. Perfusion was routinely initiated less than 4 min after skin incision. Next, the sternum was split, the thoracic aorta was cross-clamped, and the intrapericardial inferior vena cava was vented to decompress the organs. The inferior mesenteric vein was then cannulated to perfuse the portal system, and the abdominal cavity was filled with ice slush. In adults, approximately 2 L of cold preservation solution (Viaspan) was infused into both the portal and the systemic arterial systems. Once the liver became palpably cold and free of blood, hepatectomy, followed by en bloc nephrectomies, was performed expeditiously [1].

Essentially the donor operation has changed very little; however, more recent experiences have demonstrated that perfusion can be initiated within 1 minute after skin incision. This is accomplished by the following detailed steps:

Preparation of the Room

1. Prepare the cannulas or tubing with tubing preflushed.
2. Assign all team members an initial role. Whether prepping and draping is necessary, coordinate each member a task in the initial period.
3. Prepare the Mayo stand, accommodating only the necessary instruments to avoid unintentional injury to team members or disruption. It is our preference to have only the following: two large blades (preferably 20 blades) on regular knife handles, a pair of curved Mayo scissors, a pair of Metzenbaum scissors, and two large 6-inch Kelly hemostatic forceps. Have available the sternal saw and sternal retractor and if available the large Balfour retractor (not shown) (Fig. 3.1).
4. At a minimum, three suction tubes should be attached to a large fluid waste management system.

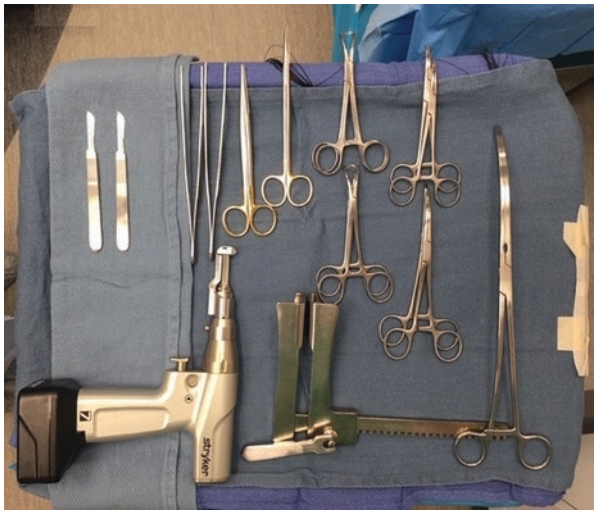

Fig. 3.1 Mayo stand showing instruments for DCD procurement

Cannulation to Cross-Clamp

5. Rapid skin incision, focused primarily periumbilically and extended toward the pubic symphysis (the target is the retroperitoneal aorta at the level of the iliac bifurcation).
   (a) If the patient has had a prior laparotomy, great care should be made to take down adhesions and avoid enterotomy.
6. Immediate evisceration of primarily the small bowel to gain exposure to the retroperitoneal aorta.
7. Sharply incise the colonic mesentery and tissue overlying the abdominal aorta.
8. Blunt dissection and encircling of the aorta with the left index finger (Fig. 3.2).
9. Incision of the aorta at the crotch of the bifurcation of the left and right iliac arteries.
10. Insertion of preflushed four-lead arthroscopic irrigation set tubing. This particular tubing has a white tapered tip to allow for easy cannulation. A large-bore cannula can be used to insert into the aorta; however, the preference for the tubing directly is to reduce the amount of resistance for flow of the flush.
11. Secure cannula with a curved Kelly hemostatic forceps or Kocher clamp.
12. Begin flush.
13. Extend midline incision cephalad to include sternotomy. Open the left chest pleura with assistant pulling on the sternum toward the ceiling.
14. Eviscerate or push the left lung cephalad to gain exposure to the thoracic descending aorta.
15. Cross-clamp using DeBakey aortic clamp:

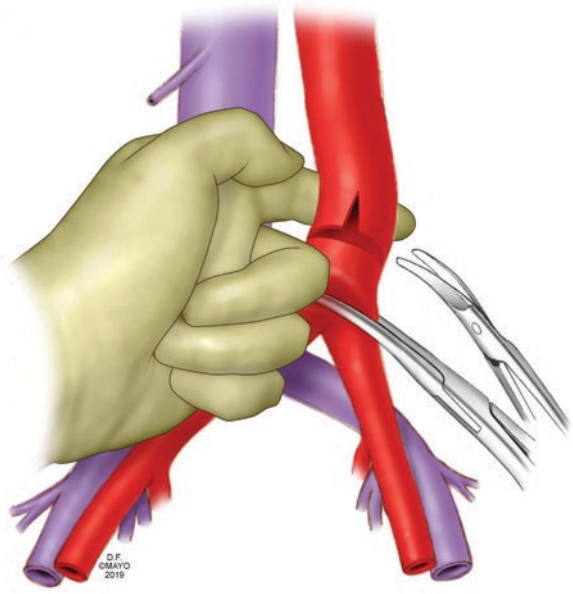

Fig. 3.2 Distal aorta immediately prior to cannulation. (Used with permission of Mayo Foundation for Medical Education and Research, all rights reserved)

(a) Special consideration regarding aortic access in the setting of prior sternotomy:
  (i) This can be performed through the diaphragm by incising the diaphragm along the left costal margin. The assistant will need to expose the chest cavity by retracting the ribcage toward the ceiling. By medially rotating the lung, the aorta along the spine can be exposed for cross-clamping.
  (ii) If transthoracic access to the aorta is preferred, access to the left chest can also be performed by transecting the left ribs all along the sternum to avoid the sternal wires and still gain access to the left chest.
  (iii) Cross-clamp abdominal aorta just below the diaphragm by releasing left triangular ligament of the liver and excising diaphragm crus. Special attention will be needed in this area not to injure a replaced left hepatic artery (if present).

16. Open pericardium.
17. Vent the suprahepatic Inferior vena cava (IVC) by incising the caval atrial junction; alternatively the lower IVC can be incised to vent with insertion of the pool-tip suction cannula to drain the effluent.
18. Open the right pleura to allow for decompression of effluent and blood into the right chest.
19. Pack the right chest and abdomen with ice.

Portal and Gallbladder Flush

20. In situ portal flush of the liver can be accomplished by cannulation of either the superior mesenteric vein (SMV) or the inferior mesenteric vein (IMV).
  (a) SMV cannulation:
    (i) Gain exposure to the SMV by having the assistant grab the transverse colon with his/her right hand and splaying out the mesenteric root by retracting the small bowel and mesentery with his/her left hand.
    (ii) Incise peritoneum of the mesentery, and carefully dissect through lymphatic and fat tissue toward the SMV, taking care not to disrupt any blood vessels.
    (iii) Encircle the SMV usually at the branch points of the ileocolic and right colic veins.
    (iv) Cannulate SMV with preflushed two-lead irrigation set tubing with the same tapered end.
  (b) IMV cannulation:
    (i) The IMV can be found at the ligament of Treitz with cephalad retraction of the bowel.
    (ii) With care, dissect the vein from the surrounding mesenteric tissue.
    (iii) Encircle the IMV and cannulate with typically a 10 F cannula.
    (iv) The cannula is best secured using 2-0 silk suture.

21. Target flush for 4 L aortic and 2 L portal flush.
22. Incise gallbladder, and flush with cold saline irrigation in bulb syringe under pressure to clear the bile duct.

Mobilization of the Liver and Hepatectomy

23. Take down the diaphragmatic attachments to the left lateral segment.
24. Incise the gastrohepatic ligament with care to identify a potentially replaced left hepatic artery; in many cases, the left hepatic artery may be difficult to appreciate. To be safe, taking the left gastric artery widely along the lesser curvature can ensure preservation of a replaced left hepatic artery.
25. Once flush is complete, perform hepatectomy beginning in the hilum. With the assistant retracting the duodenum with his/her left hand, begin dissection superficially taking all the omental fat around the porta hepatis.
26. Identify the hepatic artery lymph node, and trace dissection toward the pancreas to identify the gastroduodenal artery (GDA).
27. Divide the GDA.
28. Then trace GDA toward common hepatic artery, gaining exposure of the portal vein.
29. Identify the splenic artery and divide.
30. Identify and divide the common bile duct.
31. With care, divide all the neurolymphatic tissues between the bile duct and portal vein, being cautious to identify a potentially replaced right hepatic artery.
32. If a right hepatic artery is noted, trace this structure into the pancreas toward the superior mesenteric artery (SMA)
33. With the pancreas and mesentery retracted caudally, divide the SMA with at least 4–8 cm of length to ensure that the replaced right hepatic artery with its origin on the SMA is preserved (usually found within 2 cm of the SMA origin off the aorta).
34. Once the SMA has been identified distally, trace the SMA toward its origin off the aorta.
35. Amputate the SMA flush with the aorta in order to preserve the branches of the renal arteries, which often insert at the level of the SMA. Preserve a small lip of the aorta cephalad to allow for extension of the aortic patch toward the celiac artery.
36. Transect the aorta at the level of the celiac artery.
37. Trace the aorta cephalad and complete the transection of the aorta supraceliac.
38. Divide all the diaphragmatic attachments between the aorta and the retrohepatic and infrahepatic IVC.
39. Complete the transection of the IVC-atrial junction within the pericardium.
40. Identify the suprahepatic IVC in the chest, and incise all the pericardial and diaphragmatic attachments around the suprahepatic IVC.
41. Completely mobilize the liver from its diaphragmatic attachments, with care not to tear the liver capsule.
42. Identify the right adrenal gland and bisect the gland.

43. Divide the infrahepatic IVC with care to preserve the right renal vein with a suitable IVC cuff as well as retaining the right adrenal vein on the retrohepatic IVC.
44. Complete hepatectomy.

Backtable Flush

45. Once removed, perform a backtable flush of the liver by cannulating the celiac artery with 10 F cannula. This can be secured with a silk tied around the celiac origin. If there is a replaced right hepatic artery, separate cannulation of the SMA will be necessary to flush the right hepatic artery as well.
46. With great care, use hemostatic clamps to clamp the splenic artery, GDA, and branches of the left gastric to prevent loss of flush.
47. Flush the liver through the artery on the backtable until effluent coming from the suprahepatic IVC is devoid of any evidence of blood; this may require another 2–4 liters of flush (Fig. 3.3).
48. Package the liver.

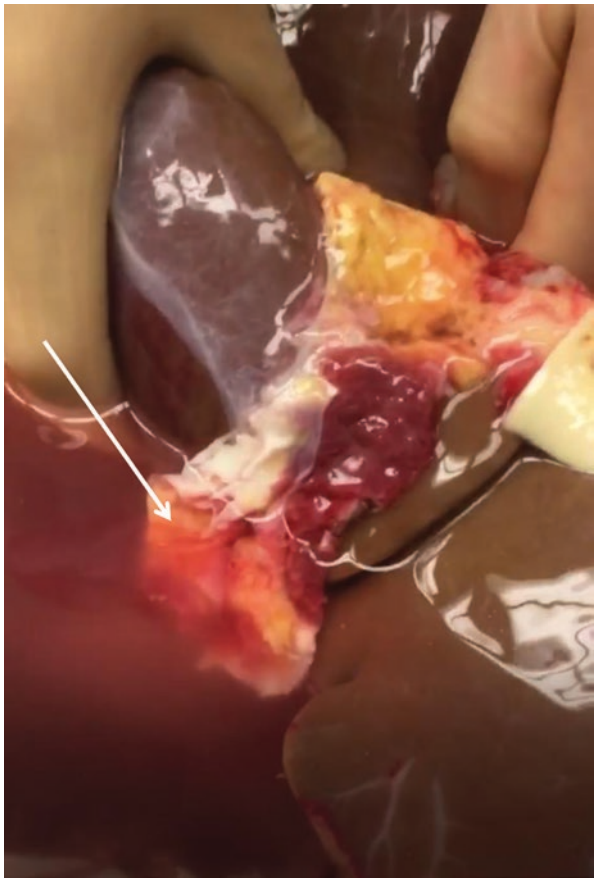

Fig. 3.3 Backtable flush of the liver. Flush until the effluent coming from the suprahepatic IVC is devoid of blood

Prior to accepting the liver for transplantation, it is critical for the donor surgeon to scrutinize the donor withdrawal flowsheet to confirm acceptable ischemic times based on hemodynamic parameters. In particular, we stress asystole-to-cross-clamp time of less than 10 minutes. An example flowsheet (Fig. 3.2) highlights the dangers of using only DWIT or incision to cross-clamp as markers for a successful donor operation. Despite a DWIT of only 47 minutes and an incision to cross-clamp at 2 minutes, the period of PEA was likely an additional 13 minutes, resulting in a total asystole-to-cross-clamp time of 17 minutes. This donor was inevitably declined in the operating room.

PEA is an area of greatest controversy. As defined by the Advanced Trauma Life Support (ATLS), PEA is defined as an organized rhythm without a palpable pulse. The definition of PEA can be further differentiated into pseudo-PEA and true PEA [8]. Pseudo-PEA is a profound state of cardiogenic shock that is inadequate to maintain perfusion pressure (a nondetectable pulse). According to ATLS guidelines, palpable pulses are lost in the carotid, femoral, and radial artery when the systolic blood pressure is less than 60 mmHg. This may correlate with some centers' definition of functional donor warm ischemia time (fDWIT) which will be discussed elsewhere in this book. True PEA represents a true uncoupling of cardiac mechanical activity from cardiac electrical activity and a complete absence of mechanical contractions. While it is paramount to not interfere with the withdrawing physicians' definition of cardiac death (either asystole or PEA), knowing what level of risk the transplant surgeon/center is willing to take must be clearly defined. Physiologically, the difference between pseudo-PEA and true PEA for the liver is likely minimal, and caution should be taken for organs from donors who endure prolonged periods of poor perfusion (Fig. 3.4).

In summary, the donor operation rests upon a clear cooperation of the donor hospital staff, OPO staff, and donor surgical team to allow for a smooth and efficient procurement that accomplishes an expedient asystole-to-cross-clamp interval of less than 10 minutes and suitable flush of the liver. With these goals in mind, a successful outcome for all parties (the donor hospital staff, the OPO, the transplant team, and most importantly the transplant recipient) can be accomplished.

DCD FLOWSHEET

PRE-OPERATIVE MANAGEMENT

Was patient extubated? Yes

Heparin: ☑ **Dosage:** 30000 units **Time:** 14:22

Withdrawal Date-Time: 04/25/2019 14:27 CDT

Agonal phase start Date-Time: 04/25/2019 14:29 CDT

Observation period start Date-Time: 04/25/2019 15:09 CDT

Pronouncement of death Date-Time: 04/25/2019 15:09 CDT

1st authorized clinician declaring death:

2nd authorized clinician declaring death: .....

Enter OR Date-Time: 04/25/2019 15:11 CDT

Surgical team separate from the donor during withdrawal and death declaration? Yes

OR time-out Date-Time: 04/25/2019 15:12 CDT

Incision Date-Time: 04/25/2019 15:12 CDT

Start of flush/cooling (cross-clamp) Date-Time: 04/25/2019 15:14 CDT

Exit OR Date-Time: 04/25/2019 18:10 CDT

Target an incision to crossclamp time within 2-3 minutes to allow for a total asystole to crossclamp time within 10 minutes.

Warm ischemic time (agonal to initiation of flush/cooling): 45 mins

Last hour urine output: 0 ml **Total urine output in OR:** 0 ml **Average urine:** ml/hr

Any Extracorporeal Support Given (ECMO, etc.): No

HEMODYNAMIC MEASUREMENTS (MINIMUM OF Q5 MIN)

	0 min (14:27)	1 min (14:28)	2 min (14:29)	3 min (14:30)	4 min (14:31)	5 min (14:32)	6 min (14:33)	7 min (14:34)	8 min (14:35)	9 min (14:36)
HR	155	82	60	62	72	67	39	89	68	69
BP	120 / 70	209 / 109	199 / 87	202 / 92	168 / 98	150 / 101	114 / 57	147 / 69	110 /43	110 / 53
MAP	87	142	124	129	121	117	76	95	65	75
RR	24	25	13	0	9	8	0	0	28	27
SaO2	99	82	22	0	0	0	0	0	0	0
	10 min (14:37)	11 min (14:38)	12 min (14:39)	13 min (14:40)	14 min (14:41)	15 min (14:42)	16 min (14:43)	17 min (14:44)	18 min (14:45)	19 min (14:46)
HR	89	89	90	97	102	102	104	103	107	99
BP	169 / 73	228 / 93	243 / 100	237 / 99	214 / 94	196 / 94	186 / 89	184 / 85	178 / 79	179 / 83
MAP	105	138	148	145	134	128	121	118	112	115
RR	28	28	22	22	29	29	30	30	26	34
SaO2	37	35	40	39	36	30	31	31	28	28
	20 min (14:37)	21 min (14:48)	22 min (14:49)	23 min (14:50)	24 min (14:51)	25 min (14:52)	26 min (14:53)	27 min (14:54)	28 min (14:55)	29 min (14:56)
HR	105	97	102	104	96	96	96	96	93	71
BP	175 / 81	172 / 79	155 / 72	139 / 68	139 / 66	145 / 66	147 / 66	135 / 63	141 / 64	64 / 32
MAP	112	110	100	92	90	92	93	87	90	43
RR	25	33	28	20	28	32	29	28	20	11
SaO2	32	22	23	20	15	21	18	16	8	0
	30 min (14:57)	31 min (14:58)	32 min (14:59)	33 min (15:00)	34 min (15:01)	35 min (15:02)	36 min (15:03)	37 min (15:04)	38 min (15:05)	39 min (15:06)
HR	29	33	36	40	39	36	38	33	30	23
BP	0 / 0	26 / 18	24 / 15	22 / 14	19 / 14	0 / 0	0 / 0	0 / 0	0 / 0	0 / 0
MAP	0	21	18	17	16	0	0	0	0	0
RR	11	7	7	8	7	6	6	0	0	0
SaO2	0	0	7	42	0	0	0	0	0	0
	40 min (15:07)	41 min (15:08)	42 min (15:09)	43 min (15:10)	44 min (15:11)	45 min (15:12)	46 min (15:13)	47 min (15:14)	48 min (15:15)	49 min (15:16)
HR	18	0	0	0	–	–	–	–	–	–
BP	0 / 0	0 / 0	0 / 0	0 / 0				– / –	– / –	– / –
MAP	0	0	0	0				–	–	–
RR	0	0	0	0				–	–	–
SaO2	0	0	0	0	–	–	–	–	–	–
	50 min (15:17)	51 min (15:18)	52 min (15:19)	53 min (15:20)	54 min (15:21)	55 min (15:22)	56 min (15:23)	57 min (15:24)	58 min (15:25)	59 min (15:26)
HR	–	–	–	–	–	–	–	–	–	–
BP	– / –	– / –	– / –	– / –	– / –	– / –	– / –	– / –	– / –	– / –
MAP	–	–	–	–	–	–	–	–	–	–
RR	–	–	–	–	–	–	–	–	–	–
SaO2	–	–	–	–	–	–	–	–	–	–

Likely unrecognized PEA

Fig. 3.4 Donor withdrawal sheet showing vitals. Caution should be taken in utilizing livers when prolonged periods of PEA are observed

Appendix 3.1: Donation After Circulatory Death Withdrawal Sheet

Time of Extubation/Withdrawal:_____ Location of Withdrawal: OR / ICU/ Other_____

Heparin given: before withdrawal / after withdrawal Dosage:_____ Time: _____

Time when sBP < 50mmHg:_____ Time when PEA:_____

Time when SpO2 < 80%: _____

Mandatory wait time: _____ Time of Death:_____

- Incision time:_____
- Aortic Cannulation time:_____
- Initiation of flush time: _____
- Cross Clamp time:_____
- Portal Vein Cannulation time:_____

Aortic Flush Volume:_____liters Portal Flush Volume:_____liters

Back Table Flush: Yes / No _____liters used

Flush Quality: _____

Time	Blood Pressure	Pulse Rate	O2 Saturation	Notes
Initial				
Time	B/P	Pulse	O2	Notes
@ 1 min				
@ 2 min				
@ 3 min				
@ 4 min				
@ 5 min				
@ 6 min				
@ 7 min				
@ 8 min				
@ 9 min				
@ 10 min				
@ 11 min				
@ 12 min				
@ 13 min				
@ 14 min				
@ 15 min				
@ 16 min				
@ 17 min				
@ 18 min				

Time	B/P	Pulse	O2	Notes
@ 19 min				
@ 20 min				
@ 21 min				
@ 22 min				
@ 23 min				
@ 24 min				
@ 25 min				
@ 26 min				
@ 27 min				
@ 28 min				
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@ 60 min				

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Predicting the Likelihood a DCD Donor Will Expire

4

Lauren Ng, W. D. Freeman, and Eelco F. M. Wijdicks

Donation after circulatory death (DCD) was the primary source of organs for transplantation prior to the 1970s but fell out of favor once brain death was recognized as a legal definition of death [1]. However, organ transplantation was soon limited by the availability of deceased donors. In response to this, the University of Pittsburgh produced the first policy for the use of organs after the withdrawal of life support in 1992, initiating both legal and ethical debates. Despite controversy, DCD donors now account for 5% of all donors and have increased donation rates as high as 30% for certain organs [1, 2]. However, 20–30% of consented donors for DCD do not die within the time limits followed by transplant centers [2]. Predicting the likelihood that a DCD donor will expire is important for transplant programs attempting to determine the correct utilization of resources, particularly when traveling a significant distance for the procurement. Prediction is also important to manage expectations of the potential donor families and loved ones. In addition to questions about the patients' clinical condition, various logistic questions that may impact the utilization of the organs and likelihood that the donor will expire need to be asked. These include the following:

- Where will the care withdrawal take place (ICU/OR/others)?
- Will the patient be extubated at the time of care withdrawal?
- Does the patient have an arterial line to monitor blood pressure?

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– What is the mandatory wait time after circulatory arrest?
– Does the donor hospital recognize pulseless electrical activity (PEA) as circulatory arrest?

Prediction based solely on clinical impression may have variable reliability, and therefore various prediction tools have been developed in an attempt to predict time to death following withdrawal of life-sustaining therapy (WLST) to assist providers in identifying suitable donors. The following three main DCD prediction tools are available:

1. University of Wisconsin DCD tool
2. UNOS criteria
3. DCD-N tool

The first two tools require temporary disconnection of the patient from the mechanical ventilator, whereas the third does not.

University of Wisconsin Tool

The University of Wisconsin Hospital and Clinics was unique in that it continued to procure organs from DCD donors since 1974. They developed the UWDCD tool which was validated in 2003 to screen potential DCD donors for the likelihood to die within 60 and 120 minutes after WLST [3]. The population included patients with severe brain injury on mechanical ventilation who were either being evaluated for brain death and had a Glasgow Coma Scale less than 5 or where a physician was ordering WLST.

This tool incorporates a spontaneous breathing trial, use of vasopressors, age, airway type, and body mass index. In the spontaneous breathing trial, patients were disconnected from the ventilator for up to 10 minutes, and at the end of this period, respiratory rate, tidal volume, negative inspiratory force, and oxygenation saturation are all recorded (Fig. 4.1). If the patient becomes hemodynamically unstable (systolic blood pressure < 80 mmHG; oxygen saturation < 70%) or rapidly decompensates, the assessment is terminated, and the patient is deemed an appropriate candidate for DCD. Body mass index was not a component of the original DCD evaluation tool; however, higher BMI was shown in subsequent analysis to have a high correlation to expiration time after WLST and was added later in a post hoc analysis. The UWDCD scoring tool as well as probability of expiration ≤60 minutes can be seen in Tables 4.1 and 4.2, respectively.

The UWDCD tool was found to have a sensitivity and specificity of predicting death within 60 minutes of 0.83 and 0.84 and 0.85 and 0.45 for predicting time to death within 120 minutes [3]. However, external validation of this tool has not shown the same results.

Step One: Place a checkmark in the box next to the appropriate category in each table

Type of Intubation	
Endotracheal	
Tracheostomy	

Vasopressor/Inotrope Status	
None	
Single Vasopressor/Inotrope	
Two or More Vasopressors/Inotropes	

Step Two: Record the patient's vital signs prior to beginning the test.

Vital Signs	
Blood Pressure	
Pulse	
Oxygen Saturation	

Step Three: Disconnect the patient from the ventilator. *After 10 minutes** record the information in each of the tables below.

Respiratory Effort?	
Yes	
No	

If yes:

Respiratory Rate

Negative Inspiratory Force (NIF)*

*RT can do this measurement using a manometer

Vital Signs	
Blood Pressure	
Pulse	
Oxygen Saturation	

Tidal Volume

* If at any time the patient becomes unstable (pulse ox <70%, systolic BP <80), it is expected that the evaluation will stop and the above parameters will be recorded.

Fig. 4.1 Steps for evaluation using the University of Wisconsin DCD tool

UNOS Criteria

The United Network for Organ Sharing DCD Consensus Committee developed criteria for predicting death within 60 minutes based on expert opinion [4]. In 2008, DeVita et al. subsequently validated these criteria in a prospective multicenter study to develop a tool while also identifying other criteria that may be better predictors for death within 60 minutes of WLST [5]. They found that the UNOS criteria identify patients who are likely to die within 60 minutes of WLST and the odds ratio for death increases with the number of criteria met with odds ratios of 2.72, 4.62, and 10.6 for one, two, and three or more criteria, respectively. As 72.7% of patients with two or more criteria died within 60 minutes of WLST, the authors suggested using that as organizational policy. The UNOS criteria as well as the probability of expiration ≤60 minutes depending on the number of UNOS criteria present can be seen in Tables 4.3 and 4.4, respectively.

The authors also created two models using nonparametric classification and regression tree analyses for predicting death within 60 minutes of WLST. One

Table 4.1 UWDCD tool with points awarded for each criteria

Criteria	Assigned points
Patient age	
0–30	1
31–50	2
Over 51	3
Body mass index	
<25	1
25–29	2
>30	3
Intubation	
Endotracheal tube	3
Tracheostomy	1
Vasopressors/inotropes	
No vasopressors/inotropes	1
Single vasopressor/inotrope	2
Multiple vasopressors/inotropes	3
Spontaneous respirations after 10 min	
Rate > 12	1
Rate < 12	3
Tidal volume (TV) > 200 cc	1
Tidal volume (TV) < 200 cc	3
NIF < 20	3
NIF > 20	1
No spontaneous respirations	9
Oxygenation after 10 minutes	
O2 sat > 90%	1
O2 sat < 80–89%	2
O2 sat < 79%	3

Table 4.2 UWDCD tool: probability of expiration based on UWDCD tool score

UWDCD tool final score	Probability of expiration in <60 min	Probability of expiration in <120 min
	%	%
10	8	26
11	13	34
12	20	42
13	28	51
14	38	59
15	50	68
16	62	75
17	72	81
18	81	86
19	87	90
20	92	92
21	95	95
22	97	96
23	98	97

Table 4.3 UNOS criteria for predicting death within 60 minutes. A score is assigned between 0 and 5 based on how many criteria are met, with higher score associated with higher likelihood of death

UNOS criteria	Percent with death ≤ 60 minutes (%)
Apnea during trial off mech vent	77
RR < 8/min during trial off mech vent	67
RR > 30 during trial off mech vent	29
LVAD	100
RVAD	100
VA ECMO	0
Pacemaker-unassisted heart rate < 30	80
PEEP ≥10 and SaO2 ≤ 92%	78
FiO2 ≥ 0.5 and SaO2 ≤ 92%	67
V-V ECMO	80
Norepinephrine or phenylephrine ≥0.2	70
Dopamine ≥15	79
IABP 1:1 (or dopamine or dobutamine ≥10 and CI ≤ 2.2)	68
IABP 1:1 and CI ≤ 1.5	100

RR respiratory rate, *VA ECMO* veno-arterial extracorporeal membrane oxygenator, *IABP* intraaortic balloon pump

Table 4.4 Probability of death based on number of UNOS criteria met

Number of UNOS criteria present	Percent with death ≤ 60 minutes (%)
0	29
1	52
2	65
3	82
4–5	76

model incorporated only patient characteristics, while the second included patient characteristics and withdrawal process variables. In the first model, they found that the most powerful predictors of death were GCS equal to 3 or the combination of GCS > 3 with SaO2/FiO2 < 230 and peak inspiratory pressure ≥ 35. This model had a sensitivity of 79%, specificity of 63%, positive predictive value (PPV) of 63%, and negative predictive value of 78% [4]. This had even higher sensitivity and specificity if vasopressors >0.2 μg/kg/min and respiratory rate < 11 off the ventilator are included. The second model where all treatments are withdrawn within 10 minutes also had very high sensitivity, specificity, positive predictive value, and negative predictive value. These rules are relatively simple but have not been externally validated. Other risk factors independently associated with an increased risk of death within 60 minutes are listed in Table 4.5.

Table 4.5 Other risk factors independently associated with an increased risk of death within 60 minutes

Independent risk factors associated with time to death < 60 minutes
Glasgow coma scale of 3
$SaO_2/FiO_2 < 230$
Peak inspiratory pressure > 35
Respiratory rate off ventilator <8
Diastolic blood pressure (10 mmHg)
$PaO_2 < 72$
Epinephrine, norepinephrine, or phenylephrine >0.2
All treatments withdrawn within 10 minutes
Endotracheal tube withdrawn
Comfort medications given during first hour after WLST

DCD-N Tool

The previous two tools do not take into account the patient's neurologic status prior to WLST. The DCD-N tool predicts the onset of circulatory death in a comatose patient with catastrophic brain damage undergoing withdrawal of life-sustaining treatment. In an initial, single-center study by Yee et al., the authors showed an association between death in less than 60 minutes after extubation in patients with irreversible brain injury and coma and the following four variables: absent corneal reflex, absent cough reflex, absent motor response or extensor posturing, and high oxygenation index [6]. This was subsequently expanded upon in a large multicenter observational study which enrolled adult patients in coma due to an irreversible brain injury undergoing WLST [7]. Patients were excluded if they were not tracheal intubated or if they were brain dead.

Data collected included age, sex, corneal reflex, cough reflex, motor response to pain, oxygenation index, and time to death after WLST. In the multivariate analysis, absent corneal reflex, absent cough reflex, extensor or no response to pain, and higher oxygenation index were associated with death within 60 minutes after WLST. Oxygenation index was defined as $100 \times ((FiO_2 \times$ mean airway pressure in cm $H_2O)/PaO_2$ in torr) where mean airway pressure is (peak airway pressure in cm H_2O + peak end expiratory pressure in torr)/2. Using ROC curve, they determined that an oxygenation index of 3.0 had the highest sensitivity and specificity for death within 60 minutes of WLST. The authors then constructed a score based on the odds ratios for each variable (Table 4.6). The authors found that a score of 3 or more identified 72% of those dying within 60 min and a score of 0–2 identified 78% of those that did not die within 60 min. Probabilities of death within 60 minutes according to specific combinations of the variables can be seen in Table 4.7.

Other Studies

While the above three tools are the ones commonly described, several other studies have investigated predictors of time to death in potential DCD donors. A large UK study analyzed all DCD liver offers and derived validated models for both

Table 4.6 DCD-N scoring

Variables	Points
Absent cough reflex	2
Absent corneal reflex	1
Extensor or no motor response to pain	1
Oxygenation index >3.0	1

Table 4.7 Probabilities of death within 60 min according to the combinations of predictive variables

Absent corneal reflex	Absent cough reflex	Extensor or absent motor response	Oxygenation index > 3.0	Score	Probability
No	No	No	No	0	0.08
No	No	No	Yes	1	0.16
Yes	No	No	No	1	0.18
No	No	Yes	No	1	0.20
No	Yes	No	No	2	0.26
Yes	No	No	Yes	2	0.34
No	No	Yes	Yes	2	0.37
Yes	No	Yes	No	2	0.40
No	Yes	No	Yes	3	0.45
Yes	Yes	No	No	3	0.48
No	Yes	Yes	No	3	0.51
Yes	No	Yes	Yes	3	0.61
Yes	Yes	No	Yes	4	0.68
No	Yes	Yes	Yes	4	0.71
Yes	Yes	Yes	No	4	0.74
Yes	Yes	Yes	Yes	5	0.87

prediction of circulatory arrest and liver graft usability [8]. In that study of 621 potential DCD donors, 400 (64%) underwent circulatory arrest within 1 h from WLST. Factors that predicted cardiac arrest within 60 min were donor age > 40 years, use of inotropes, and absence of a gag/cough reflex.

Suntharalingam et al. investigated time to death in 91 potential DCD donors. In that study, they demonstrated that younger age, higher FiO2, and mode of ventilation were independently associated with shorter time to death [9].

A multicenter study by Brieva et al. evaluated death within 60 minutes after WLST in 318 DCD eligible patients [10]. In that study, three donor classification rules were expressed for the prediction of death in less than 60 min:

(i) Spontaneous resp. rate 0–10/min and GCS score 3
(ii) Spontaneous resp. rate 0–10/min and GCS score 4–15 and systolic BP 0–84 mmHg
(iii) Spontaneous resp. rate ≥ 11/min and PEEP ≥11

Using these three levels, the authors had a sensitivity of 0.82 and a positive predictive value of 0.80. Using only intensive care unit specialist prediction on whether the donor would expire or not within 60 min, the authors demonstrated comparable sensitivity (0.87) and PPV (0.78). Prediction of the time to death on the basis of

clinical impression has previously been investigated [11]. In that study, clinical judgment of the treating intensivist had a sensitivity of 73% and a specificity of 56% to predict death within 60 minutes.

Conclusion

Several prediction models have been developed to assist providers in screening appropriate DCD candidates. As previous authors have stated, using indices to predict time to death inevitably will result in missed opportunities for donation [12]. Even patients who are deemed highly unlikely to expire within 60 minutes based on all of the scoring systems sometimes expire quickly. For each transplant program, there may be variability in the acceptable probability threshold for likelihood that the donor will expire within 60 minutes in order to commit to a DCD organ procurement. In addition, this threshold may also vary from case to case based on distance and potential resources consumed. The aforementioned scoring systems are useful in providing some guidance as to how likely it is that a donor will expire. While the three scoring systems highlighted above are the only ones which have undergone external validation, each is fraught with limitations. UNOS criteria relies heavily on hemodynamic support which may exclude other populations, both the UWDCD and UNOS criterias require that the patient be taken off the ventilator which is not often practical, and the DCD-N tool is validated in patients with severe brain injury. Over all, neurologic and respiratory characteristics are the most predictive of death within 60 minutes of WLST. These scoring systems are all designed to predict which patients will expire within 60 minutes. Since most programs accepting DCD livers have acceptable DWIT between 20 and 40 minutes, these models do not represent ideal tools for predicting a usable DCD liver graft. Additional studies are needed to develop a more sensitive and specific prediction tool to help capture appropriate patients for DCD; however, it is likely that with any potential DCD donor, there will always be a level of uncertainty.

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Warm Ischemia Time

5

Kristopher P. Croome and C. Burcin Taner

Donation after circulatory death (DCD) donors differ from donation after brain death (DBD) donors in that they experience a period of obligatory donor warm ischemia time (DWIT) prior to initiation of cold perfusion of organs. Initial studies investigating liver transplantation using liver grafts from DCD donors linked prolonged DWIT to biliary complications and graft loss [1–3]. While most authors agree that prolonged DWIT results in hepatic ischemic injury, debate exists on the length of DWIT or hemodynamic parameters following withdrawal of life support that determine whether a liver graft can be used with reasonable safety. Undoubtedly, less ischemic organ damage occurs if the donor progresses quickly to circulatory death as opposed to maintaining a heartbeat in the presence of significant hypoxia or hypotension. The present chapter provides a summary of the literature on DWIT.

Definitions

Total Donor Warm Ischemia Time

The time from withdrawal of life-sustaining measures to cold organ flush/cross clamp in the donor [4].

Donor Warm Ischemia Time (DWIT)

There is some ambiguity in the literature on the definition of DWIT. Some studies use the term DWIT to describe the time from withdrawal of life-sustaining measures to cold organ flush/cross clamp in the donor (synonymous with total donor warm

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ischemia time). Other studies use the term DWIT to describe the time from a drop below a certain threshold for hemodynamic parameters (systolic blood pressure (sBP) or oxygen saturation (O_2 sat)) until cold organ flush/cross clamp in the donor. This second interpretation of DWIT is, in essence, a functional warm ischemia time.

Functional Donor Warm Ischemia Time (f-DWIT)

A time of warm ischemia that incorporates the impact of hemodynamic parameters and oxygenation during withdrawal of life support. The concept of a functional warm ischemia time arose from the notion that individual events during DCD procurement, such as variations in hemodynamics, mandatory wait period, and time from incision to cannulation of the aorta and cross clamp, all of which are included in total DWIT, may have different impact on the outcome of the liver graft [5]. Previous studies have defined the start of f-DWIT based on different hemodynamic parameters (such as drop in mean arterial pressure (MAP) or sBP) or by a drop in oxygen saturation below a specific level. f-DWIT terminates at the time of cold organ flush/cross clamp. While the concept of f-DWIT is ubiquitously accepted, no consensus on what parameters specifically define f-DWIT exists [6]. The United Kingdom has reached a consensus in which f-DWIT is defined as time between systolic blood pressure below 50 mmHg and cold organ flush [7].

Withdrawal Phase (of Warm Ischemia Time)

Withdrawal phase is the time interval from withdrawal of ventilatory support to circulatory arrest. This period may also sometimes be referred to as the agonal phase.

Acirculatory Phase (of Warm Ischemia Time)

Acirculatory phase is the time interval from circulatory arrest to the initiation of cold perfusion.

Circulatory Arrest/Cardiopulmonary Arrest

Circulatory arrest is defined by impalpable/undetectable pulse. This may be most accurately measured by a pulse pressure of zero determined by arterial line.

Pulseless Electrical Activity (PEA)

PEA is a clinical condition characterized by impalpable/undetectable pulse in the presence of sufficient electrical discharge [8]. In PEA, cardiac contractions and hence tissue perfusion are lacking, despite electrical impulses. PEA generates no

circulation; therefore, the electrical activity may be inconsequential in a death determination. PEA is generally observed a period of time prior to electrical standstill. Importantly, for the purposes of organ recovery, during PEA, there is no perfusion of blood into organs. A study by Rhee et al. demonstrated that electrical standstill occurred with a delay of 19 min following circulatory arrest (PEA) in a porcine withdrawal of life support model [9].

Electrical Standstill

Cardiac flatline or electrical standstill is the state of total cessation of electrical activity from the heart.

Mandatory Wait Time

A mandatory waiting time from cessation of cardiorespiratory function that is observed to ensure that autoresuscitation does not occur. This period may also sometimes be referred to as the "no-touch period." Some DCD policies define the mandatory wait time as a 'time-out' period after declaration of death, whereas others define it as a "time-out" period before declaration of death. Whether declaration of death in the DCD setting requires a prior waiting period (following cessation of cardiorespiratory function) or such declaration requires a subsequent time-out period, in no instance shall organ procurement proceed until both the waiting period and declaration of death are completed [10]. The American Society of Transplant Surgeons (ASTS) recommends a mandatory wait period of 2 minutes, whereas the Institute of Medicine recommends 5 minutes [10]. The mandatory wait time differs by country and between hospitals. In Italy, a Mandatory waiting time mandatory wait time of 20 minutes is required [11].

Declaration of Death

Declaration of death is the responsibility of the patient's treating care team. ASTS guidelines state that members of the procurement team shall not be in the presence of the potential donor from the time of withdrawal of support until declaration of death. Assessment for cessation of cardiorespiratory function is made using accepted medical standards, in compliance with donor hospital policy and local laws [10]. Many hospitals recognize PEA as cessation of cardiorespiratory function, and therefore it represents an acceptable criterion. Acceptable criteria for declaration of death may differ by country, by hospital, or by personnel performing the declaration.

Donor Hepatectomy Time (DHT)

The time from initiation of aortic perfusion to the end of the hepatectomy and removal of the liver from the donor.

Cold Ischemia Time (CIT)

The UNOS definition of CIT is the time from cross clamp in the donor until reperfusion of the liver in the recipient.

Recipient Warm Ischemia Time (rWIT)

rWIT is the time from when graft is taken out of cold preservation solution until the time the graft is reperfused.

The relationship of the various components of WIT is shown in Fig. 5.1.

Association Between Warm Ischemia Time and Outcome

Table 5.1 provides a list of studies that have investigated various parameters of DWIT and their associations with outcomes following liver transplant using DCD donors such as graft failure and ischemic cholangiopathy (IC).

Total Donor Warm Ischemia Time

In a large study based on national Scientific Registry of Transplant Recipients (SRTR) data, Mateo et al. found that total DWIT >30 minutes was associated with a HR 2.34 of graft loss compared to a DBD graft. In addition, authors found that low-risk recipients with low-risk DCD livers (DWIT <30 min and CIT < 10 h) achieved graft survival rates that were not significantly different from recipients with DBD grafts [2]. Another study based on national SRTR data by Lee et al.

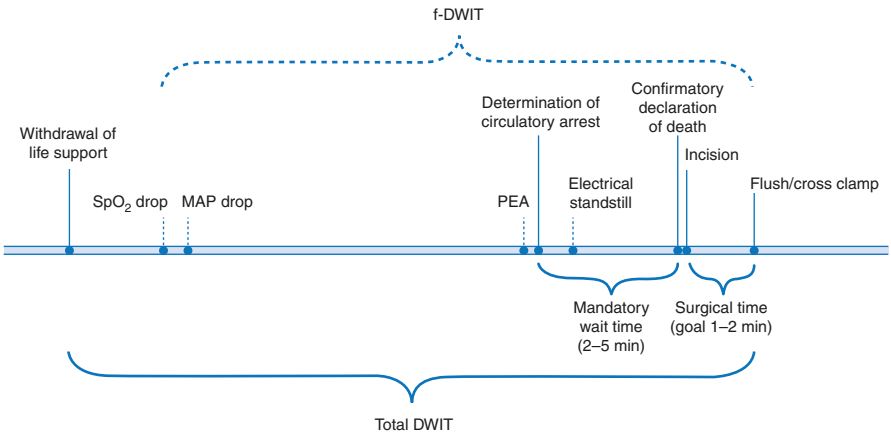

Fig. 5.1 The relationship of the various components of WIT

Table 5.1 List of studies that have investigated various parameters of DWIT and their associations with outcomes following DCD liver transplant such as graft failure and ischemic cholangiopathy (IC)

					Associated with	
Study	Year	*N*	Source	Parameter	Graft failure	IC
Mateo	2006	367	UNOS Registry	Total DWIT >30 minutes	Yes	NA
Lee	2006	874	UNOS Registry	Total DWIT >15 min, DWIT >30 min	Yes	NA
Chan	2008	52	Single center	Total DWIT	NA	No
				MAP <50 mmHg	NA	No
				MAP <35 mmHg	NA	No
				SpO_2 < 70%	NA	No
Ho	2008	39	New England Organ Bank	sBP < 50 mmHg for >15 min	Yes[a]	Yes[a]
				Total DWIT	No[a]	No[a]
de Vera	2009	141	Single center	Total DWIT >20 minutes	Yes	No
Mathur	2010	1567	UNOS Registry	Total DWIT >35 min	Yes	NA
Hong	2011	81	Single center	MAP <60 mmHg for >20 min	Yes	NA
Taner	2012	200	Single center	Asystole to CC	NA	Yes
				Total DWIT	NA	No
				sBP < 50 mmHg	NA	No
				SpO_2 < 30	NA	No
Abt	2013	110	Multicenter	Slope of sBP in first 10 minutes after extubation (SBP10)	Yes	NA
				Total DWIT	No	NA
Doyle	2015	49	Single center	Total DWIT	NA	No
				SpO_2 < 70%	NA	No
				sBP < 50 mmHg	NA	No
				Asystole to CC	NA	No
Firl	2016	98	Single center	Hemodynamic trajectory (cluster 1)	Yes	No
Kubal	2016	30	Single center	Total DWIT	NA	No
				SpO_2 < 70% or MAP <50 mmHg	NA	No
Kalisvaart	2017	93	Single center	SpO_2 < 80%	Yes	No
				SpO_2 < 80% (>13 min)	Yes	No
Coffee	2017	249	Multicenter	SpO_2 < 60	No[a]	No[a]
				Total DWIT	No[a]	No[a]
				MAP ≤ 50 mmHg	No[a]	No[a]
Schlegel	2018	1153	UK database	sBP < 50 mmHg	Yes	NA

[a]Composite outcome of graft failure and IC

developed a DCD risk index. In that study, an incremental increase in graft loss was seen with total DWIT >15 min (HR 1.37) and total DWIT >30 min (HR 1.77) compared to total DWIT ≤15 minutes [12]. Based on data from studies such as the two above, guidelines from the American Society of Transplant Surgeons (ASTS) in 2009 recommended total DWIT to be less than 30–45 min for better results [10].

Subsequently a single-center study by de Vera et al. demonstrated that inferior graft survival was associated with a total DWIT >20 min [3]. A study by Mathur et al. using

SRTR data found that donor warm ischemia time ≥ 35 min significantly increased graft failure rates (HR 1.84) [13]. In a study by Kubal et al., a significantly higher total DWIT was observed in a group of patients that developed IC [14]; however, upon multivariate regression, total DWIT was no longer a significant predictor of IC.

Functional Donor Warm Ischemia Time

The 2006 Report of a National Conference on Donation after Cardiac Death suggested that to better define DWIT, a more descriptive definition of what occurs after withdrawal of treatment was necessary [15]. It was felt that less ischemic damage may occur if the donor progresses quickly to death as opposed to maintaining a heartbeat in the presence of significant hypoxia and hypotension. They recommended that going forward, transplant centers should collect minute-by-minute donor hemodynamic data during the period between extubation and initiation of cold perfusion. Previously published national and society guidelines for functional DWIT can be seen in Table 5.2 [10, 16, 17, 18].

Blood Pressure and O_2 Saturation

In a study by Ho et al. looking at data from the New England Organ Bank DCD database, the authors investigated the association between donor hemodynamic factors following the withdrawal of life support and a composite endpoint of graft loss and the development of IC [1]. The authors demonstrated that a significantly higher rate of graft loss or IC was observed if the sBP <50 mmHg for >15 minutes. In the same study, no association between graft loss and IC was seen based on total DWIT. A single-center study by Chan et al. found no association between the following hemodynamic parameters and the development of IC: time from a MAP of

Table 5.2 Published national and society guideline for functional donor warm ischemia time (DWIT)

The American Society of Transplant Surgeons (ASTS) [10]
Recommendation: total DWIT <30–45 minutes
Functional DWIT defined as MAP < 60 mmHg
Recommendation: functional DWIT < 20–30 minutes
The British Transplantation Society (BTS) [16]
Functional DWIT defined as sBP <50 mmHg
Recommendation: functional DWIT < 30 minutes
Eurotransplant [17]
Functional DWIT defined as SpO_2 <80% or MAP <50 mmHg
The Spanish National Transplant Organization [18]
Functional DWIT defined as sBP <60 mmHg
Recommendation: functional DWIT < 30 minutes
2020 ILTS Consensus Conference on DCD
Functional DWIT defined as SpO2 <80% and/or MAP <60 mmHg
If functional DWIT exceeds 30 min, an increased risk for graft loss should be taken into account

≤50 mmHg to cross clamp, time from a MAP ≤35 mmHg to cross clamp, and an oxygen saturation of <70% to cross clamp [19]. That study also found no association between total DWIT and IC. Guidelines from the ASTS in 2009 recommended f-DWIT (interval between significant ischemic insult, such as a drop in mean arterial pressure below 60 mmHg, and initiation of perfusion) to be under 20–30 min for better results [10].

In a single-center study by Hong et al., a risk score to predict graft failure after liver transplantation with DCD liver grafts was created. A mean arterial pressure (MAP) <60 mmHg for >20 min after withdrawal of life support was associated with a HR 1.9 of graft failure [20].

A single-center study by Doyle et al. found no correlation between DWIT, duration of SpO_2 <70%, duration of sBP <50 mmHg or time from asystole-cross clamp, and the development of IC [21].

In a study by Kalisvaart et al., duration of SpO_2 <80% was associated with a higher rate of severe ischemia-reperfusion injury (AST > 300 U/L) [22]. In addition, SpO_2 <80% for >13 minutes was associated with increased complications and increased 90-day graft loss (26% vs 6%) compared to SpO_2 <80% for ≤13 min. On multivariate regression, SpO_2 <80% for >13 minutes was associated with increased graft loss (HR 3.30). No association between SpO_2 <80% and IC was observed.

A multicentered study by Coffey et al. investigated multiple components of functional DWIT and found no association on adjusted analysis between total DWIT, MAP ≤50 mmHg, sBP ≤50 mmHg, and SpO_2 ≤60% and a composite outcome between graft loss and IC [23]. While none of the parameters reached statistical significance in the adjusted analysis, the authors did find that time of SpO_2 ≤60% was longer among patients who developed post-transplant complications.

A study by Schlegel et al. developed a DCD risk score utilizing data from the UK DCD registry, SRTR data, and Birmingham single-center data and found that duration of sBP <50 mmHg was associated with inferior graft survival [24]. An incremental increase in graft loss was observed for sBP <50 mmHg when comparing groups with time ≤20 min, time >20 min, time ≤30 min, and time >30 min.

Asystole to Cross Clamp

A large single-center study by Taner et al. investigated if there was any association between components of f-DWIT and the development of IC [5]. In that study, only time from asystole-cross clamp was a significant predictor of IC. Total DWIT, time from sBP <50 mmHg to cross clamp, and time from O_2 sat <30% to cross clamp had no significant association with IC. On multivariate analysis, each minute increase in asystole-cross clamp duration was associated with a 16% increase in odds for development of IC. Our institution puts significant emphasis on the time from asystole to cross clamp and aims to keep it less than 10 minutes. If one assumes 2–3 minutes of PEA before circulatory arrest is called and then a 5-minute mandatory wait time

from circulatory to arrest until pronouncement of death, that leaves at most 2–3 minutes from incision to cross clamp, and therefore having an experienced surgical team is important.

Hemodynamic Trajectory

In a study by Abt et al., the authors investigated three methods to summarize the hemodynamic changes after extubation: (1) the area under the systolic blood pressure curve (AUCSBP), (2) the slope of the systolic blood pressure regressed onto the time from extubation until cross clamping, and (3) the slope of the systolic blood pressure regressed onto the time from extubation but calculated with only the values during the first 10 minutes after extubation (SBP10) [25]. On multivariate regression models incorporating donor and recipient covariates, SBP10 had the closest association with graft survival (HR 1.08). SBP10 was then dichotomized into values above or below the median (27.2 mmHg/minute). Patients with SBP10s steeper than the median had an estimated 5-year graft survival rate of 76%, whereas patients with slopes less than the median had a 5-year survival rate of 45%. In that study, total DWIT was not associated with graft failure.

In a study by Firl et al., donors were divided into three clusters based on their hemodynamic trajectory following withdrawal of life support: those who gradually decline after withdrawal of life support (Cluster 1), those who maintain stable hemodynamics followed by rapid decline (Cluster 2), and those who decline rapidly (Cluster 3) [4]. When looking a MAP trajectory, the 1-, 3-, and 5-year graft survival of the slow decliner (Cluster 1) (73.5%, 62.0%, and 62.0%) was significantly worse than that of the rapid decliner (Clusters 2 and 3) (93.2%, 82.2%, and 75.8%). When looking at O_2 trajectory, the 1-, 3-, and 5-year graft survival of the slow decliner (Cluster 1) (81.5%, 66.8%, and 66.8%) was significantly worse than the rapid decliner (Clusters 2 and 3) (94.3%, 87.7%, and 76.9%). The authors concluded that despite longer total DWIT, Cluster 2 donor livers had similar graft survival to Cluster 3 donor livers. No association between hemodynamic trajectory cluster and IC was observed.

Reasons for Variability in Association Between DWIT and Outcomes

Review of the literature on the impact of DWIT in DCD liver transplantation yields conflicting results. A major reason for this heterogeneity may be the lack of uniformity of both DWIT and outcome measures such as IC. Many studies have utilized various definitions of functional WIT based on different hemodynamic parameters and oxygenation during withdrawal of life support. Many of the single-centered studies may also lack the statistical power to adequately identify important parameters [26]. In order to move forward with investigating DWIT further, consensus on the various definitions of DWIT and f-DWIT is, as well as multi-institutional collaboration, needed.

Monitoring

Accurate monitoring of the potential donor's hemodynamic parameters and oxygenation during withdrawal of life support is paramount. A sample flowsheet is given in **Appendix.**

Blood Pressure

Blood pressure monitoring with an arterial cuff is not sufficiently accurate at lower blood pressure, nor does it provide continuous data to make it a desirable option during the withdrawal phase. Previous authors have suggested blood pressure monitoring with arterial line could be mandated to help standardize practices during procurement [5]. In a previous study, 62% of hospitals in one OPO (organ procurement organization) did address declaration of death as irreversible cessation of circulation without elaboration on the method of confirmation, whereas only 11% stated to use arterial line for declaration of death [27]. Using an arterial line may also allow the pronouncing physician to accurately identify when the donor is in PEA and therefore is in circulatory arrest.

O_2 Saturation

O_2 saturation is done almost exclusively with pulse oximetry. The accuracy of pulse oximetry, however, is limited in the setting of hypotension and severe hypoxia [28]. Previous authors have suggested that the accuracy of pulse oximetry decreases significantly with arterial hemoglobin saturation levels below 75–80% [22]. As such, the utility of O_2 saturation, except in the initial phase of withdrawal, is limited.

Donor Hepatectomy Time (DHT)

Several recent reports have suggested that DHT may be associated with outcomes following DCD LT [29, 30]. In a study from the United Kingdom, DHT > 60 minutes was associated with primary non-function (PNF) [29]. An abstract from the Netherlands demonstrated that DHT > 90 minutes was associated with both IC and early graft loss [31]. Whether prolonged DHT is itself a risk factor, or simply a proxy for donor surgeon inexperience or other factors, is unknown.

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6 Ischemia-Reperfusion Injury and Therapeutic Strategy in Donation After Circulatory Death Liver Transplantation

Toru Goto and Markus Selzner

Abbreviations

cDCD	Controlled DCD
DAMPs	Damage-associated molecular patterns
DCD	Donation after circulatory death
HMBG-1	High-mobility group box 1
HMP	Hypothermic ex situ machine perfusion
IC	Ischemic cholangiopathy
IRI	Ischemia-reperfusion injury
ITBLs	Ischemic-type biliary lesions
MP	Machine perfusion
NMP	Normothermic ex situ machine perfusion
NRP	Normothermic regional machine perfusion
ROS	Reactive oxygen species
SECs	Liver sinusoidal endothelial cells
TLR	Toll-like receptor
tPA	Tissue plasminogen activator
uDCD	Uncontrolled DCD

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Introduction

Ischemia-reperfusion injury (IRI) is common during transplantation when blood flow is restored and oxygen and nutrients are returned to the liver following ischemic injury. Although donation after circulatory death (DCD) is one important strategy to expand the donor pool, it is associated with severe reperfusion injury. Liver grafts from DCD donors are exposed to the agonal phase during donation resulting in an additional warm ischemia time with insufficient blood supply.

Liver IRI is regulated by several molecular pathways. Reperfusion injury results in significant changes in hepatocytes and liver sinusoidal endothelial cells (SECs). The prolonged ischemic period results in a depletion of adenosine triphosphate (ATP) with an activation of mediators of apoptosis and necrosis in liver cells. After reperfusion, neutrophils and liver macrophages (Kupffer cells) are activated in damaged livers, which amplify IRI by secretion of paracrine and autocrine signals, such as reactive oxygen species (ROS), lipid peroxidation, and damage-associated molecular patterns (DAMPs) [1].

In this chapter, we will focus on mechanisms of IRI in hepatocytes and bile ducts and discuss therapeutic strategies targeted on molecular mechanism of IRI in liver transplantation using DCD donors.

Molecular Mechanisms of IRI: Ischemic Period

According to the revised Maastricht classification in 2013 [2], DCD transplantation was categorized into two major types: controlled DCD (cDCD) and uncontrolled DCD (uDCD).

In cDCD, during the agonal phase, the oxygen saturation and the blood pressure are decreasing following withdrawal of life-sustaining therapies (WLST), and donor death is declared 2–5 minutes after a no-touch period [3]. Following death declaration, cold flush or regional perfusion is performed, and the organs are procured. Warm ischemia time has been variably defined, but it is necessary to consider the agonal phase (from WLST to cardiac arrest) as a relative ischemia time. A retrospective study in five major liver transplant centers determined that functional DWIT with $SpO_2 \leq 60\%$ is an important predictive parameter for postoperative complications in DCD liver transplantation [4].

In uDCD, the donor underwent an unexpected cardiac arrest outside the hospital with unsuccessful cardiopulmonary resuscitation before determination of death. A prolonged time period exists between cardiac arrest and arrival at the hospital prior to death declaration. The extent of the ischemia is more uncertain in uDCD, making the post-transplant severity of IRI difficult to predict.

Prolonged warm ischemic injury of more than 30 minutes is a well-known risk factor for post-transplant liver failure [5–10]. During ischemia, the cell death is mainly caused by metabolic disturbances [11]. Depletion of oxygen causes cell hypoxia that results in an inhibition of the electron transport in the respiratory chain and a decrease in intracellular ATP levels. ATP-dependent ion channels such as Na^+/

K^+ adenosine triphosphatase (ATPase), Na^+/H^+ exchanger, and Ca channels start to fail, which induces depolarization of the cell membrane with accumulation of intracellular Na^+ and Ca^{2+} and cellular edema. This activates proteases, lipases, phospholipases, and ATPases promoting hepatic apoptosis and necrosis. At the same time, anaerobic respiration induced by insufficient oxygenation supply causes lactic acidosis that further activates intracellular proteases. The increase of Ca^{2+} influx and accumulation of adenosine diphosphate (ADP), adenosine monophosphate (AMP), and phosphate in hepatocyte lead to mitochondrial membrane permeability transition (MMPT) [12]. MMPT induces mitochondrial swelling and allows soluble molecules with a molecular weight of less than 1500 kDa to pass through the "ionic mega-channels" of the mitochondrial membrane and further enhances the liver damage [13]. Furthermore, warm ischemia decreases phospholipid cardiolipin (diphosphatidylglycerol), which is an essential predominant mitochondrial phospholipid and increases oxidized form of cardiolipin in hepatocyte [14]. These pathways cause mitochondrial dysfunction and promote cell death (Fig. 6.1).

After procurement with an organ preservation solution, the liver is stored on ice (at 4 degrees Celsius). This second ischemic phase is called cold ischemia time (CIT) and is associated with cold ischemic injury until liver is successfully reperfused in the recipient. During this time, liver metabolism is reduced, and ATP stores within cells are depleted less rapidly [15]. SEC is sensitive against cold storage [16, 17]. ATP depletion during the ischemic phase in SEC induces not only mitochondrial dysfunction but also actin-fiber disassembly [18] and the release of matrix metalloproteinases (MMP-2, MMP-9) [19]. This results in an expression of von Willebrand factor (vWF) and P-selectin on the endothelial cell surface, which promotes thrombosis after reperfusion [20].

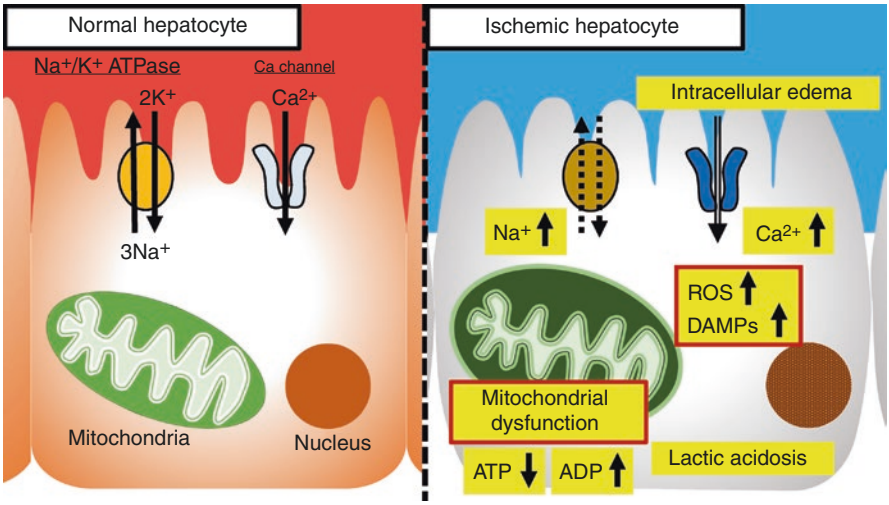

Fig. 6.1 Mechanism of cell damage in ischemic period. *Abbreviation*: ROS reactive oxygen species, DAMPs damage-associated molecular patterns, ATP adenosine triphosphate, ADP adenosine diphosphate

Molecular Mechanism of IRI: Reperfusion Period

While the warm and cold ischemic phases condition the liver cells to preservation injury, it is the reperfusion phase when the apoptotic and necrotic pathways are executed, and the cell death occurs. Reperfusion increases the intracellular Ca^{2+} concentration and the production of reactive oxygen species (ROS) by several pathways such as neutrophil migration and inflammatory cytokines and chemokines such as TNF-α, IL-1β, IFN-γ, and IL-12 (Fig. 6.2). This leads to irreversible cellular and mitochondrial changes and cell death.

Reperfusion injury involves numerous parenchymal cells as well as non-parenchymal cells that interact in a network of simultaneous events prompting pro-inflammatory change and cell injury.

Hepatocytes develop cell swelling, lactic acidosis, and mitochondrial dysfunction induced by ATP depletion and hypoxia during the ischemic phase. After reperfusion, the surplus oxygen is not used in the respiratory chain which results in the generation of oxygen free radicals that lead to cell death [21]. In addition, damaged hepatocytes secrete DAMPs such as HMGB-1, histone/DNA, and ATP to activate Kupffer cells and neutrophils as a sterile inflammation [22]. These productions of ROS and DAMPs promote more severe damage of hepatocytes.

Sinusoidal endothelial cells (SECs) play a key role to control sinusoidal blood flow, oxygen supply, and delivery of nutrients for liver tissue by regulating vascular tone [23]. SEC injury gives rise to cell swelling as well as detachment. Mitochondrial injury results in decreased NO (nitric oxide) production and depletion of NO stores.

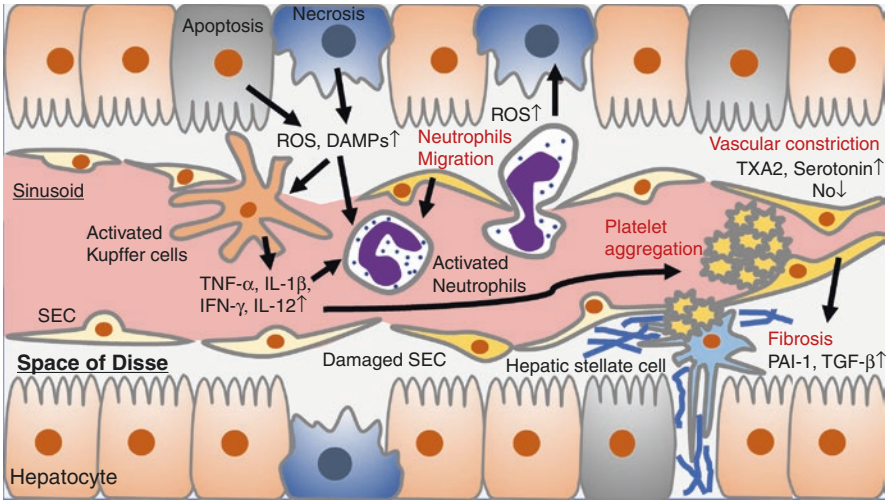

Fig. 6.2 Main mechanism of ischemia-reperfusion injury. *Abbreviation*: SECs Liver sinusoidal endothelial cells, ROS reactive oxygen species, DAMPs damage-associated molecular patterns, TNF-α tumor necrosis factor-α, IL-1β interleukin-1β, IFN-γ interferon-γ, IL-12 interleukin-12, TXA2 thromboxane A2, NO nitric oxide, PAI-1 plasminogen activator inhibitor-1, TGF-β transforming growth factor-β

The balance between the vasorelaxation effect of NO and the vasoconstrictor effects of TXA2 (thromboxane A2) from platelet becomes disturbed, which leads to an increase of the vascular tone and decrease of the hepatic blood flow [24, 25]. In addition, activated SECs express P-selectin which enhances platelet adhesion and activation. Adhesion of platelet further promotes cell death and decreases sinusoidal microcirculation by inducing congestion and reducing flow [26, 27].

Kupffer cells play a central role in the pro-inflammatory cascade after reperfusion. Under normal circumstances in the absence of preservation injury, Kupffer cells present circulating antigens from the blood to T cells and induce tolerogenic T cells to produce anti-inflammatory cytokines (IL-10) [28]. In contrast, during IRI, Kupffer cells recognize DAMPs from hepatocytes and SEC through Toll-like receptors 3, 4, and 9 and secrete pro-inflammatory cytokines such as TNF-α, IL-1β, IFN-γ, and IL-12. These mediators induce neutrophil migration to the liver and the release of ROS from neutrophils and promote platelet adhesion on SEC [29–31].

Neutrophils are main actors during IRI. After reperfusion, the complement system is activated and enhances production of complement protein 3a (C3a), complement protein 5a (C5a), and the membrane attack complex (MAC). This complement activation leads to the recruitment of pro-inflammatory cells including neutrophils to the damaged liver and promotes in cell death [32, 33]. In the liver, neutrophils detect chemokines such as CXCL1 and CXCL2 secreted by activated Kupffer cells, which guides them into the sinusoids [34]. Chemokines also bind to glycosoaminoglycans on the vascular surface of SEC. When neutrophils reach the SEC, chemokine-chemokine receptor interactions activate the integrins. Neutrophils bind SEC through integrin CD11b/CD18a (Mac-1) on the neutrophils and intracellular adhesion molecule-1 (ICAM-1) on SEC [35]. Neutrophils also respond to inflammatory signals (DAMPs) in the liver, such as high-mobility group box 1 (HMBG-1) and DNA fragment released from injured hepatocytes. These substances enhance the production of ROS from neutrophils through DAMP receptors including Toll-like receptor (TLR) [36]. DNA fragments activate TLR9 on neutrophils, which plays a significant role in neutrophil migration, activation, and production of ROS [37]. Damaged hepatocytes release the HMGB-1, which activates TLR4 and amplifies hepatic injury [38]. This cascade causes further migration of inflammatory cells, and liver tissue damage creates a positive feedback loop [39].

Platelets have been recognized as important players within the hepatic reperfusion injury cascade. Activated Kupffer cells by DAMPs from hepatocytes and SEC release TNF-α. TNF-α induces the P-selectin on SEC and promotes platelet adhesion and activation [40]. This leads to microthrombosis in sinusoid and induces apoptosis of SEC [27]. On the other hand, SECs express CD39 (ectonucleoside triphosphate diphosphohydrolase-1 (ENTPD1)) on the luminal side, which is a regulator of ATP and ADP in platelets. When SECs are injured, CD39 activity decreases and ADP increases in the extracellular environment. ADP is a key inducer of platelet aggregation, and platelets are activated [41]. Furthermore, damaged SECs can result in endothelial fenestrations allowing platelets to enter the space of Disse. Platelets attach to the collagen type III in space of Disse and aggregate, which is called “extravasated platelet aggregation” [42]. Activated platelets release negative mediators, such as thromboxane A2 (TXA2) [24],

serotonin [27], plasminogen activator inhibitor-1 (PAI-1) [43], and TGF-β [44]. TXA2 and secretin can induce portal hypertension, while PAI-1 and TGF-β promote hepatic fibrosis and suppression of liver regeneration.

Therapeutic Strategies

Minimizing Ischemia Times

It is important to realize that minimizing ischemia is a low-cost and highly effective way to reduce preservation injury in liver grafts from DCD donors. Warm ischemia has severe effects in DCD grafts, but the length of warm ischemia does not linearly correlate with the severity of injury [45]. Prolonged CIT of more than 8 hours is a risk factor for graft failure and ischemic cholangiopathy [6–9, 46–48]. To shorten the cold ischemia time, some institutes start the recipient hepatectomy prior to the procurement team's return when using grafts from DCD donors [7, 49]. Other possible strategies to minimize warm ischemic injury are ante-mortem procedures such as donor anticoagulation, administration of vasodilators, and femoral cannulation for regional perfusion. Limitations include legal and cultural restrictions as well as the limited scientific evidence of the beneficial effects of antemortem strategies on postoperative outcomes [50].

Thrombolytic Therapy

Biliary complications are common after DCD liver transplantation. Ischemic-type biliary lesions (ITBLs) and ischemic cholangiopathy (IC) occur in 12% to 50% of DCD transplantations resulting frequently in graft loss [7, 10, 51, 52]. These biliary complications are thought to be caused by insufficient arterial blood supply of the intra- and extrahepatic bile ducts. While the liver parenchyma receives the dual blood flow from the hepatic artery and the portal vein, the blood supply for bile duct comes only from hepatic artery via peribiliary vascular plexus [53]. Dries et al. analyzed biliary injury of 128 liver transplants including 29 from DCD donors. The authors demonstrated that 92% of the bile epithelium was injured at the end of cold storage with a luminal epithelium loss >50%. In addition, the peribiliary glands which promote biliary regeneration were damaged in 57% of the superficial periluminal side and 18% in deep bile duct wall. Furthermore, the mural stroma necrosis, vascular injury, intramural bleeding, and inflammation worsened after reperfusion [54].

To dissolve the microthrombi and to obtain sufficient blood flow in biliary microcirculation, some transplant programs used thrombolytic therapy during back-table preparation or implantation of the liver graft. Hashimoto et al. reported their experience with the tissue plasminogen activator (tPA) flush on the back table for 22 DCD liver grafts [55]. Several other groups reported the use of tPA during DCD liver transplantation, and a systematic review indicated that thrombolytic therapies in

DCD liver transplantation statistically decreased ITBLs and retransplantation rate and improved 1-year graft survival without the risk of increasing blood transfusion [53]. However, the efficacy of thrombolytic therapy is still controversial in the absence of randomized controlled trials and the differences within the tPA injection protocols. In addition, there is a significant variation in functional DWIT and CIT between studies, which makes the comparison of the different trials difficult [56]. This topic is covered in more depth in Chap. 8, "tPA and Thrombolytic Therapy."

Machine Perfusion

Machine perfusion (MP) is a novel strategy for preservation of DCD grafts. Machine perfusion can be performed as in situ and ex situ machine perfusion. Ex situ machine perfusion has been performed at physiologic temperatures (warm perfusion) with oxygen and nutrition, while cold (4 °C degrees) ex situ machine perfusion has been developed with or without oxygen.

Ex situ MP is currently categorized into three groups: post-static cold storage (SCS) MP, replacing cold storage with MP, and ischemia-free liver transplantation without warm or cold ischemic preservation [57]. In post-SCS MP, liver graft is perfused after cold storage and transport of the liver graft to the recipient hospital. With preservation MP, the perfusion starts at the donor hospital after cold flush and continues until transplantation. Ischemia-free liver transplantation is a novel method to connect the perfusion machine to the donor vessels and continue perfusion until reperfusion without any ischemia. In clinical settings, perfusate temperature and perfusate type differ between each perfusion strategy. Two different temperature settings have been used during machine perfusion: hypothermic MP (HMP, 0–12 degrees) and normothermic MP (NMP, 35–38 degrees). Although each perfusion has its own protective effects against IRI, the basic merits of MP in both settings are decreased preservation injury, graft assessment, and graft reconditioning, compared with SCS.

Hypothermic Oxygenated Ex Situ Machine Perfusion

Oxygenated HMP increases ATP and attenuates the inflammatory IRI cascade compared with static cold storage. Oxygenated HMP reduces mitochondrial injury [58] and improves ATP storage during preservation [15]. Furthermore, compared with SCS group, HMGB-1, which is one of DAMPs and representative of nuclear damage, was lower, Kupffer cell activation was suppressed, and expression of vWF on LSECs was significantly decreased in HMP group [58]. In a matched control clinical trial, Schlegel et al. demonstrated that liver grafts from DCD donors with oxygenated HMP had significantly lower graft loss at 5 years after transplantation (HMP-DCD 8% vs SCS-DCD 32%) [59]. Oxygenated HMP in DCD liver grafts also decreased biliary injury after transplantation by reducing biliary fibrosis with less activated myofibroblasts compared with SCS-preserved grafts [60]. In a clinical trial, Rijn et al. demonstrated that oxygenated HMP-DCD liver transplantation reduced IRI of the bile duct when compared with DCD-SCS controls, with less

mural stroma necrosis and better preservation of periluminal peribiliary glands after reperfusion [61, 62]. This was associated with a significantly lower rate of graft loss by ischemic cholangiopathy (HMP-DCD 0% vs SCS-DCD 10%) [59] (Fig. 6.3a).

Normothermic Ex Situ Machine Perfusion (NMP)

The liver is metabolically active during normothermic ex situ perfusion, which offers the opportunity to assess the hepatocyte and cholangiocyte viability. Aminotransferase levels in the perfusate can be determined as hepatocyte injury maker. As hepatocellular functional parameters, lactate clearance, bile volume and quality (bile pH, bicarbonate and glucose levels), and glucose consumption can be measured [63]. Several markers during normothermic ex situ perfusion were reported to be associated with post-transplant primary non-function liver. Mergental et al. defined viability criteria during NMP. These viability criteria consisted of lactate clearance, pH maintenance, bile production, vascular flow patterns, and liver macroscopic appearance based on data of human discarded livers [64].

NMP has been demonstrated to replenish ATP levels in hepatocyte [65–68], significantly lower aminotransferase after transplantation, and result in better survivals in pig DCD liver transplant models [69]. Recently, Jassem demonstrated that NMP leads to an upregulation of gene expression of tissue regeneration and platelet function and a reduced expression of immune-related genes. NMP induces regulatory T cells and reduces the proportion of CD4-positive T cells producing IL-2, IL-4, IFN-γ, and IL-17 and CD8-positive T cells producing IFN-γ. This results in a suppression of neutrophil infiltration and reduction of parenchymal cell death compared with SCS [70]. Nasralla et al. reported the first randomized trial of NMP with 220 human livers including 53 DCD livers. They demonstrated lower level of graft injury (peak AST NMP 488.1 vs SCS 964.9 IU/L), lower discarded rate (NMP 11.7% vs SCS 24.1%), and lower rate of early allograft dysfunction (NMP 10.2% vs SCS 29.9%) [71].

NMP also decreases biliary IRI and promotes bile regeneration in DCD liver grafts. NMP-DCD livers showed mild epithelial injury, while SCS-DCD showed diffuse epithelial injury in extrahepatic duct and the peribiliary gland. Furthermore, Ki-67 staining revealed active cholangiocyte regeneration in NMP-DCD livers in the bile duct lumen and superficial and deep peribiliary gland, whereas Ki-67 staining was absent in SCS-DCD [72].

As a new type of perfusion, Boteon et al. demonstrated that a combined perfusion of HMP and NMP (2-hour HMP and 4-hour NMP) had 1.77 times higher ATP levels and lower tissue expression markers of oxidative injury (4-hydroxynonenal) and inflammation (CD11b, vascular cell adhesion molecule) compared with 6-hour NMP in ten human discarded livers (DCD 70%) [73] (Fig. 6.3b).

Normothermic In Situ Regional Perfusion (NRP)

Normothermic in situ regional perfusion was developed to assess the organ function in cDCD and uDCD prior to organ excision in the donor. NRP restarts blood flow to the abdominal organs after death declaration via extracorporeal membrane oxygenation (ECMO) prior to the graft cooling. Watson et al. compared NRP-DCD ($n = 43$)

a

Author	Year	Donor type, N	Preservation	Perfusion	Perfusion duration (min)	WIT (min)	CIT (min)	peak AST/ALT (U/L)	PNF	Ischemic cholangiopathy	Graft survival
Dutkowski et al.	2015	DCD 25	HMP	PV only, open circuit	118 (101-149)	18 (17-21)	188 (141-264)	1808 (AST) / 1239 (ALT)	0%	0%	90% (1 year)
		DCD 50	SCS	–	–	17.5 (16-20)	395 (349-447)	2848 (AST) / 2065 (ALT)	6%	22%	69% (1 year)
		DBD 50	SCS	–	–	–	386 (286-425)	1473 (AST) / 1124 (ALT)	0%	4%	96% (1 year)
Rijn et al.	2016	DCD 10	HMP	HA, PV, open circuit	126 (12-135)	15 (13-17)	NA	966 (ALT)	0%	10%	100% (1 year)
		DCD 20	SCS	–	–	16 (14-18)	503 (476-526)	1658 (ALT)	0%	4.5%	67% (1 year)
Schlegel et al.	2019	DCD 50	HMP	PV only, open circuit	120 (96-144)	36 (31-40)	264 (210-312)	1226 (ALT)	0%	8%	94% (5 year)
		DCD 50	SCS	–	–	25.5 (21-31)	282 (258-318)	1331 (ALT)	4%	22%	78% (5 year)
		DBD 50	SCS	–	–	–	300 (240-300)	1425 (ALT)	2%	2%	Showed in Figure

b

Author	Year	Donor type, N	Preservation	Perfusion	Perfusion duration (min)	WIT (min)	CIT (min)	peak AST/ALT (U/L)	PNF	Ischemic cholangiopathy	Graft survival
Selzner et al.	2016	10 (DCD 2, DBD 8)	NMP	HA, PV, closed circuit	480 (340-580)	DCD: NA (28-29)	NA	619 (ALT)	0%	0%	100% (3 months)
		30 (DCD 6, DBD 24)	SCS	–	–	DCD: NA (28-29)	534 (523-783)	949 (ALT)	0%	0%	100% (3 months)
Ravikumar et al.	2016	20 (DCD 4, DBD 16)	NMP	HA, PV, closed circuit	5580 (210-1110)	DCD: 21 (14-31)	NA	417 (AST)	0%	NA	NA
		40 (DCD 8, DBD 32)	SCS	–	–	DCD: 15 (9-23)	534 (252-684)	902 (AST)	0%	NA	NA
Bral et al.	2017	10 (DCD 4, DBD 6)	NMP*1	HA, PV, closed circuit	690 (198-1350)	21 (16-26)	167 (95-293)	1252 (AST)	0%	0%	NA
		30 (DCD 8, DBD 22)	SCS	–	–	NA	233 (64-890)	839 (AST)	0%	NA	NA
Nasralla et al.	2018	121 (DCD 34, DBD 87)	NMP	HA, PV, closed circuit	547.5 (372.5-710.5)	DCD: 21 (17-25)	126 (106.5-143.0)	488.1 (AST)	0.8%	DBD 7.4% DCD 11.1%	95% (1 year)
		101 (DCD 21, DBD 80)	SCS	–	–	DCD: 16 (10-20)	465 (375-575)	964.9 (AST)	0%	DBD 5.4% DCD 26.3%	96% (1 year)

c

Author	Year	Donor type, N	Preservation	Perfusion	Perfusion duration (min)	WIT (min)	CIT (min)	peak AST/ALT (U/L)	PNF	Ischemic cholangiopathy	Graft survival
Watson et al.	2018	DCD 43	NRP	NRP	123 (103-130)	30 (26-36)	382 (303-502)	633 (ALT)	0%	0%	97.7% (90 days)
		DCD 187	SCS	–	–	27 (22-32)	444 (395-493)	1154 (ALT)	7%	27%	89.8% (90 days)
Hessheimer et al.	2019	DCD 95	NRP	NRP	120 (79-136)	18 (13-23)	315 (265-365)	N	2%	2%	88% (3 years)
		DCD 117	SCS	–	–	22 (19-26)	340 (285-383)	N	3%	13%	76% (3 years)

Fig. 6.3 Clinical evidence of ex vivo machine perfusion for DCD liver graft. (**a**) Hypothermic ex situ perfusion. (**b**) Normothermic ex situ perfusion. ∗1 1 liver was not perfused because of portal vein torsion. (**c**) Normothermic regional perfusion. *Abbreviation*: WIT warm ischemia time, CIT cold ischemia time, PNF primary non-function, DCD donation after cardiocirculatory death, DBD donor after brainstem death, HMP hypothermic machine perfusion, NMP normothermic machine perfusion, NRP normothermic regional perfusion, HA hepatic artery, PV portal vein, NA not available

with non-NRP-DCD (n = 187) liver transplantation. The NRP-DCD group had decreased liver injury (peak ALT; 633 vs 1154 IU/L), lower early allograft dysfunction rate (3.5% vs 5.0%), and lower IC (0% vs 27%) [74]. Hessheimer et al. reported that NRP group showed significantly lower ITBLs (2% vs 13%) and lower graft loss (12% vs 24%) compared with super-rapid recovery group [75] (Fig. 6.3c).

Conclusion

IRI in liver transplantation is induced by a simultaneous activation of parenchymal and non-parenchymal cells within the liver. In liver grafts from DCD donors, the prolonged ischemia times are a crucial factor for postoperative liver function and bile duct injury. To reduce graft injury and improve post-transplant graft function, minimizing WIT and CIT is critical. In addition, novel preservation methods, such as cold and warm ex situ perfusion, as well as in situ regional perfusion, are promising approaches to improve reperfusion injury in DCD grafts. Currently, several organ perfusion settings demonstrated feasibility and improved results in transplantation with DCD grafts. It is expected that future research will result in the development of new targeted drugs for more effective protection against IRI and reconditioning of grafts from DCD donors in the future.

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Donor Selection in DCD Liver Transplantation

7

Miriam Cortes-Cerisuelo and Andrea Schlegel

Abbreviations

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMI	Body max index
CIT	Cold ischemia time
CVA	cerebrovascular accident
DAA	Direct-acting antiviral medications
DBD	Donation after brain death
DCD	Donation after circulatory death
DCD-RI	DCD-risk index
DM	Diabetes mellitus
DRI	Donor risk index
ET-DRI	Eurotransplant Donor Risk Index
fDWIT	Functional donor warm ischemia time
GGT	Gammy-glutamyl-transferase
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HMP	Hypothermic machine perfusion
HOPE	Hypothermic oxygenated perfusion
IC	Ischemic cholangiopathy
ITU	Intensive care unit
KCH	King's College Hospital

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MELD	Model of End Liver Disease
NHS	National Health Service
NHSBT	National Health Service Blood and Transplant
NMP	Normothermic machine perfusion
NRP	Normothermic regional perfusion
PNF	Primary non-function
UCLA	University of California at Los Angeles
UHB	University Hospitals Birmingham
UK	United Kingdom
UK-DCD-Risk Score	United Kingdom Donation after Circulatory Death Risk Score
UNOS	United Network of Organ Sharing
USA	United States of America

Introduction

The overall success story of liver transplantation with a steadily improved outcome has led to a broadening of recipient indications with subsequent higher need for donor livers, while the number of acceptable grafts remained stable [2, 36]. In this context, livers from controlled donors after circulatory death (DCD, category 3 of Maastricht) are increasingly considered for transplantation and classified as "marginal" or from extended criteria donors (ECD) [24, 25, 40, 105]. Although DCD liver transplant programs are active in several countries with acceptable outcomes reported, multiple definitions and different cut-off values for risk factors, including donor warm ischemia time, exist in context of different national regulations (Fig. 7.1) [76, 86]. To avoid severe complications after DCD liver transplantation, the majority of transplant centres has limited the acceptance criteria for certain donor risk factors in this field [23, 35, 67, 76]. Despite the overall comparable outcomes achieved to the average liver transplant from donors after brain death (DBD) cohort today, such restrictive policy is one reason behind the remaining high discard rates of 10–80% of DCD liver offers worldwide [24, 25, 30, 35, 52, 72, 76, 82, 84]. The critical evaluation of specific donor and recipient risk factors has not only improved the general awareness of the cumulative donor risk but also pushed certain boundaries for single donor risk factors, including, for example, donor age, body mass index (BMI), or donor past medical history, particularly liver function tests [76, 91] mainly in centres with a large experience in DCD donor utilization. Additional careful selection and a tailored allocation of DCD grafts to certain recipients appear very important to achieve good outcomes [63, 91, 100]. In this context, several groups have used the available national datasets to develop new prediction models and define cut-offs, when to say "no" to a specific DCD donor or combination with a certain recipient [12, 59, 91]. This chapter describes different donor and graft factors with impact on outcomes and highlights the selection process in this challenging

field of liver transplantation. Additionally, we report on future changes and the potential impact of new preservation technology on the decision process and the DCD liver allocation pathway.

Donor Risk Factors

The acceptance of donor livers for transplantation is currently based on personal experience, knowledge from historical case series and steadily growing national and international datasets, collected throughout the last 50 and 15 years, for overall and DCD liver transplantation, respectively; it is also influenced by the current need of donor livers according to the number of patients on the waiting list in different transplant centres and the availability of DBD livers. Although we have learned to successfully transplant DCD livers despite a higher risk compared to DBD grafts, we however struggle to accept different donor risk combinations, for example, in context of the macroscopic aspects of a graft or in donors, where the liver is macroscopically normal with donor risk factor cut-offs modestly exceeded. Although most risk factors are clinically recognized today (Fig. 7.1), the impact of many parameters alone or in combination remains under assessment, and uniform acceptance criteria or thresholds are largely missing [47, 90].

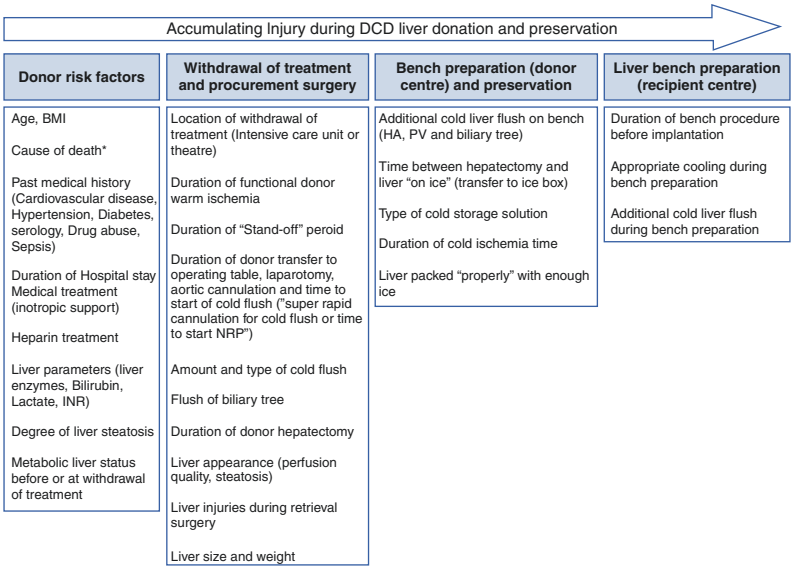


Fig. 7.1 Donor and graft factors with impact on the utilization of DCD donors before and DCD livers after treatment withdrawal and procurement. BMI Body-Mass-Index, DCD donation after circulatory death, HA hepatic artery, INR international normalized ratio, NRP normothermic regional perfusion, PV portal vein. ∗cause of death: reason for admission and/or death in DCD donation: although donor does not fulfil brain death criteria

Donor Age

Elderly livers are generally considered particularly vulnerable to additional injury transmitted through warm or cold ischemia with less regenerative capacity and an increased risk to develop complications [29, 36, 97, 106] such as graft dysfunction and biliary related. Donor age has therefore always been recognized as one main risk factor in DCD liver transplantation, and the majority of centres categorically advise against the utilization of livers from DCD donors older than 65 years, 60 years or even 50 years of age [26, 36, 44, 90, 93, 95]. In contrast, some countries with otherwise significant waiting list mortality frequently use DCD livers from donors at any age (Table 7.1) [32, 39, 94, 114]. Such clinical practice is also based on experience and recent cohort studies, where authors have demonstrated that DCD liver transplantation from donors above 60 and even 70 years of age can achieve equal good outcomes, given other risk factors remain low [26, 90].

Donor Cause of Death and Duration of Hospital Stay

In countries with a very active DCD donation program, elderly donors with an *intracranial haemorrhage (ICH)* or another vascular event, who experienced a healthy life in terms of other risk factors, are generally kept short on intensive care unit (ITU) until withdrawal of treatment (WOT) and are generally accepted as good donors. According to the guidelines of the British Transplantation Society (BTS), donors with a hospital stay of ≤5 days are classified as good or low risk (Fig. 7.1, Table 7.1) [3]. In contrast, the community may invest with a prolonged ITU stay into younger people, who were admitted following an *out-of-hospital cardiac arrest (OOHCA)* or severe trauma with significant downtime and reanimation, which may result in hypoxic brain injury (HBI) with subsequent organ donation. Although historically donors with OOHCA were frequently declined, their utilization is routine practice today, with however no precisely defined guidelines [17]. Multiple factors, including the duration of initial downtime, the required amount of ongoing cardiovascular support at offer and donor liver enzymes and function, including INR and the metabolic donor situation, have been demonstrated to impact on the decision to accept such a donor or not [71, 87]. Some argue that the OOHCA may even have primed the liver tissue, similar to ischemic preconditioning, and would lead to an improved early liver function with lower liver enzymes after transplantation [71]. Available data on this specific DCD donor source remain however scarce, and most centres follow the general suggestion to repeat liver enzymes and function tests in donors with previous elevated values to demonstrate the downward trend and confirm liver recovery from the initial insult of ischemia prior to WOT [16, 71].

Some centres follow similar criteria applied for split liver donors and accept DCD grafts with liver enzymes of ≤300 U/L; however, further evidence is needed. Abdominal *donor trauma* or reanimation may also impact on the liver with acquired parenchymal injuries, often rather small without significant involvement of hilar structures or hepatic veins. Limited or unclear liver trauma should not be the main deterrent to decline a DCD donor prior to graft evaluation, given the overall risk is acceptable [73].

Table 7.1 Overview on recommended risk factor thresholds for DCD donor livers

Donor and graft risk factors	Good or "ideal" DCD	Extended DCD	Suggested parameter threshold per country
Donor age (years)	≤40 y ≤50 y ≤60 y	>60 y >70 y	Belgium, ≤70 y; France, ≤70 y Italy, ≤65 y; the Netherlands, ≤60 y Spain, ≤90 y; Switzerland, any donor age UK, ≤80 y; USA, ≤40–50 y
Donor BMI (kg/m^2)	≤ 30 kg/m^2 ≤ 25 kg/m^2	>30 kg/m^2 >25 kg/m^2	Considered as risk factors No clear cut-off given
Donor body weight (kg)	≤100 kg	>100 kg	
Elevated donor liver enzymes (AST, ALT, bilirubin, GGT)	–	–	
Donor hospital/ITU stay (days)	≤5 days	>5 days	
Donor agonal phase ("first warm ischemia time") (min)[a]	≤ 20 min ≤ 30 min	>20 min >30 min	Known risk factor, no general and absolute cut-off given
Donor functional warm ischemia time (min)[b]	≤20 min	>20– 30 min >30 min	Belgium, ≤30 min; France, ≤30 min Italy: No cut-off (graft assessment) The Netherlands: No defined cut-off (asystolic time considered) Switzerland: No cut-off (graft assessment) UK: ≤30 min
Donor asystolic warm ischemia time (min)	≤15 min	>10 min >15 min	Known risk factor, no general and absolute cut-off given
Graft steatosis Macrosteatosis (%) Microsteatosis (%)	None Minimal (≤5%)	Any steatosis >5–10% >15%	Considered as risk factor Logistical challenge (pathology assessment) No clear cut-off defined, often declined based on macroscopic evaluation
Cold ischemia time (hrs)	≤6 hrs ≤8 hrs	>8 hrs >10 hrs	General aim for short cold ischemia time, no absolute cut-off

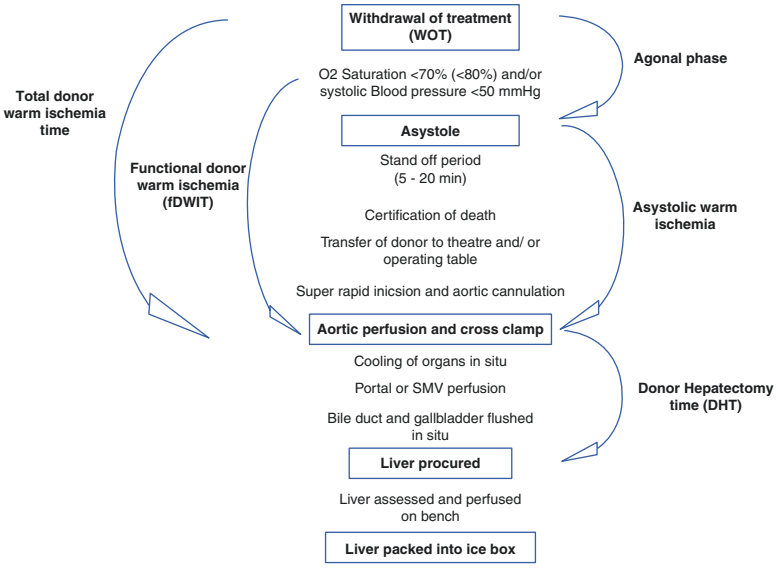
ALT alanine aminotransferase, *AST* aspartate aminotransferase, *GGT* gamma-glutamyl-transferase

[a]Time between withdrawal of treatment in donor and circulatory arrest, considered mainly in the USA

[b]Functional donor warm ischemia time: different countries and even centres follow three main definitions: MAP <50 mmHg until flush, systolic BP <50 mmHg until flush, oxygen saturation <70% until flush

Donor Past Medical History

In addition to the main cause of donor death, the past medical history may significantly impact on the acceptance of a specific DCD donor. In addition to a potential negative effect on arterial vessels, the perfusion quality and a possibly difficult donor cannulation due to severe arteriosclerosis, donors with arterial hypertension or *diabetes mellitus* may have an accumulation of fat in the hepatocytes.



Definitions:
fDWIT is defined as the period from sustained fall of systolic blood pressure (i.e. at least 2 minutes) below 50 mmHg or non-Invasive oxygen saturation below 70% untill the onset of in situ cold perfusion.
Agonal phase is the time from treatment withdrawal to circulatory arrest.
Donor Hepatectomy time is the time from aortic perfusion until liver is in ice.
Asystolic warm ischemia time is the time from circulatory arrest to the perfusion of the organs

Fig. 7.2 Definitions and timeline from donor withdrawal of treatment to DCD liver transport

Particularly in combination with other risk factors, including extensive *cardiovascular disease* or elevated liver enzymes, some centres are reluctant to accept or even evaluate such livers (Figs. 7.1, 7.2, 7.3, and 7.4). The real impact of those risk parameters, including arterial hypertension, cardiomyopathy and elevated inotrope requirements prior to donation, remains however very difficult to capture, and data are very limited. Increased *inotropic support* or known donor right heart failure with assist devices may contribute to a chronic impairment of the liver through functional outflow obstruction with subsequent chronic liver congestion and fibrosis [61]. Although we may well expect a short donor warm ischemia time after WOT, because such DCD donors may proceed rather quickly, there is a general reluctance to utilize such livers, unless a transplant centre has the ability to assess the metabolic graft status on a perfusion device prior to implantation as a frozen section of donor liver tissue may not provide conclusive results. Although some centres have reported an increased risk of graft loss from donors with norepinephrine, clear guidelines what to accept in DCD donors are not available [11, 71]. One main concern to utilize donors with elevated inotropic support is the effect on the quality of liver perfusion already in the donor with a higher risk for the development of ischemic cholangiopathy after transplantation.

Parameters	Case 1	Case 2	Case 3	Case 4
Donor age	72 y	77 y	43 y	46 y
Donor cause of death	ICH	ICH	RTA	RTA
Donor hospital stay	1 days	2 days	4 days	3 days
Donor functional warm ischemia time	19 min	23 min	28 min	26 min
Cold ischemia time	5 hrs 28 min	6 hrs 3 min	6 hrs 30 min	Estimated 6 hrs
Recipient age	54 y	56 y	52 y	Declined for transplanttation due to macroscopic aspect (steatosis)
Recipient underlying disease	ALD	ALD, HCV, HCC	HBV, HCC	
Implantation time	21 min	29 min	27 min	
Outcome	Severe graft dysfunction, multiorgan failure	Full function, recipient discharged in 7 days	Full function, recipient discharged in 9 days, first signs of ITBL after 5 months	

Fig. 7.3 Examples of human DCD liver transplantation with donor, graft and recipient risk parameters and outcomes

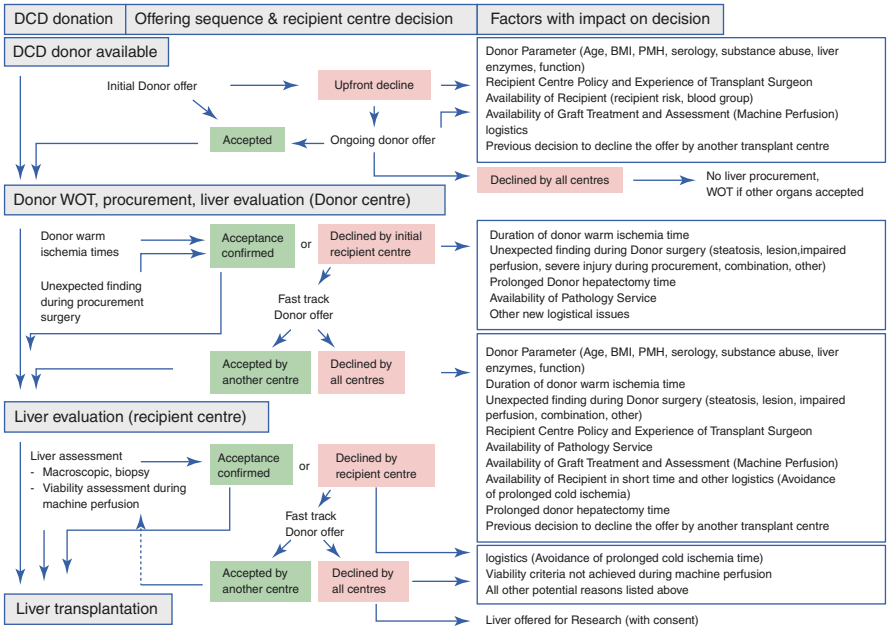


Fig. 7.4 Decision-making based on donor risk factors, procurement surgery, viability testing and logistics

Looking at recommendations for split liver transplantation, donors should have only a very limited cardiovascular support of maximal 8 μg norepinephrine/kg/min or 15 μg dopamine/kg/min to remain classified as cardiovascular stable and "transplantable", and the expected threshold for DCD donors would therefore be presumably low. Others reported acceptable dopamine donor treatment dosages of 6–10 μg/kg/min [71].

Deranged Donor Liver Parameters

Elevated donor liver tests are often linked to donor drug abuse or previous OOHCA arrest, and livers with peak transaminases of ≥1000 U/L are frequently transplanted today [48, 70]. Although no clear guidelines have been reported, the majority of transplant surgeons remains reluctant to accept such donor livers, particularly in combination with a DCD situation and an elevated serum bilirubin or an impaired coagulation profile, quantified, for example, through an elevated international normalized ratio (INR), unless a downward trend in transaminases has been demonstrated. In this context, a recent analysis from the UNOS dataset did not show a link between peak donor transaminases and outcome [60]. Another parameter considered by many is the *metabolic status* of a potential donor, assessed, for example, by lactate with blood gas analysis. Although high *lactate* values may represent an impaired pulmonary or kidney function, or be influenced by the donor ventilation, some transplant surgeon may decline such DCD livers if lactate values are severely elevated, because such impaired capacity to clear lactate might reflect the poor quality of the donor liver. Livers with previous warm and cold ischemia are known to have developed a metabolic energy depletion with subsequent accumulation of lactate, pyruvate and other purine derivates, which is expected to progress during preservation and implantation, when the metabolic situation is significantly impaired due to an overall very high or too high risk [19, 85].

The next parameter of historical interest is the *gamma-glutamyl-transferase (GGT)*, which could be linked to a history of alcoholic liver disease with impaired liver function or tissue quality with potential fatty liver infiltration or fibrosis. However, an elevated GGT may well be linked to multiple other conditions, including diabetes, renal failure or pancreatic disease, parenteral nutrition or infection prior to donation [68, 115]. Unfortunately, not all centres or countries allow further donor investigations with ultrasound or even liver biopsy prior to WOT, and many DCD donors with an elevated GGT might become declined in context of previous alcohol history prior to macroscopic liver assessment at procurement (Figs. 7.1 and 7.4). Although no strict cut-off values were reported with regard to acceptance of donor livers based on the plasma GGT, this parameter was recently included in the European Donor Risk Index (ET-DRI) in combination with other donor risk parameters to evaluate the donor risk in DBD and DCD liver transplantation [9].

Donor Body Mass Index, Body Weight and Hepatic Steatosis

The size or body mass index (BMI) has always been considered an important risk factor in liver transplantation. However, guidelines appear scarce and several thresholds were suggested by many. Although a few anecdotal reports are available, where some donors were identified with a limited amount of steatosis, despite a very high BMI (e.g. >40 kg/m^2), such livers are however prone to be declined before visualization. A few thresholds of donor BMI (≤30 kg/m^2 or ≤25 kg/m^2) have been suggested to be respected in order to limit advanced liver steatosis or fatty liver disease in donors, although the evidence for a clear link between BMI and liver fat content remains low and often depends on further assessment including cross-sectional imaging, which appears difficult as routine procedure in organ donors in some countries [21, 90]. Increased donor BMI and body weight does also impact on the duration of the procurement surgery and importantly on the time required for cannulation with further impairment of the perfusion quality and donor hepatectomy time, which has been demonstrated to impact on outcome after DCD liver utilization grafts [8, 41]. In addition, a high donor BMI may increase the risk of procurement injuries in the livers, including capsular tears or vascular injuries, due to poor visualization in combination with impaired graft quality and the DCD situation. Experienced DCD donor surgeons are required when such additional technical difficulties are expected. The potential impact of donor surgery parameters is described further in Chap. 3.

There is hesitancy by many transplant programs to accept DCD livers with macrosteatosis, and therefore the data on this topic are limited. The usage of these donors has generally been avoided given the potentially additive risk from using donor livers that are both steatotic and from a DCD donor [27, 99, 102]. In addition, several previous reports have suggested that DBD donors with mild to moderate macrosteatosis may be at an increased risk of ischemic-type biliary strictures [4, 45]. Given the inherent concerns with ischemic-type biliary strictures or ischemic cholangiopathy (IC) in all DCD liver grafts, it seems reasonable that there has been a reluctance to potentiate this risk with the addition of donor macrosteatosis.

A recently published multicentre study provided the first in-depth analysis of outcomes with DCD liver transplantation based on the degree of macrosteatosis [28]. In that study, patients undergoing DCD liver transplantation with a moderate macrosteatosis (30–60%) donor liver had a higher rate of post-reperfusion syndrome (PRS) (53.9% vs. 26.2%; $p = 0.002$), post-reperfusion cardiac arrest (7.7% vs. 0.3%; $p < 0.001$), primary non-function (PNF) (7.7% vs. 1.0%; $p = 0.003$), early allograft dysfunction (EAD) (70.8% vs. 45.6% and 8.3%; $p = 0.02$) and acute kidney injury (AKI) (39.1% vs. 19.4%; $p = 0.02$) than patients with undergoing DCD liver transplantation with a no steatosis donor liver. No difference in any of the above-mentioned perioperative complications were seen between patients undergoing DCD liver transplantation with a mild macrosteatosis (5–29%) donor liver and those undergoing DCD liver transplantation with a no steatosis donor liver, except for a higher rate of EAD (56.8% vs. 45.6%; $p = 0.04$). No difference in ischemic cholangiopathy(IC),

vascular thrombosis/stenosis or graft and patient survival was seen between the three groups. The authors concluded that DCD donors with mild macrosteatosis <30% can be utilized with no increase in perioperative complications and similar patient and graft survival compared to DCD donors with no steatosis, however in context of an otherwise limited overall donor risk. When utilizing DCD donors with moderate macrosteatosis, higher rates of PRS, PNF, post-reperfusion cardiac arrest, EAD and AKI are generally anticipated. A single-centre study from the UK performed a subanalysis on histology reports from 233 DCD liver transplantations for steatosis [92]. In their multivariate analysis, macrosteatosis and microsteatosis were not found to impact graft survival. It should, however, be noted that only 5/233 DCD liver transplants had moderate macrosteatosis ≥30% and, therefore, the analysis was largely based on mild macrosteatosis (94/233). An abstract has previously been published investigating 27 recipients of DCD liver transplants with ≥30% steatosis (combined microsteatosis and macrosteatosis). In that analysis, patient and graft 1-year survival rates were 91.8% and 90.4% for DCD livers with <30% steatosis vs. 92.6% and 92.6% for those with ≥30% combined micro-/macrosteatosis ($p = 0.47$) [5]. Two studies from a single centre in Hangzhou, China, also describe their outcomes with steatotic DCD liver transplantation. The first of this studies included 6/127 patients with macrosteatosis 20–30% and 10/127 patients with macrosteatosis 31–60% [116]. That study demonstrated that macrovesicular steatosis >20% was associated with increased graft loss (HR 2.97). The second of these studies included 14/131 patients with macrosteatosis >20% [117]. That study demonstrated that macrosteatosis in the DCD graft liver was an independent risk factor of developing hyperkalemia and post-reperfusion syndrome in the recipients.

Donor Warm Ischemia Time

Donor warm ischemia time (DWIT) in controlled DCD donation is very inconsistently reported with various definitions and thresholds described among centres and countries (Table 7.1) [43, 47, 58, 105].

The initial period after WOT, also described as *agonal phase*, is considered as crucial by many, for example, in the USA, with either hypoxia or hypotension as initiator [18, 58]. In contrast, the second phase, reported as “no flow” or *asystolic warm ischemia time*, occurring between circulatory death and cold organ flush, is nominated by others as predictor of outcome [47, 51]. The majority of transplant centres base their decision, however, on the duration of a *functional donor warm ischemia time (fDWIT)*, defined by a peripheral donor blood hypoxia, starting at oxygen saturations of <80% or <70% or when the systolic or mean arterial pressure (MAP) decreases below <50 or <60 mmHg (Table 7.1, Figs. 7.2 and 7.3) [39, 58, 59, 91] and the cardiac arrest happening within the first hour from withdrawal. The agonal period from oxygen saturation below 80% has been associated with severe ischemia reperfusion injury with an up to threefold increased risk of graft loss [58]. And some authors have described that livers from donors gradually deteriorating with the MAP are at higher risk to fail compared to donors which withdraw rapidly

[43]. Although the risk factor fDWIT is the most inconsistently reported parameter and liver acceptance criteria vary even between transplant surgeons in one centre [73], DCD livers are generally described as "ideal" when the fDWIT is ≤20 minutes [3]. The very selective policy of some experienced DCD liver transplant centres has led to excellent outcomes with an overall low complication rate [35]. Other reports have paralleled this policy and demonstrated a clear link between prolonged fDWIT and more complications [53, 63, 91]. Some European countries, including Italy, the Netherlands or Switzerland, however, routinely accept DCD grafts with a prolonged fDWIT of more than 30 or even 40–60 minutes due to an overall limited donation rate in combination with a prolonged stand-off period of up to 20 minutes prior to donor hepatectomy (Table 7.2) [32, 109, 114]. One option to reduce the fDWIT is to perform donor WOT already in operation theatres and allow relatives to join the procedure there, which is practised in some centres. Donor cannulation prior to WOT is applied, for example, in Spain and may cut down a few extra minutes of the DWIT; however, "assessments or other manipulations" in the potential organ donor are frequently not accepted in most other countries [50, 90].

Additionally, surgeons in centres where extended DCD livers are accepted routinely apply machine perfusion technology, either hypothermic oxygenated approaches (HOPE) alone or in combination with normothermic regional perfusion (NRP) or controlled oxygenated rewarming (COR) to improve liver function and assess viability [31, 34, 96, 98]. A more detailed overview on donor warm ischemia time and further consequences in DCD transplantation is highlighted in Chap. 5 of this book.

Donor Infections

Another frequently discussed potential donor risk factor is a positive virology for hepatitis or immunodeficiency virus. The majority of recommendations or guidelines follow the general suggestions for deceased organ donors. For example, grafts from *hepatitis B virus* (HBV) core antibody (cAb)-positive donors are classified acceptable for the use in recipients with HBV-related cirrhosis with no negative effect on graft or patient survival after transplantation [57]. In addition, such livers can be transplanted into recipients with positive antibody status (IgG HBcAb-positive) following previous exposure to HBV without development of relevant cirrhosis. Such recipients require immunoglobulin treatment and viral prophylaxis. Here, most guidelines from DBD liver donation apply in DCD donors. The utilization of HBVcAb-positive donor livers for naïve recipients has significant variability by transplant program and by country due to the requirement for long-term antiviral treatment following liver transplantation. Hepatitis B vaccination is strongly recommended in such candidates prior to liver transplantation [101]. Despite the general ability to utilize such viral positive grafts in combination with treatment prophylaxis, some centres and countries are reluctant to do this in context of the additional risk of a DCD liver, which then requires also such expensive antiviral treatment.

A similar strategy applies to *hepatitis C* (HCV)-positive donors, where a certain level of donor fibrosis or early cirrhosis is usually expected at time of organ offer. Here,

Table 7.2 Overview of allocation models in DCD liver transplantation

Model	Database	Data collection	Principle of allocation	Risk factors	Suggested cut-off	End points	External validation	Arguments	Disadvantages
DCD as cumulative risk factor									
Donor risk index (DRI)	US national, $n = 20{,}023$ (DBD and DCD)	1998–2002	Donor based	DCD yes/no	DRI > 1.5 (1.4–1.8)	Graft survival	Europe	Single value for each donor	Pre-MELD era, hazard model, donor age-related, no recipient variables
European-DRI	Eurotransplant database, $n = 5939$ (DBD and DCD)	2003–2007	Donor based	DCD yes/no (HR 1.71)	ET-DRI > 1.8	Graft survival	No	Adjustment of DRI in Europe	No recipient variables, donor GGT not always available, hazard model
Donor liver index (DLI)	UK national, $n = 5586$ (DBD and DCD)	2000–2014	Donor based	DCD yes/no (HR 1.89)	DLI > 1.82	Graft survival	No, validation set from UK, $n = 2343$	Single value for each donor, metric	"High risk" livers >DLI 1.82 achieve 5-year graft survival of 80%, hazard model, no recipient variables
Combined donor-recipient-based systems (specific DCD risk factors)									
UCLA-DCD score	UCLA, single centre, $n = 81$ (DCD)	1994–2010	Division of risk	D: 2; R: 3; CIT	>4 points (high risk)	Graft survival	No	Donor and recipient factors	Hazard ratio, small cohort, 21% (17/81) in high-risk group)
DCD-risk index	KCH, single centre, $n = 261$ (DCD)	2005–2013	Division of risk	D: 1; R: 3; CIT; DHT	>4 points (high risk)	Graft survival	No	Donor and recipient factors + hepatectomy time	Hazard ratio, fDWIT (>25 min) and CIT (>10 hrs) get only limited points
UK-DCD risk score	UK national, $n = 1153$ (DCD)	2000–2015	Division of risk	D: 3; R: 3, CIT	>10 points (futile)	Graft survival	UNOS dataset	Donor and recipient factors, Framingham risk scheme	Risk factor retransplantation, not further specified

BMI body mass index, *DCD* donation after circulatory death, *UCLA* University of California Los Angeles, *DLI* donor liver index, *DRI* donor risk index, *ET-DRI* European-Donor Risk Index, *UK* United Kingdom, *D* donor, *R* recipient, *CIT* cold ischemia time, *DHT* donor hepatectomy time = duration of donor hepatectomy, *KCH* King's College Hospital, *GGT* gamma-glutamyl-transferase, *HR* hazard ratio

the majority suggests performing a histopathological assessment to estimate the level of fibrosis and inflammation prior to utilization, which may imply similar logistical challenges as described above, possibly extending the duration of cold ischemia time. Additionally, in the current era, most candidates with HCV cirrhosis have been successfully treated before liver transplantation [6]. Prior to utilization of an HCV-positive donor, the availability of antiviral treatment after transplantation needs to be ensured. With the modern treatment regimen in place, an increasing number of transplant centres would also consider *human immunodeficiency (HIV)-positive* donors as additional liver source for HIV-positive recipients. However, there is a lack of reports in the field of DCD liver transplantation from HIV-positive donors with general reluctance to expose the recipient to such additional risk in context of DCD organ donation.

Bacterial or fungal infections are frequently present in up to 60% of deceased organ donors and mainly arise from the respiratory or urogenital tract. The transmission of bacterial or fungal infections from the donor with subsequent recipient mortality has been described, with however excellent outcomes after transplantation given appropriate antibiotic treatment is applied in the DBD donor and recipient [69]. However, the community lacks similar reports in the setting of DCD transplantation, being generally reluctant to accept such donors with significant signs of infection, with an underestimated remaining risk.

Donor Malignancies

With regard to donor malignancies, the same guidelines apply for DCD donors as for deceased donors in general. Low-grade basal or squamous cell carcinomas, primary brain tumours without evidence of extracranial metastases and carcinoma in situ are considered for transplantation [80]. Caution is required in donors with a history of solid organ neoplasms with an unpredictable metastatic behaviour or a risk of late recurrence, including breast or lung cancer. Here, the 5-year disease-free rule applies for all organ donors, including DCD, and a meticulous assessment of the entire abdominal and thoracic cavity, especially in elderly donors, including lymph nodes, during organ retrieval is obligatory. A large number of almost 500 donors were utilized for transplantation despite the remote history of malignancy with no cancer transmission in more than 1200 solid organ transplantations [62].

Overall, a few DCD donors might become lost, based on the fact that pathological assessment of lesions, found during donor procurement surgery, requires additional time with subsequent prolonged cold ischemia, which is generally suggested to avoid.

Impact of Procurement Surgery

Not only the location of WOT, in main theatres, anaesthesia or ITU contribute to the outcome in DCD liver transplantation, one main risk factor is the experience of the donor surgeon or team. The time between “super-rapid” laparotomy and cannulation

plus organ flush followed by a quick hepatectomy appears crucial to protect the liver recipient from potentially life-threatening complications (Figs. 7.2 and 7.3) [15]. However, the factor *donor hepatectomy time* (DHT) was just recently included into the overall risk assessment in DCD liver transplantation, and only very few reports are available [8, 41, 63]. Ideally, the DCD donor liver should be removed from the donor within 30 minutes following introduction of cold in situ flush to limit the time, where the organs are not perfectly cooled [56, 104]. One recent retrospective analysis has demonstrated a median DHT of 35 minutes considering all retrieval teams across the United Kingdom (UK) [41]. Other studies from the UK and the Netherlands report an impaired outcome when DCD livers with a prolonged DHT above 40 or 60 minutes were utilized [63, 108]. In some countries, donor pretreatment is allowed, for example, with heparin, administered before WOT or determination of death during stand-off period [14]. Most procurement teams add heparin to the first litre of preservation solution, used for perfusion into the aorta (preferably pressurized). Although some centres prefer a low-viscosity perfusion fluid for DCD liver procurement to ensure a homogenous organ perfusion and to reach the small arterioles feeding the bile ductules, the evidence in the literature is partially lacking. A recent analysis in the UK demonstrated no difference comparing, for example, low- and high-viscosity solutions, and reports from European datasets showed conflicting results [8, 110].

Multiple other parameters were meticulously documented during DCD organ procurement in the UK. For example, the time required to pack the liver into the ice box for transport was recently found to impact on outcome [8]. Additional donor factors, including donor BMI and previous surgery or the level of atherosclerotic transformation of the aorto-iliac axis, have further impact on the quality of in situ donor flush and the time needed to cannulate and remove the donor liver.

Next, an extensive *flush of the biliary tree* in situ prior to and on the bench after donor hepatectomy has always been nominated as important protective tool to remove old toxic bile from the liver and subsequently reduce the development of biliary strictures [13, 46, 77]. However, such protective strategy is routinely done during any procurement surgery and remains difficult to objectively assess, in terms of type or amount of suggested flush solution required.

Cold Ischemia Time

In context of donor warm ischemia, each additional hour cold ischemia time (CIT) is generally considered to significantly increase the overall risk. It has been reported that every additional hour of CIT increases the risk of graft failure by 1.17 [1]. The impact of CIT on outcomes has therefore been assessed by many with various reported thresholds (>4, >6, >8 or > 10 hours) and what to accept (Table 7.1, Figs. 7.1 and 7.4) [44, 47, 63, 91]. Today, where Internet and imaging transmission between donor and recipient surgeon team are routinely available, the CIT can be successfully limited and almost accurately estimated. The cumulative donor risk appears, however, of greater importance compared to CIT as single risk factor alone.

For example, a good DCD liver of <60 years, with a limited fDWIT of ≤20 minutes and no steatosis might handle an 8-hour period of CIT without significant complications after liver transplantation [91]. In contrast, when an elderly DCD graft is exposed to more than 20 minutes of fDWIT, an additional prolonged CIT may lead to impaired liver function with an elevated risk to develop a PNF or later biliary complication [41, 91]. Although both DCD livers may well provide a good liver function in the recipient, without any later complications, the current uncertainty to reliably predict this has led to the general reluctance to accept such DCD graft. Logistical challenges with subsequent prolonged CIT and the higher risk of liver dysfunction still contribute to the significant discard rate of DCD livers today, where the metabolic liver assessment with accurate prediction of post-transplant graft function and the risk of biliary complications remains inappropriate.

Other Contributing Risk Factors

Multiple other donor risk factor together with the medical donor treatment applied prior to WOT may well impact on the liver metabolism and quality (Figs. 7.1 and 7.4). Such factors include, for example, the donor treatment with heparin or tissue plasminogen activator (tPA), the location of treatment withdrawal and duration of the bench preparation of the graft in the donor and recipient centre [14, 49]. Although clinically well known, most factors are not well assessed with only low-level evidence from small, single-centre retrospective cohort studies (Fig. 7.1).

Donor Selection Pathway and Impact of Prediction Models

The entire spectrum of donor (and recipient) risk factors in combination with transplant logistics and centre experience impacts on the final decision to accept a certain DCD liver or not. Various selection or decision pathways occur therefore in the clinical practice worldwide and depend also on national regulations and allocation systems (Fig. 7.4). Most countries allocate DCD livers according to a centre-oriented system, which enables the combination of a specific DCD liver with a recipient of choice [12]. For example, in the UK, where centres suggest graft types for a specific candidate at the multidisciplinary listing meeting, the on-call team may select the recipient in the corresponding blood group in accordance to the presumed donor quality and the recipient risk. This may lead to an upfront DCD liver decline, if no recipient is listed to be medically fit enough to receive “any graft” or an extended DCD liver (Fig. 7.4). In contrast, in the Netherlands and, for example, Switzerland, DCD grafts are nationally allocated according to the sickest first policy. Such countries have a relatively high percentage of DCD donors and frequently use novel machine perfusion technology to improve and evaluate the graft before final acceptance and implantation (Fig. 7.4) [33, 79]. In this context, multiple pathways and offering sequences are possible for a DCD liver (Fig. 7.3), and only a very limited number of prediction models exists to support the decision-making, which

is largely based on experience, donor and recipient risk in combination with the current logistical situation in the particular transplant centre. In context of cold storage minimization, logistical factors with impact on the decision include, for example, the distance between donor and recipient centre, the need for pathological liver assessment, the theatre and ITU capacity (ongoing transplantation in the accepting centre) and the availability to bridge such potentially time-consuming factors with new preservation technology (Fig. 7.4) [73].

Novel liver perfusion approaches have a great potential to "relax" the entire system of DCD liver transplantation and increase the safety of the procedure including the procurement and the transplant. Additionally, new communication technology, direct contact between donor and recipient surgeon and photo documentation have helped to limit the CIT in most cases and enable the implanting surgeon to start the transplant procedure prior to graft arrival and direct visualization if needed.

Tools to Quantify Donor and Recipient Risk

Although allocation and risk analysis is a hot topic in liver transplantation, only a very limited number of scores have been provided by different groups to support a more objective risk assessment [9, 42, 53, 59, 63]. The majority of prediction models is based on a limited number of key parameters and leads to varying score points according to the regression coefficient [37]. However, while most scores have been designed for DBD liver transplantation with the main end point's mortality or graft loss, their application in the setting of DCD grafts is relatively limited. The following two main concepts of risk assessment are currently available: firstly, "DCD" as a cumulative risk factor included in another general prediction model, which summarizes further donor risk factors, and secondly, a combination of specific donor (D) and recipient (R) risk factors, which builds a sum of risk factors, also defined as balance systems with a threshold suggested by authors. Here, three models are currently available. Hong et al. have described the first combined tool in 2011, the *UCLA-DCD Score*, which is a hazard-derived model, combining cold ischemia time with two donor and three recipient risk factors [53, 91]. For D-R combinations, allocated above the suggested threshold of 4 score points, authors recommend to decline the liver [53]. Importantly, the best predictor was HCV positivity combined with hepatocellular carcinoma (HCC) (3 points), which will however impact less in the future, due to the recent development of direct-acting antiviral medications (DAA) [6, 91]. In contrast, well-known predictors of early graft failure, for example, fDWIT, contributed only with a limited number of score points [53].

Another interesting prediction model is the *DCD-risk index (DCD-RI)*, developed from the single-centre DCD transplant cohort at the King's College Hospital (KCH) in London [63]. This model is similar to the UCLA score with comparable hazard calculations. Authors considered two donor and three recipient risk parameters, with a sum of 0–14 score points [63]. Importantly, the underlying recipient

disease appeared as a dominant risk parameter in addition to the duration of donor HT [63]. In context of the strict selection policy in their centre, authors described a narrow interquartile range for the parameter fDWIT in their development cohort, which results in a limited point distribution of only 1 score point, applied even for DCD livers with a relatively long fDWIT of >25 minutes. A similar picture occurs from the parameter cold ischemia time, where only 1 point is distributed to livers with a CIT of more than 10 hours. In the UK and also worldwide, only a few DCD grafts experience such long storage times [23, 55, 76].

The third model is the *UK-DCD Risk Score*, which combines three donor and three recipient factors in addition to CIT [91]. Donor age, body mass index (BMI) and functional donor warm ischemia time (fDWIT) were the donor risk factors with highest impact on graft survival [91]. Expectedly, previous transplantation and disease severity, expressed by the lab MELD, were identified from the pool of recipient risk factors in addition to recipient age and duration of CIT (Table 7.2), all accumulating to a total of 0–27 points [91, 103]. In context with the predicted graft survival at each score point, three risk classes were defined. For example, a D-R match with more than 10 points was classified as "futile" and achieved a very limited 1- and 5-year graft survival of <40% and < 20%, respectively [91]. Based on such low graft survivals, combinations above 10 score points were classified futile and were suggested not to be considered for transplantation, unless there was room to exchange the recipient to reduce the overall risk [90]. In contrast, low-risk D-R combinations, with maximum 5 score points, achieved a graft survival of 80%, similar to an average DBD liver transplant cohort (low-risk group) [88, 91]. The point system appears very practical and enables an easy calculation of the model, which provides a good specificity of 95.0% and positive predictive value (PPV) of 71.0% and 86.1% related to the suggested threshold of 10 score points [91].

Despite the development of such new prediction models with the ability to capture an overall donor and recipient risk, all tools available have *shortcomings* [89, 91]. The parameter donor warm ischemia time is, for example, not available at organ offer and may lead to later decline of the graft during procurement surgery, when it exceeds national- or centre-suggested maximum duration (Fig. 7.3). With novel communications tools, CIT can be almost accurately estimated but is however not available at donor offer and may be influenced by all other logistical issues, which may occur. When D-R combinations achieve initially more than 10 points in the UK-DCD Risk Score, the on-call team can either choose a different recipient or decline the liver. If other centres do not show interest, the offer may return to the initial centre for free selection of candidate and the use of machine perfusion to improve and assess the graft viability (Fig. 7.4) [78]. Based on an increasing number of transplantations, where new perfusion approaches are applied, we may well expect an overall risk reduction from "futile" category to the high-risk group; however, more research is required and expected in this field in the next 5 years [39, 83, 92, 98]. Another clear disadvantage of all prediction models is the lack of graft steatosis as risk factor [38, 65, 96] together with multiple other factors, potentially transmitting risk and their inconsistent definitions applied in large databases from different regions and multiple countries.

Models Which Include DCD as Cumulative Risk Factor

The concept of the *donor risk index (DRI)* was introduced in 2006 by Feng et al. (Table 7.2) [42]. The main difference to models with the combined D-R balance systems is that the factor "DCD" is included in the DRI as single risk parameter. Further factors with impact on outcome in this model include donor age and split graft, African-American race, cardiovascular accident (CVA) as cause of death and low donor height [42]. The DRI is a continuous metric for each donor liver [12, 42, 89]. In addition to the validation in America and Europe, the DRI was further modified with the development of the *Eurotransplant (ET)-DRI* in 2012 [10]. Based on the Eurotransplant cohort, similar risk factors were considered. Outcome prediction by both models, the original DRI and the European version, was similar. Five-year graft survival reached 61% in a combined DBD and DCD cohort [9, 42]. Importantly, reliable prediction in liver transplantation strongly depends on the additional consideration of recipient risk factors, which are generally lacking here. Authors suggested to consider a DRI threshold of ≤1.8 points, because the use of livers with a DRI of >1.8 points showed already inferior survival rates, when used for low MELD recipients (≤15 points). Of note, the overall risk transmitted through the DCD component in these models was a hazard ratio of 1.71 (CI 1.27–2.29, $p < 0.001$), irrespective of the duration of the donor warm ischemia time [42].

Another novel model, developed from the UK national transplant database, is the *donor liver index (DLI)* and involves the following donor parameters: age, split graft, smoking, height, donor gender and plasma bilirubin [22]. The factor DCD was considered with an additional risk of HR of 1.89. In general, authors showed good correlation of the DLI with the other two models, DRI and ET-DRI [22], which is probably based on the categorical DCD donor variable (yes, no), covering a number of scenarios from rapid donor deterioration to prolonged hypoxia and hypotension, which are all supposed to transmit the same risk considering the DLI (Table 7.2) [22].

Finally, all prediction models have *limitations* in terms of selected parameters, due to their development from retrospective national datasets with missing values and the underestimated effect of huge variations in the donor and recipient protocols.

Absolute Contraindication to DCD Liver Donation

The majority of "absolute contraindications" does not include donor or recipient risk factors, which are mainly influenced by centre policy, team or surgeons' experience and logistical circumstances in the particular hospital. In the near future, new preservation technology will change the current selection policy and further push the boundaries of risk factor thresholds, particularly in centres where such technology is reliably used to predict graft viability. This will also lead to a further extension in recipient risk factors, including the medical risk and possibly HCC acceptance criteria, when more livers with expected good outcomes become available. Today, disseminated multisite bacterial donor infection or fungaemia, which is not under control through antibiotic treatment, is one main contraindication for organ

donation in general. Next, as mentioned earlier, the use of HBVcAb-positive or HCV antibody-positive donors in HBV-negative or HCV-negative recipients, respectively, remains different among centres and depends also on the availability for treatment after liver transplantation. In addition, the presence of an active haematological malignancy or extracranial metastases of a brain tumour is a contraindication to organ donation, irrespective of the type of deceased donor.

How to Increase the Safe Utilization of DCD Livers in the Future?

Multiple parameters may be addressed to understand the overall risk and improve outcomes further in DCD liver donation and transplantation. For example, a meticulous documentation of donor parameters, including the blood pressure and saturation before and after WOT, may help to discriminate between an instable donor during a prolonged agonal phase and a stable donor for more than 30 or even 60 minutes with sudden deterioration just prior to circulatory death. Along with a better understanding of the metabolic situation of each DCD liver, such detailed information may increase the liver utilization through the implementation of less stringent criteria, to avoid liver declines based on a putative prolonged agonal phase (>30 minutes), while the donor remained completely stable instead [111]. Long withdrawal periods are not an absolute contraindication to organ donation. Future studies should therefore also aim for an improved definition of clinical and physiological variables to be assessed during the withdrawal period.

Next, the enormous variations in risk parameter definition and reporting of suggested acceptance criteria will be addressed by an upcoming consensus conference in 2020. In addition, the majority or retrospective reports present only limited data on the exact number or percent of utilized DCD liver grafts and a lack of discrimination of reasons for declining the graft. This is very important to compare the impact of new preservation technology on outcome and utilization rate in this field.

Although cold storage remains an effective preservation method for standard grafts, with low cost and simplicity, there is a growing interest in new perfusion technologies while their impact appears two folded: first, to improve the liver graft, to reduce the reperfusion injury and to assess and predict liver viability already before implantation. The optimal preservation approach should therefore act on mitochondria, which appear as initial trigger of the reperfusion injury cascade [64]. Several competitive strategies are currently explored and include, for example, *normothermic machine preservation*, which is presented to replace the majority of cold ischemia time [81]. Another approach is the end ischemic normothermic liver perfusion with functional liver assessment [66, 75, 114]. Experts in this field have suggested an initial combination of markers, measured during perfusion to explore the liver viability with prediction of later liver function in the recipient [66, 74, 75, 112, 114]. In situ liver evaluation is the concept of *normothermic regional perfusion (NRP)*, where organs undergo normothermic perfusion after donor cardiac arrest and prior to initiation of cold flush. Similar to the ex situ approach, markers to

assess liver injury are measured to decide whether to procure and transplant the liver or not [113]. NRP can also facilitate the organ procurement converting a super-rapid technique into a conventional procurement, minimizing the risk of damage [107].

Others suggest end ischemic perfusion technologies, such as *HOPE* alone or as a component of controlled oxygenated rewarming (COR) [33, 54, 65, 96]. Such cold perfusion provides a high oxygen concentration for liver cells to enable mitochondrial reconditioning prior to reperfusion of the liver at implantation or during normothermic perfusion on a perfusion device [7, 20].

Despite the ongoing evaluation of multiple new techniques, most studies include a very selective liver cohort, where risk factors are not uniformly described. Importantly, the cumulative risks of livers, which were declined prior to machine perfusion or based on viability assessment during perfusion, are frequently not reported [66, 78, 81, 113]. Comparisons of different perfusion approaches are therefore difficult, as are conclusions regarding superiority of one technique over another, while the results of only one randomized controlled trial is currently available [81]. Detailed summaries on all perfusion approaches are provided in Chaps. 13, 14, and 15.

Key Points

- DCD category 3 is the most common type of DCD grafts used worldwide and therefore with increased potential to play a significant role in increasing the donor pool.
- Donor selection, refined surgical techniques during the procurement and the transplant and patient's selection are key factors to achieve good results when using livers from DCD donors.
- Further evidence on the cumulative effect of donor risk factors is still to be determined.
- Novel ex situ and in situ perfusion technologies are rapidly gaining popularity in the transplant community, with increasing evidence of improved outcomes in DCD liver transplantation and the potential to increase organ utilization further.
- New biomarkers quantified during machine perfusion will serve as prediction tool, possibly in combination with donor and recipient risk factors to expand the acceptance criteria for DCD transplantation further.

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8 Thrombolytic Therapy in Liver Transplantation Using Grafts from Donation After Circulatory Death Donors

Marit Kalisvaart and Jeroen de Jonge

Introduction

Biliary complications remain the most important challenge in liver transplantation using grafts from donation after circulatory death (DCD) donors. Especially ischemic-type biliary lesions (ITBL) are seen more often when DCD grafts are used [10, 19]. The high incidence of this complication is thought to be the result of microthrombi formation in the peribiliary vasculature during the obligatory donor warm ischemia time (DWIT). In DCD donation, after withdrawal of treatment, there is a period of declining organ perfusion until circulatory arrest (agonal phase), followed by complete warm ischemia until the start of cold in situ perfusion (asystolic phase) [13]. In combination with the regular cold preservation and rewarming of the organ, this can cause severe injury to the donor liver. Early studies have highlighted the hypothesis that cardiac arrest in DCD donors leads not only to ischemic injury but also to the formation of blood clots in the microvasculature of the organs, including the liver [16]. Contradictory findings have been presented on the coagulation process before and after circulatory arrest. Forensic studies have shown that platelets are less active with an alteration in clot formation after circulatory arrest and presence of a rather activated fibrinolytic system [14, 26]. This suggests that there would not be an increased fibrin formation. However, perfusion of end organs in DCD donors is associated with high resistance and inadequate parenchymal perfusion, which would actually suggest the formation of fibrin and microthrombi. This could be the result of microthrombi formation directly before circulatory arrest,

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because this is characterized by normal coagulation in the presence of hypotension and impaired organ perfusion, a known risk factor for clot formation [24].

Anticoagulation and Fibrinolysis

In donation after brain death (DBD) donors, microthrombi formation is prevented through high-dose heparin administration before start of the organ procurement. The timing of heparinization in DCD donation varies in different countries, as in some countries, pre-mortem heparinization in the DCD donor is not allowed due to the strict legal separation between patient care to a possible donor and treatment to optimize organ procurement. Therefore, some groups add heparin to the preservation fluid [18]. Heparin will prevent the new fibrin formation but is not effective in the removal of pre-existing microthrombi that have formed before the organ procurement during the agonal and asystolic phase [24]. Profibrinolytic agents, like plasminogen activators, are required to remove these clots, and such agents have shown to be useful in the treatment of early hepatic artery thrombosis (HAT) in liver transplantation [1, 23]. In contrast to the dual arterial and portal blood supply to hepatocytes, the blood supply of the biliary system is said to solely depend on arterial blood via the biliary vascular plexus [20]. Due to the dependence of the biliary plexus on the arterial blood supply and the high incidence of ITBL in DCD liver transplantation, it has been hypothesized that the additional use of plasminogen activators in these grafts could prevent the subsequent development of ITBL.

ITBL: Microthrombi or Ischemic Injury?

The use of thrombolytic therapy in DCD liver transplantation is based on the assumption of microthrombi formation in the arterial biliary plexus, causing insufficient blood and oxygen supply to the biliary tree at reperfusion. However, microthrombi formation has been investigated in a histological analysis by a Dutch group [29], and their results showed that liver grafts from DCD donors do not have an increased risk of microthrombi formation, contradicting the microthrombi hypothesis and potential benefit of thrombolytic therapy. An additional study [21] highlighted the importance of injury to the peribiliary glands and biliary vascular plexus in the pathogenesis of ITBL in DCD liver grafts. Arteriolonecrosis and loss of these glands, but not the formation of microthrombi, were associated with the development of ITBL. Furthermore, no difference in microthrombi formation was observed between liver grafts from DCD and DBD donors. Similar results were observed in another study on microthrombi formation and the risk of ITBL in recipients of liver grafts from DBD donors [6].

A Spanish study on the coagulation profile in blood of uncontrolled DCD (Maastricht type II) donors [28] using rotational thromboelastomeric analysis demonstrated hyperfibrinolysis, rather than increased coagulation, indicating that there is no rationale for additional thrombolytic therapy in this setting. This group also compared the effect of both pre-mortem heparin and thrombolytic therapy

on the incidence of ITBL in an experimental porcine transplantation model [9]. Interestingly, although heparin did not prevent microvascular clot formation, it offered cytoprotective effects, reflected in improved flows during regional perfusion and better biochemical, functional and histological parameters after transplantation follow-up. No beneficial effect of thrombolytic therapy was observed.

Clinical Studies with Thrombolytic Therapy in Liver Transplantation Using Grafts from DCD Donors

Potential agents that can be clinically used are streptokinase, urokinase and recombinant tissue-type plasminogen activator (r-tPA; Actilyse) [24]. There are two options for the administration of thrombolytic therapy (Fig. 8.1). As the first option, thrombolytic therapy can be given during the organ procurement. Most centres give the initial largest dose at the start of the aortic flush in a room temperature solution and an additional smaller dose in the hepatic artery on the backtable. Thrombolytic agent will be left in the hepatic artery during cold storage and finally be flushed out before reperfusion of the graft. It should be noted that the function of tPA in clot lysis has been shown to be less in case of hypothermia [30].

The second option is thrombolytic therapy during the implantation procedure. It can be administered (1) into the hepatic artery before the portal vein and arterial anastomosis and washed out at simultaneous arterial and venous reperfusion or (2) after portal reperfusion during the hepatic artery anastomosis with subsequent flush-out after arterial reperfusion [11, 25].

Studies investigating the use of thrombolytic therapy in DCD liver transplantation are shown in Table 8.1 [2, 8, 15, 17, 22, 25]. Up to now, six studies have analyzed this

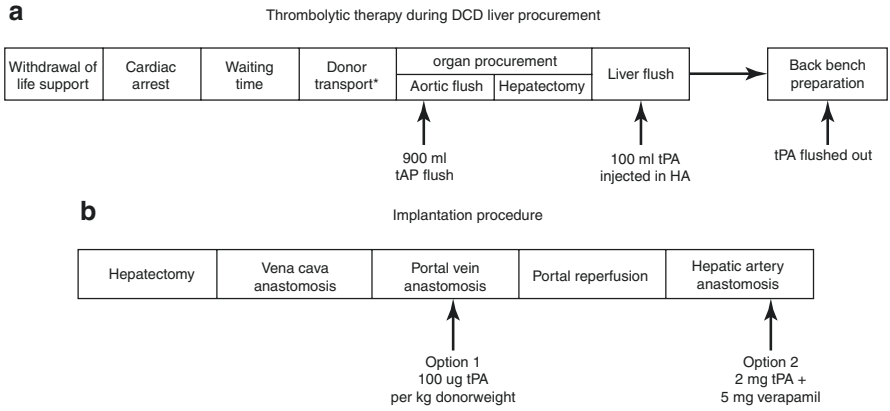

Fig. 8.1 Regimens for thrombolytic therapy in DCD liver transplantation. Thrombolytic therapy administration during (**a**) DCD liver procurement or (**b**) the liver implantation procedure. ∗Donor transport: Moving the donor from the location where the withdrawal of treatment took place (intensive care unit or recovery) to operation theatre

Table 8.1 Clinical studies investigating thrombolytic therapy in donation after circulatory death liver transplantation

	Year	Country	Study	tPA (*n*=)	Control (*n*=)	Type of plasminogen activator	Dosage of thrombolytic therapy	Heparin dosage	ITBL	HAT	RBC units[a] (vs. control)	1-year graft survival (vs. control)
Lang	2009	China	Retrospective	140	220	Urokinase	2MU + 1MU	?	1.4% (vs. 0.9%)[b]			
Hashimoto	2010	USA	Retrospective	22		tPA	0.5 mg/100 g of graft	30.000 U	9%	0%	10	81%
Seal	2015	Canada, USA	Retrospective	85	33	tPA	2 mg; 100 ug/kg[c]	30.000 U; 1000 U/kg[c]	3.5% (vs. 1.2%)[b]	2%	3.2 (vs. 3.1)	96% (vs. 70%)[b]
Kubal	2016	USA	Retrospective (2 eras)	30	61	tPA	100 mg	300 u/kg[c]	0% (vs. 18%)[b]	0% (vs. 3%)	3 (vs. 4)	88% (vs. 80%)
Pietersen	2016	NL	Retrospective	17	28	Urokinase	250.000 IU	5000 U	41% (vs. 43%)	–		
Bohorquez	2017	USA	Retrospective	100	38	tPA	2 mg	5000 U	3% (vs. 5%)	3% (vs. 8%)	3.4 (vs. 4.5)	92% (vs. 76%)[b]

The numbers and percentages in brackets represent the results in the control group (no tPA), in case a comparative study was performed

[a]Units of red blood cells (median) transfused during the liver transplantation procedure

[b]Statistically significant

[c]Donor weight

agent, most of them in North America. tPA was used in four studies and urokinase in the two remaining studies. The use of urokinase was first described by a Chinese group [17], and they showed a lower incidence of ITBL (1.4% vs. 5.9%) when urokinase was used. However, no data on excessive bleeding, other complications and survival was reported. The first Western clinical experience with tPA [8] yielded encouraging results with a relatively low rate of ITBL (9%), but no comparative analysis with those who did not receive tPA was performed. Also, excessive post-reperfusion bleeding was observed in 63% of the recipients. The four following studies [2, 15, 22, 25] presented comparative analyses, and two groups reported a significant lower rate of ITBL. The rate of hepatic artery thrombosis (HAT) was relatively low in all studies, and no impact of tPA was observed. There was no increased RBC transfusion observed when tPA was used. As shown in Table 8.1, the tPA dosage range and calculation varied widely between studies. This and the limited function of tPA in in lower body/organ temperatures makes it difficult to assess the best dosage administration of tPA to reach adequate fibrinolysis and limit the bleeding risk.

A systematic review and meta-analysis [11] compared the results of these studies (using tPA) and also included the preliminary results of a randomized study. Pooled data of four studies (n = 249) showed a significant reduction in ITBL in the tPA group. Furthermore, less graft failures resulting in retransplantation was observed in this group, compared to those who did not receive tPA. No excessive amount of RBC transfusion was required in the tPA group according to the meta-analysis. The results of the randomized controlled trial was not included in our table, as the data was only presented as a conference abstract (American Transplant Congress 2015) [5] and the full manuscript has not been published.

The potential financial benefit of thrombolytic therapy was studied by an American group [12]. This cost analysis showed a risk reduction of 15.7% for ITBL when tPA was administered and a number needed to treat of 6.4 (costs $50.353). Given that the costs of treating ITBL would be $81.888, this would lead to a savings of $31.528.

The major limitation of the aforementioned studies and the subsequent meta-analysis [11], however, is their retrospective character. None of the studies are randomized, and they have relatively short follow-ups. Extra care to meticulously flush the grafts at the backtable in the tPA group could have biased the results, along with a major risk for bias in the studies that compared the outcomes with a control group, as thrombolytic therapy has been introduced relatively recently and a historical cohort functions as a control group with transplants performed in the early days of DCD liver transplantation. In general, centres have implemented new strategies to improve the outcome of DCD liver transplantation over the years, including standardizing the retrieval technique and minimizing cold and donor and implantation warm ischemia time, better donor and recipient selection, that have altogether shown to improve the outcome of DCD liver transplantation [3, 7, 27]. Therefore, the benefit of treatment with tPA or urokinase demonstrated by these studies might be based on factors as increasing centre experience, better procurement technique and donor-recipient selection rather than application of tPA [4].

In conclusion, the lack of scientific evidence precludes a decisive answer on the efficacy of thrombolytic therapy to prevent ITBL in DCD liver transplantation. Although retrospective results suggested a benefit from this therapy, the actual improvements may have been the result of the overall improvement in DCD practice over the last years. Also, recent histological studies contradict microthrombi formation as a cause in the development of ITBL. Before any recommendation on the routine use of thrombolytic therapy in DCD liver transplantation can be given, a randomized study showing its benefit is required. In individual cases, the assumed benefit can be weighed against the substantial risk of increased bleeding and the considerable additional costs of a so far unproved therapy.

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Recipient Selection in DCD Liver Transplantation

9

Humberto Bohorquez, Ari J. Cohen, and George E. Loss

Under normal conditions, the liver expends most of its energy performing normal metabolism while energy investment in tissue repair is minimal. By contrast, in the posttransplant period, hepatic cellular damage may be extensive and the resulting necessary repair widespread, and there may be a concomitant compromise of normal hepatic metabolism. Thus, a successful liver transplant relies on two simultaneous processes: a rapid and sustainable repair while maintaining the basic hepatic metabolic functions necessary for patient survival. Any factor that alters the balance of this fragile donor-recipient equation can compromise the final outcome. For instance, a very ill, complex, debilitated patient that demands extrahepatic metabolic requirements may disrupt liver repair and regeneration; on the other hand, a liver allograft that requires significant repair can compromise metabolic functions [1] (Fig. 9.1).

In donation after brain death liver transplantation (DBD-LT), hepatic allograft function is compromised due to hepatic ischemic/reperfusion injury sustained either at the time of death or during the procurement, preservation, and/or implantation of the allograft. This injury is often more pronounced in donation after circulatory death liver transplants (DCD-LT) because the liver is exposed to additional warm ischemia, acidosis, proinflammatory stimuli, cell stress, and energy depletion during the process of withdrawing life support.

Careful recipient selection is key in the DCD-LT where transplant liver allografts undergo severe metabolic stress. Recipient candidates who have significant metabolic needs and/or poor functional reserve, such as patients with advanced liver disease (extremely high MELDs), hemodynamic instability, or fulminant hepatic failure, will tolerate EAD (or primary non-function) poorly. Thus, these patients should be avoided when selecting recipients for DCD-LT. For the

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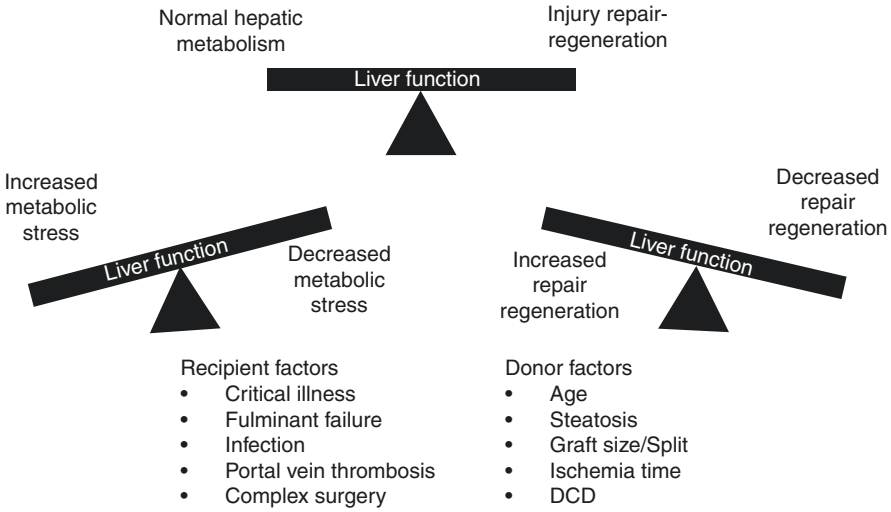

Fig. 9.1 Liver metabolism in liver transplantation. (Adapted from de Jonge and Olthoff [1]. With permission from McGraw-Hill LLC)

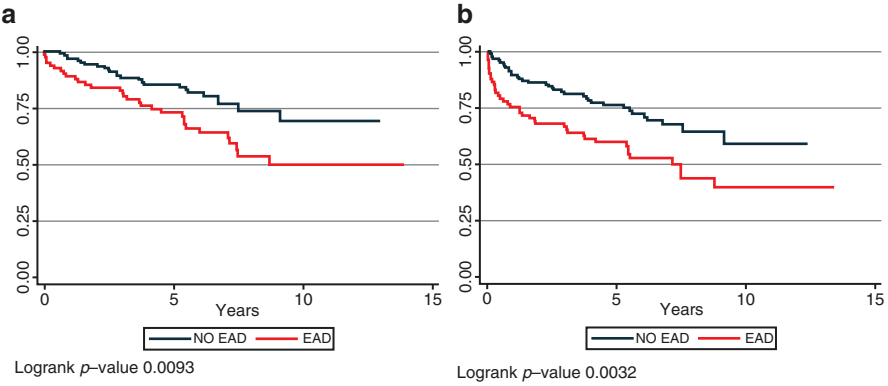

Fig. 9.2 Outcomes in DCD liver transplantation according to the presence of early allograft dysfunction. Patient (**a**) and graft (**b**) survival. (Reprinted from Lee et al. [2]. With permission from John Wiley & Sons)

same reasons, DCD livers should be avoided in patients with potential complex liver transplant operations where prolonged ischemia times, excessive bleeding, or other potential operative complications could increase ischemic injury to the allograft and compromise either allograft function or its subsequent regeneration [2]. Recipients of a DCD-LT that suffer or display early allograft dysfunction have been shown to have inferior outcomes compared to DCD-LT recipients that do not (Fig. 9.2). General principles to follow when selecting a DCD-LT recipient can be seen in Table 9.1.

Table 9.1 DCD-LT recipient selection

Minimize surgical complexity by avoiding:
Difficult hepatectomy (redo LT, prev. Liver resection)
Complex vascular reconstruction
Cases where the complexity may result in prolonged CIT
Minimize tenuous environment for an already marginal graft by avoiding:
High vasopressor requirements
Massive transfusion
Poor oxygenation (hepatopulmonary syndrome)
Select a recipient that can tolerate early allograft dysfunction by avoiding:
Patient intubated in the ICU
Patients with a significant cardiac history
Patients with compromised renal function
Select a recipient in which you will have access to the biliary tree post-LT by avoiding:
Roux-en-Y

The concept of optimizing recipient selection as a way to balance the risk of using a potential marginal organ (e.g., DCD) is not new. In a study evaluating 367 DCD-LT patients from the United Network for Organ Sharing (UNOS) database, Mateo et al. defined a Recipient Cumulative Relative Risk (RCRR) using the risk factors of age, medical condition at the time of transplantation, retransplantation status, the need for dialysis, and serum creatinine [3]. Overall 1-year graft survival for DCD-LT versus DBD-LT was 71% versus 80%. Three-year graft survival was 60% for DCD-LT versus 72% for DBD-LT (p <0.001). However, low-risk recipients (RCRR < or = 1.5) receiving low-risk DCD livers (DWIT <30 min and CIT <10 h, n = 226) achieved comparable graft survival rates to recipients of DBD allografts (81% vs. 80% at 1 year and 67% vs. 72% at 3 years, p = 0.23) (Fig. 9.3). The authors concluded that liver allografts from DCD donors may be used with favorable graft survival rates when low-risk grafts are transplanted in a low-risk setting, underscoring the importance of recipient selection and recipient/donor matching.

In another study reviewing 108 DCD-LTs from a single center, Grewal et al. concluded that strict formal recipient selection criteria were not essential for good outcomes in DCD-LT. However, the authors conceded that selection bias likely occurred in their cohort with surgeon avoidance of certain recipients whose clinical history would likely result in a prolonged CIT or in excessive metabolic demands. Few DCD allografts were used for combined liver/kidney transplants (n = 9) and retransplantation (n = 7), compared with the DBD-LT control group. A significantly greater number of HCC patients (usually more stable patients) were in the DCD-LT group. Older DCD donors (>60 years age) were allocated to patients with lower MELD score. Thus, recipient selection, even when not formally practiced, appears to contribute to favorable outcomes in DCD-LT [4].

Mathur et al. examined data from the Scientific Registry of Transplant Recipients (SRTR) to identify factors that predict outcome after DCD-LT [5]. In this report evaluating 1567 DCD-LTs between 2001 and 2008, significant recipient factors

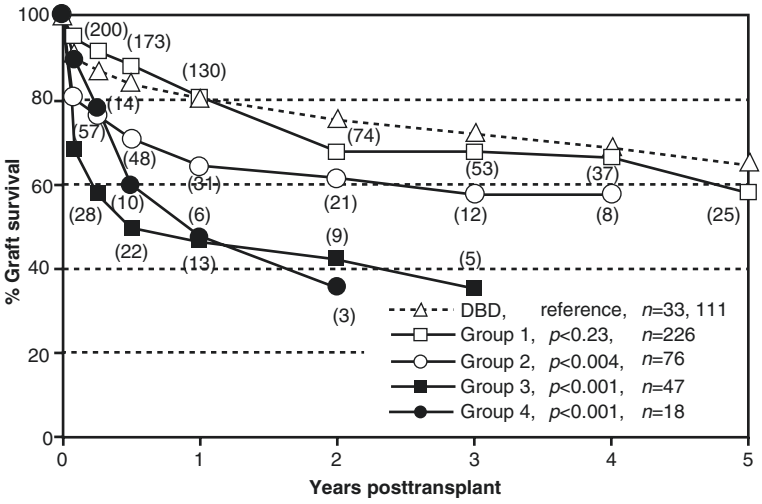

Fig. 9.3 Graft survival of low- and high-risk recipients receiving low- or high-risk liver allografts. Group 1: low-risk recipients, low-risk grafts (CIT <10 h and DWIT <30 min); group 2: low-risk recipients, high-risk grafts (CIT >10 h or DWIT >30 min); group 3: high-risk recipients, low-risk grafts; group 4: high-risk recipients, high-risk grafts. DBD donors are represented by triangles. (Reprinted from Mateo et al. [3]. With permission from John Wiley & Sons)

predicting graft failure were age >54, male sex, African-American race, HCV positivity, the presence of a metabolic disorder, model for end-stage liver disease (MELD) score >34 at transplant, hospitalization at time of transplant, and the need for life support at the time of transplant [5]. More recently, Paterno et al., again using an updated SRTR database, examined 2107 DCD-LTs and found that recipient admission to ICU at time of transplant as well as high recipient MELD score were the two most important recipient factors associated with DCD graft loss [6]. Croome et al. demonstrated that improved results with DCD-LT have been observed over time based on SRTR data [7]. Concurrent with these improvements was a decrease in the proportion of DCD-LT recipients that were in the ICU or on a ventilator at the time of LT, suggesting that programs were more reluctant to utilize DCD donors for critically ill patients.

Older recipient age impacts liver transplant outcomes. Short- and long-term survivals in this population are influenced by the increased risk of death due to cardiovascular events, malignancy, and frailty, all of which are common in patients over 60 years of age. Liver allograft dysfunction or other potential complications such as biliary strictures or renal dysfunction are poorly tolerated in older recipients. Therefore, the benefits of using a marginal or DCD organ in an older recipient (age >60 years) should be carefully weighed against the specific medical/surgical risks of the potential elderly recipient including, but not limited to, the risk of waiting for a better organ offer [8, 9].

Recipient-Donor Matching in DCD-LT

LT is a complex procedure. Multiple factors at multiple stages of the process, from donor ICU management to the allograft procurement and preservation to allograft implantation, all influence outcomes [10]. In general, allografts with the highest risk such as those with advanced age, prolonged functional warm ischemia times, prolonged total warm ischemia times, and/or prolonged cold ischemia time are matched with lower-risk recipients in an attempt to optimize outcomes. Based on this philosophy, multiple prediction models have been developed to identify the best possible combination of donor and recipient profiles [11–14] (Table 9.2).

In a study from King's College, Khorsandi et al. analyzed 261 DCD-LTs and developed a donor-recipient stratification risk predictive model for DCD-LT graft survival. They named their predictive model the DCD risk index (DCD-RI) [12]. Only objective data were included in the index formula. Donor liver steatosis, regarded as a subjective factor, was notably excluded. Using a Cox regression hazard model, three recipient variables were identified that predicted poor graft survival: primary indication for LT, classified in low (AIH, PSC, NASH, HBV, cholestatic), standard (metabolic), and high (ALD, HCC, HCV, cryptogenic, other); MELD >25; and retransplantation status. Other variables in the score included CIT >10 h, DWIT >25 min, and donor hepatectomy time. The score defined three risk groups as low (DCD-RI <1), standard (DCD-RI 2–4), and high (DCD-RI >5) with a 5-year graft survival rates of 86%, 78%, and 34%, respectively. This study also included selection bias as recipients with expected difficult/prolonged hepatectomy or acute liver failure were mostly avoided; likewise, donor liver grafts with prolonged WIT were discarded.

More recently, the UK-DCD risk score has been proposed as a way to avoid futility in DCDC-LT and improve DCD graft utilization [13]. The scoring system was devised after evaluating DCD-LTs in the UK national transplant database (Fig. 9.4).

Table 9.2 Donor-recipient scores in DCD-LT

	Ref.	Population	Level	Recipient factors	Donor factors	Other factors	End point
UCLA-DCD score	11	81	Single center	Cause of liver disease: HCV, HCC; BMI >30, re-Tx	Hep B core, MAP <60 mmHg for >20 min	CIT >6 h	Graft survival
DCD risk index (DCD-RI)	13	261	Single center	Cause of liver disease, MELD>25, re-Tx	None	CIT >10 h, DWIT >25 min, donor hepatectomy time	Graft survival
UK-DCD futile risk score	14	1153	National	Age, MELD, re-Tx	Age, BMI	f-DWIT, CIT	Graft survival

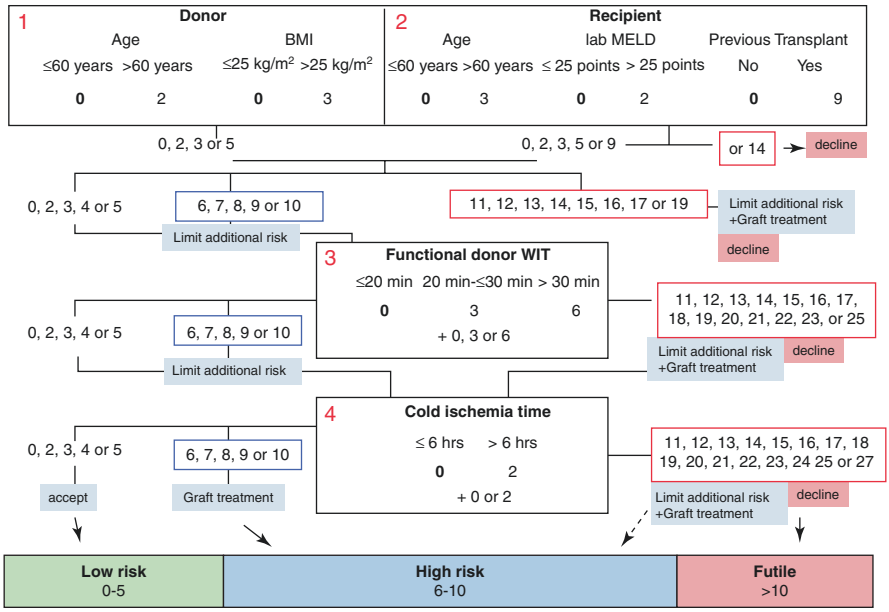

Fig. 9.4 Composite formulation of UK-DCD Risk Score. (Reprinted from Kalisvaart et al. [13]. With permission from Taylor & Francis)

Pertinent recipient risk factors included in the scoring system are age, MELD score, and retransplantation status. Donor/allograft risk factors include age, BMI, and functional donor warm ischemia time (f-DWIT). The authors stratified risk into three groups based on a point system: low (≤5 points), high (6–10 points), and futile (>10 points) (Fig. 9.3). One-year graft loss rates for the low, high, and futile groups were 5%, 18%, and 60%, respectively. Five-year graft loss was 15% in the low-risk group, 40% in the high-risk group, and 80% in the futile group. The scoring system was subsequently validated using the United Network for Organ Sharing database. By finding the lowest combined donor-recipient score, this tool can be used to select the best recipient for a given DCD liver. There are few limitations in this study. First, the score does not include information about graft steatosis, an important variable in LT. Moreover, the score depends on f-DWIT which is inconsistently defined across transplant centers and procurement organizations. Also, this score could not be validated in a Spanish population where the donor age is higher, suggesting some limitations in its application [14].

Surgical Complexity

The technical complexity of LT plays a substantial role in outcomes and is affected by recipient factors such as previous abdominal surgeries, central obesity, history of intra-abdominal infection, presence and chronicity of ascites, and/or presence and

extension of portal vein thrombosis [15–19]. Each of these factors can significantly impact operative and ischemia times, intraoperative blood loss, and hemodynamic stability, thus compromising the conditions for organ reperfusion. Identifying these risk factors is particularly important when considering extended criteria donor allografts, such as DCD livers, since they may be more susceptible to suboptimal reperfusion conditions [20].

Although assessment of recipient surgical complexity plays an essential role in donor-recipient matching and organ acceptance, it has not been sufficiently incorporated in the most widely used predictive models for donor quality (donor risk index [DRI] score) [21], recipient selection (MELD score, MELD-sodium) [22, 23] or recipient-donor matching for post-LT outcomes (donor-MELD score, Survival Outcomes Following Liver Transplantation [SOFT] score, Balance of Risk [BAR] score, UK-DCD risk score for donation after cardiac death [DCD-LT]) [13, 24–26].

Since January 2015, all patients listed for LT at Ochsner Medical Center were categorized according to their estimated surgical complexity based on the recipient's surgical and medical history, physical examination, and cross-sectional imaging. Our goal was to better understand the role of surgical complexity in transplant outcomes as well as to facilitate donor-recipient matching and expedite the placement of expanded criteria grafts. Each potential recipient was assigned a surgical risk score of A (low), B (moderate), or C (high) (Table 9.3). The score was initially assigned after the pretransplant surgeon evaluation and subsequently confirmed at the time of presentation of the patient to the recipient selection committee. Each listed patient was flagged with a surgical risk score, and discussion of this classification was an integral part of the on-call workflow at the time of an organ offer (Table 9.3).

Between January 2015 and June 2018, 483 LT recipients were assigned a surgical risk score and subsequently received a liver transplant (Table 9.4). Recipients in category B had higher mean BMI ($A = 26.7$ (24–31), $B = 33.4$ (27.1–38.6), $C = 25.3$ (23.9–29.5), $p < 0.001$). A diagnosis of HCC was more common in category A ($A = 26.6\%$, $B = 32.2\%$, $C = 6.25\%$, $p < 0.001$). As expected, category C had the higher incidence of recipients with PV thrombosis ($A = 9.4\%$, $B = 11.3\%$, $C = 31.3\%$, $p < 0.001$)—PVT thrombosis in group A recipients was an incidental finding at transplant. Retransplantation patients in groups A and B were due to clerical errors and misclassification ($A = 0.3\%$, $B = 1.8\%$, $C = 27.1\%$, $p < 0.001$). More patients in categories B and C had previous abdominal surgeries and received SLK ($A = 25.9\%$, $B = 68.7\%$, $C = 81.35\%$, $p < 0.001$ and $A = 10.3\%$, $B = 25.3\%$, $C = 20.8\%$, $p < 0.001$, respectively).

Table 9.3 Pre-listing surgical risk categorization

	Surgical complexity
Group A: low	LT alone, absence-moderate obesity; patent PV, no upper abdomen surgeries (except lap chole)
Group B: moderate	Combined LKT, moderate to severe obesity, history of SBP, previous upper abdomen operations, PV thrombosis
Group C: high	Retransplantation, previous hepatobiliary or foregut surgery, PV cavernous transformation

Table 9.4 Recipient's attributes of categorization

	A. Low complexity	B. Moderate complexity	C. High complexity	A vs. B	B vs. C	A vs. C
	N = 320 (66.3%)	*N* = 115 (23.8%)	*N* = 48 (9.9%)	*p* value	*p* value	*p* value
Age	58.0 (50.0–63.0)	59.0 (54.0–64.5)	57.0 (45.0–62.0)	0.232	0.020	0.055
BMI	26.7 (24.0–31.0)	33.4 (27.1–38.6)	25.3 (23.9–29.5)	<0.001	<0.001	0.628
MELD-Na at LT	20.0 (14.3–26.0)	22.0 (14.5–28.5)	27.0 (19.0–34.0)	0.058	0.006	<0.001
HCC (%)	26.6	32.2	6.25	0.252	<0.001	0.002
SLK (%)	10.3	25.3	20.8	<0.001	0.553	0.025
Previous abdominal surgery (%)	25.9	68.7	81.3	<0.001	0.103	<0.001
PVT (%)	9.38	11.3	31.3	0.553	0.002	<0.001
Previous Tx (%)	0.94	0.87	27.1	0.948	<0.001	<0.001

Values are expressed in median (interquartile range)

Table 9.5 Donor characteristics by categories

	A. Low complexity *N* = 320 (66.3%)	B. Moderate complexity *N* = 115 (23.8%)	C. High complexity *N* = 48 (9.9%)	A vs. B	B vs. C	A vs. C
Donor age	46 (32–57)	40 (28–52.5)	38 (25–52)	0.030	0.133	0.002
Donor BMI (kg/m^2)	28.7 (24.3–33.9)	26.7 (23.1–30.7)	25.3 (22.8–29.4)	0.015	0.195	0.003
No local donor (%)	59.7	45.2	39.6	0.007	0.511	0.009
Match sequence number recipient	14 (4–220)	7 (3–15)	3 (2–8.25)	0.003	0.837	0.038
Hard-to-place livers (%)	40	16.5	10.4	<0.001	0.319	0.000
DCD (%)	13.8	4.3	0	0.006	0.144	0.006
Liver donor risk index	1.59 (1.23–1.93)	1.31 (1.15–1.62)	1.33 (1.15–1.56)	<0.001	0.302	<0.001
CIT (min)	322 (277–378)	311 (273–368)	337 (266–389)	0.106	0.378	0.957
DWIT (min)	29 (27–33)	29 (29–30)	28 (25.8–31)	0.753	0.150	0.207

Values are expressed in median (interquartile range)

Patients in group A received a higher proportion of DCD-LT (*A* = 13.8%, *B* = 4.3%, *C* = 0%, *p* <0.001), nonlocal donor (*A* = 59.7%, *B* = 45.7%, *C* = 39.6%, *p* <0.001), higher donor BMI (*A* = 28.7 (24.3–33.9), *B* = 26.7 (23.1–30.7), *C* = 25.3 (22.8–29.4) kg/m^2, *p* = 0.003), and higher donor risk index (DRI) livers (*A* = 1.59 (1.23–1.93), *B* = 1.31 (1.15–1.62), *C* = 1.33 (1.15–1.56), *p* <0.001) than group B or C (Table 9.5).

Table 9.6 Intra- and postoperative outcomes by categories

	A. Low complexity $N = 320$ (66.3%)	B. Moderate complexity $N = 115$ (23.8%)	C. High complexity $N = 48$ (9.9%)	A vs. B	B vs. C	A vs. C
Operative time (min)	297 (266–342)	328 (278–407)	384 (302–458)	<0.001	0.007	<0.001
Intra-op RBC transfusion (U)	3 (1–5)	4 (1–7)	7.5 (2.7–16)	<0.001	<0.001	<0.001
No requirement of RBC (%)	25.6	22.6	10.4	0.522	0.071	0.021
Intra-op cell saver (cc)	524 (200–1150)	662 (254–1740)	1460 (382–4060)	<0.001	0.020	<0.001
Intra-op RRT (%)	30.9	53	77.1	<0.001	0.003	<0.001
Waiting time (days)	29.5 (8.2–95.3)	49 (11–138)	24.5 (9.7–140)	0.005	0.759	0.093
Hospital LOS (days)	9 (7–14)	10 (7–17)	12.5 (8.7–26.5)	0.010	0.106	<0.001
ICU LOS (days)	2 (2–4)	2 (2–3.8)	3 (2–5)	0.148	0.050	<0.001
Reoperation first week (%)	15.6	13.1	43.8	0.388	<0.001	<0.001
EAD (%)	14.7	15.7	20.8	0.787	0.359	0.207

Values are expressed in median (interquartile range)

The effect of surgical complexity on perioperative variables is presented in Table 9.6. Mean operative time increased with increasing surgical complexity ($A = 297$ min, $B = 328$ min, $C = 384$ min, $p = 0.006$). Likewise, the mean number of RBC units transfused during the transplant operation as well as cell saver utilization increased with the complexity of the case ($A = 3$ U (1–5), B = 4 U (1–7), $C = 7.5$ U (2.75–16), $p < 0.001$ and $A = 540$ cc (200–1150), $B = 662$ cc (254–1740), $C = 1460$ cc (382–4060), $p < 0.001$, respectively).

One-year patient and graft survival rates were significantly lower in category C ($A = 92.5$, $B = 91.3$, $C = 81.2\%$, $p = 0.01$ and $A = 91.8$, $B = 88.7$, $C = 81.2$, $p = 0.019$, respectively).

We applied the UK-DCD risk score to the 44 DCD-LT patients in the low surgical risk A group and the 5 DCD-LT patients in the moderate surgical risk B group. Forty-eight of the 49 UK-DCD scores were ≤10. One patient in group A had a UK-DCD score of 11. Observed 1-yr patient and graft survival was 100% in these 49 patients.

While our numbers are small thus far, our improved outcomes regardless of the UK-DCD score suggest that incorporation of a surgical risk score may improve the predictive value of that scoring system. If validated, this could result in the utilization of more DCD livers through a more accurate risk-prediction system.

The LT surgical complexity is affected by many recipient factors, such as previous abdominal surgeries, prior LT, grade of obesity, history of intra-abdominal

infection (e.g., spontaneous bacterial peritonitis), presence and severity of ascites, presence of portal vein thrombosis, progression to cavernous thrombosis that influences LT operative time, surgical bleeding, ischemia time, length of stay, and other outcomes [27–29]. These factors are actively considered against numerous specific donor factors at the time of an organ offer. Prospectively categorizing all potential LT candidates according to their surgical complexity serves two purposes. Firstly, at the time of listing, it allows the transplant team to estimate the donor characteristics that will better suit a specific recipient, including their potential candidacy for DCD graft. Secondly, it provides a pool of potential candidates optimally suited for a DCD graft, an extended criteria graft, a last-minute offer, a hard-to-place liver, or an open offer, a rescue allocation strategy already used in other countries [30].

Considering surgical complexity allows a better operative planning and resource utilization, elements that are not always considered in the donor-recipient matching scores but are important for patient outcomes [31].

In our experience, stratifying patients according to expected surgical complexity accurately predicts operative risk (e.g., predicts longer operative time and increased transfusion requirements) and allows us to rapidly match a higher-risk organ with a lower-risk recipient expediting organ placement, and it allows us to achieve patient and graft survival rates using marginal organs that compare favorably to those achieved using standard criteria organs.

Patient with Renal Dysfunction

Acute kidney injury (AKI) is a frequent complication after DCD-LT. In an early report of 88 patients, Leithead et al. reported a high incidence of AKI in DCD-LT compared with DBD-LT [32]. This observation was confirmed by the same group in a cohort of 1152 patients where they also found that the only predictor of renal dysfunction after DCD-LT was a high-peak perioperative aspartate aminotransferase, a surrogate marker of hepatic ischemia reperfusion injury [33].

Moreover, in a retrospective study examining 368 DCD-LTs, AKI was observed in 65% of the recipients and categorized as severe AKI in 41%. The length of combined DWIT correlated with AKI severity: 61 min in recipients without AKI up to 69 min in recipients with the most severe form of AKI (p <0.001). On multivariable analysis, increasing duration of the combined WIT was associated with an increased risk of developing severe AKI (odds ratio, 1.032 per every extra minute; 95% confidence interval, 1.014–1.051; p <0.001) [34, 35].

By contrast, in an analysis of 1325 primary LTs (of them, 168 DCD-LTs), the Mayo Clinic group did not find any association between DCD organ utilization and either AKI or ESRD, even though early allograft dysfunction was more common in recipients of DCD allografts [36].

The evidence strongly suggests that DCD-LT, particularly with prolonged ischemia times, is associated with the development of renal dysfunction, and therefore, caution is advised when using DCD liver allografts in recipients with preexisting renal dysfunction.

DCD Simultaneous Liver Kidney Transplant

Initial studies investigating the outcomes of simultaneous liver kidney (SLK) transplant using grafts from DCD donors described inferior outcomes compared to those using grafts from DBD donors (DBD-SLK) based on SRTR data from 2000 to 2010 [37, 38]. These studies demonstrated inferior patient survival as well as inferior liver and kidney graft survival with DCD-SLK compared to DBD-SLK transplant. In contrast, a single-center report described similar 1 year patient and graft survival for 5 DCD-SLK and 32 DBD-SLK transplants [39]. Another single-center report published similar 1-year outcomes for 12 DCD-SLK compared to 54 DBD-SLK transplants; however, the DCD-SLK group had inferior patient, liver graft, and kidney graft survival at 3 and 5 years post SLK, respectively [37]. More recently, a study demonstrated that improvement in DCD-SLK outcomes has taken place over time based on SRTR data in the contemporary era [40]. That study found no difference in patient, liver graft, or kidney graft survival between DCD-SLK and DBD-SLK in the modern era (2011–2018). Performing DCD-SLK transplants was concentrated in a relatively small number of centers, as the 10 most experienced centers had performed over 50% and the 20 most experienced centers had performed almost 75% of the DCD-SLK transplants in the United States to date. Donors used for DCD-SLK tended to be younger (mean 33 years) with low KDPI (mean 38) and short DWIT (mean 17 min). Kidney-delayed graft function (DGF) was not investigated in that study. The two single-center studies investigating DCD-SLK contained data on post-SLK DGF. In both of these studies, DCD-SLK had a higher rate of kidney DGF compared to DBD-SLK [37, 38].

Primary Sclerosing Cholangitis

Patients with primary sclerosing cholangitis (PSC) are at an increased risk of developing post-LT biliary strictures due to recurrent PSC [41, 42]. With this in mind, some concerns have been raised about the utilization of DCD donors for PSC patients, given that DCD grafts are themselves at an increased risk of biliary strictures. UNOS registry data have suggested a higher rate of graft failure in patients with PSC receiving a DCD-LT, as demonstrated by an interaction term between DCD and PSC (HR 1.76) [43]. Potential mechanisms for inferior outcome in this situation could be related to increased ischemia reperfusion injury, leading to an autoimmune insult and a predisposition to recurrent PSC [43]. In contrast, a subsequent large single-center study from the UK demonstrated no difference in non-anastomotic biliary complications, graft survival, or patient survival in patients with PSC undergoing DCD- or DBD-LT [44]. Given the well-described increased risk of biliary complications with DCD-LT, one must also be cognoscente about potential access to the biliary tree post LT. Recipients with PSC or other recipients who may require a roux-en-Y hepaticojejunostomy will have more limited access to the biliary tree than recipients with a duct-to-duct anastomosis should biliary

strictures or other biliary complications arise. In addition, a previous large multicentered study suggested that roux-en-Y hepaticojejunostomy itself, even for patients without PSC, may be associated with a higher rate of IC than duct-to-duct biliary reconstruction [45].

Hepatocellular Carcinoma

Previous reports have demonstrated that proportionally, DCD livers are used more frequently than DBD livers in patients with HCC [4, 46]. This may be due to the tendency to use extended criteria organs in recipients with lower biological MELD scores because of the perception that these recipients are better able to tolerate an extended criteria organ [47]. A previously published paper examining the data from the SRTR database suggested that even after adjustments for the inherent inferiority observed in DCD allografts, as well as other known risk factors, there was an inferior survival for HCC recipients of DCD allografts versus recipients of DBD allografts [48]. In that paper, early HCC recurrence was postulated as one potential explanation for the observed difference in survival between the DCD and DBD groups, although HCC recurrence itself was not studied. Authors of other non-transplant studies have shown an association between ischemia reperfusion injury and stimulation of growth of micrometastases and an increase in adhesion of tumor cells [49, 50].

Despite the potential biologically plausible mechanism and initial SRTR survival data, a subsequent large single-center study demonstrated no difference in the rate of recurrence of HCC between DCD- and DBD-LT (12.3% and 12.1% respectively) [51]. In addition, the authors commented that if ischemia reperfusion injury in the DCD allografts was felt to be an important factor in recurrence, a higher proportion of recurrences would have been seen in the liver in the DCD group, when in fact liver as the primary site of recurrence was seen in 65% of recipients in the DBD group and only 37% of recipients in the DCD group.

Hepatitis C Virus and DCD

Hepatitis C virus (HCV) recurrence was previously a major issue following LT. With the ubiquitous availability of directly administered antiretroviral therapy (DAART), clinically significant HCV recurrence following liver transplantation has been almost completely eliminated in many countries. Several single-center reports have described higher rates of early hepatitis C virus recurrence in patients receiving DCD versus DBD liver grafts [52, 53], while others have shown no difference [54, 55]. A previously published meta-analysis demonstrated no difference in HCV recurrence between DCD- and DBD-LT recipients [56]. Except in scenarios where there is limited access to DAART, the significance of HCV recurrence following DCD-LT is likely low.

Summary

DCD-LT increases the risk of preservation-reperfusion injury and early allograft dysfunction. On the whole, the literature suggests that careful matching of a relatively high-risk organ (DCD allograft) with low medical and surgical risk recipient offers the best opportunity to optimize outcomes. Careful recipient selection should avoid debilitated and severely ill patients as well as patients with potential technical complexities that lead to prolong ischemia times and/or excessive bleeding. Likewise, the use of DCD livers in recipients with preexisting renal dysfunction should take into account the risks of exacerbating renal injury versus the risk of not waiting for a better organ offer. A few donor-recipient matching systems exist, but each has its limitations. The Ochsner liver transplant surgical risk scoring system allows us to expeditiously match potential recipients with marginal/DCD organs.

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Outcomes in DCD Liver Transplantation

10

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Abbreviations

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the receiver operating characteristic curve statistic
BAR score	Balance of risk score
BMI	Body mass index
CIT	Cold ischemia time
CVA	Cerebrovascular accident
DAA	Direct-acting antiviral medications
DBD	Donation after brain death
DCD	Donation after circulatory death
DCD-RI	DCD-Risk Index
DM	Diabetes mellitus
DRI	Donor Risk Index
EAD	Early allograft dysfunction
ECMO	Extracorporeal membrane oxygenation
ERCP	Endoscopic retrograde cholangiopancreatography
fDWIT	functional donor warm ischemia time
GDA	Gastroduodenal artery
GGT	Gamma-glutamyl-transferase
HAS	Hepatic artery stenosis
HAT	Hepatic artery thrombosis
HBV	Hepatitis B virus

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HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HMP	Hypothermic machine perfusion
HOPE	Hypothermic oxygenated perfusion
IC	Ischemic cholangiopathy
ICU	Intensive care unit
IT	Implantation time
KCH	King's College Hospital
MELD	Model of End Liver Disease
NHS	National Health Service
NHSBT	National Health Service Blood and Transplant
NMP	Normothermic machine perfusion
NRP	Normothermic regional perfusion
OLT	Orthotopic liver transplantation
PNF	Primary nonfunction
PTC	Percutaneous transhepatic cholangiography
ROS	Reactive oxygen species
UHB	University Hospitals Birmingham
UK	United Kingdom
UK-DCD-Risk Score	United Kingdom Donation After Circulatory Death Risk Score
UKELD	United Kingdom Model of End-Stage Liver Disease
UNOS	United Network of Organ Sharing
USA	United States of America

Introduction

Liver transplantation has progressed from an experimental status to a standard treatment for end-stage liver disease and malignant liver lesions [10]. In addition to the ongoing improvement of surgical techniques, anesthesiologic and medical management, as well as donor and graft assessment, more livers from extended criteria donors (ECD) are frequently accepted. Liver transplantation from donation after circulatory death donors (DCD) was recently shown to be more beneficial compared to prolonged waiting for a presumably better DBD liver in the United Kingdom (UK) [111]. In the past decade, many countries have implemented a DCD liver transplant program (Fig. 10.1), which led to an increasing number of retrospective single-center or cohort studies, based on pooled national data (Table 10.1). Despite this success story, the utilization rate of DCD livers remain quite poor in many countries [69, 74, 83, 107, 114]. In order to better understand the overall donor and recipient risk, new tools were defined to suggest thresholds when to decline a certain donor-recipient combination in context of a predicted impaired outcome [39, 55, 103, 104]. However, which survival and complication rates to accept depends also on the number of available organs and the risk a center or country is willing to accept [18, 69].

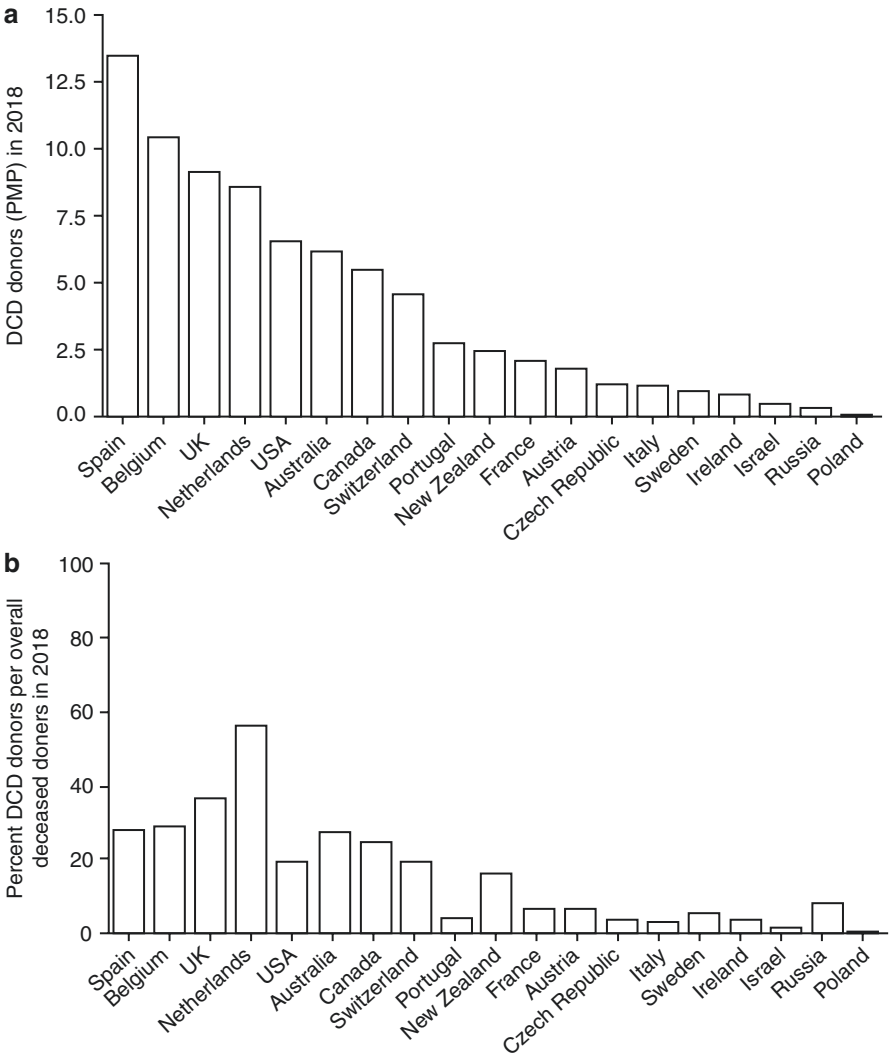

Fig. 10.1 Donors after circulatory death registered worldwide in 2018. (**a**) DCD donors in 2018 (PMP: per million population per country). (**b**) Percent DCD donors in relation to all deceased donors, which underwent procurement surgery. PMP per million population, DCD donation after circulatory death, UK United Kingdom, USA United States of America. (Based on data from annual report 2018: www.irodat.org)

In this chapter, we describe current outcomes reported after liver transplantation from controlled DCD donors with a specific focus on graft and patient survival, liver function, and biliary complications. In addition, we highlight the impact of DCD liver transplantation on other organ systems, including the kidneys, and we describe the rate of acute and chronic rejections. Finally, new tools to transparently quantify

Table 10.1 Overview on outcomes after adult liver transplantation from controlled DCD donors between 2010 and 2019

Author and year	Cohort	Time frame	Study type; no. of DCD transplants (*n*)	Risk factors ± suggested cutoff	PNF (%)	Biliary complications (%); (AS(%); IC (%))	Vascular complications (%)	Graft survival 1–3–5-10 y (%)	Patient survival 1–3–5-10 y (%)	Retransplantation (%)
USA/Can.										
Mathur 2010	UNOS, national	2001–2009	Retrospective *n* = 1567	Donor age > 50 y, DWIT >35 min, CIT > 6 h, recipient age > 55 y, MELD >35, male gender	–	–	–	78,65,-,-	83,78,-,-	13.6
Foley 2011	Wisconsin, USA	1993–2008	Retrospective *n* = 87	Donor age > 60, DWIT 30 min, BMI 25 kg/m^{2}2, MELD >20	2.3	47 (IC 34)	–	69,-,56,43	84,-,68,54	19.0 (1 y)
Bellingham 2011	Wisconsin, USA	1980–2008	Retrospective *n* = 87	–	–	51.5	–	69.4,59.6,56,42.9	84,71.8,68,54.4	13.9
Jay 2011	UNOS, national	1996–2007	Retrospective *n* = 1113	Donor age > 40 y, CIT > 12 h, regional sharing, recipient age > 60 y, HCV, HCC, renal insufficiency	–	–	–	–	82, 71,-,-	14.7

Taner 2012	Mayo Florida, USA	1998–2010	Retrospective $n = 200$	Race, DWIT	2.5	27 (IC 12)	HAT 3.5	80.9,72.7,68.9,-	92.6,85,80.9,-	10.5
Vanatta 2013	Memphis, Tennessee, USA	2006–2011	Retrospective $n = 38$	Donor age, DWIT, CIT, macrosteatosis, procurement team, donor location	2.6	18.4 (IC 7.9)	HAT 0 HAS 10 ICV thrombus 2.6	92, 74,-,-	92, 80,-,-	2.6
Lee 2014	Mayo Florida, USA		Retrospective $n = 205$							
Doyle 2015	Washington, USA	2005–2014	Retrospective $n = 49$	After 2009 donor age > 45, DWIT>20 min	0	Bile leak 14.3 AS[§] 16.3 IC 8.5	0	-,-,79.5,-	-,-,87.1,-	6.1
Firl 2015	Cleveland, Ohio, USA	2005–2014	Retrospective $n = 92$	Increasing donor age	6.5	27.2 (IC 6.5)	HAT 1.1 PVT 1.1	83, 72, 66,-	–	2.2
Croome 2016	UNOS, national	2003–2014 (three eras)	Retrospective $n = 3199$	Donor age, CIT, recipient age, MELD, ventilation, HCV, eras 2 and 3	–	–	–	Era 1: 72,62,55,- Era 2: 79,69,63,- Era 3: 85,75,67,-	Era 1: 87,76,72,- Era 2: 88,77,73,- Era 3: 90,88,-,-	–
Scalea 2016	UNOS, national	2002–2014	Retrospective $n = 2185$	Donor age > 50, CIT > 6 h, donor BMI	–	Overall strictures (1 year) 33	–	-,-, 61,-	–	–
Croome 2017	Mayo Florida, USA	1998–2015	Retrospective $n = 300$	-	–	27 (AS 9, IC 11.7; bile leak 11.7)	HAT 2.3 HAS 4.3	86.1,78.4,73.2,-	92.3,86.1,80.3,-	–

(continued)

Table 10.1 (continued)

Author and year	Cohort	Time frame	Study type; no. of DCD transplants (*n*)	Risk factors ± suggested cutoff	PNF (%)	Biliary complications (%); (AS(%); IC (%))	Vascular complications (%)	Graft survival 1–3–5-10 y (%)	Patient survival 1–3–5-10 y (%)	Retransplantation (%)
Goldberg 2017	National, IDOL consortium	2005–2014	Retrospective *n* = 744	Donor age > 40 y, center volume, DWIT	–	Overall strictures (6 months): 21.8 (IC 11.8)	–	–	–	–
Bohorquez 2017	Ochsner, New Orleans, USA	2003–2015	Retrospective *n* = 138, two groups	DWIT	0	24.6 (IC 3.6)	HAT 4.3	Early: 76.3,73.7,- Late: 92,91.4,-,-	Early:86.8,84.3,-,- Late: 93, 89.2,-,-	5.8
Kollmann 2018	Toronto, Canada	2009–2017	Retrospective *n* = 77	Immediate posttransplant complications	1.3	5.2 (AS: 2.6, IC 2.6)	HAT 0	88.3,83.2,69.2,-	92.2,85.4,71.6,-	3.9
Croome 2018	Three centers, USA	2002–2016	Retrospective *n* = 471∗	Donor age increase >50 y, diabetes, CIT, MELD >30, recipient ventilated, on ICU	–	Donor ≥50 y: 32.3 (AS 16.1, IC 11.6)	Donor ≥50 y: 1.9	Donor ≥50 y: 87,75.6,71.8,-	Donor ≥50 y: 91.1,84.2,81.6,-	–
Europe										
Dubbeld 2010	The Netherlands, national	2001–2006	Retrospective *n* = 55	DWIT, CIT, RWIT, transplant center	1.8	IC 24	HAT 7.3 Other 7.3	74,68,-,-	85,80,-,-	18.2
DeOliveira 2011	London, UK	2001–2010	Retrospective *n* = 152	No statistical difference	–	19.7 (IC 2.6)	HAT 2.6	-,-,78,-	-,-,80,-	1.3

Mallik 2011	Cambridge, UK	2004–2010	Retrospective $n = 32$	–	–	50 (IC 18.8)	–	95,-,-,-	100,-,-,-	–
Meurisse 2012	Leuven, Belgium	2003–2010	Retrospective $n = 30$	Donor age > 60 y, DWIT >30 min, CIT > 8 hrs	0	50 (IC 33.3)	–	90, 82.1,-,-	93.3, 85.5,-,-	3
Callaghan 2013	UK, national	2005–2010	Retrospective $n = 352$	–	–	6% cause of graft loss, 4% strictures require intervention	–	-,72.7,-,-	-,80.6,-,-	–
Detry 2014	Liège, Belgium	2003–2012	Retrospective $n = 69$	Donor age	0	20.3 (AS 14.5, IC 1.4, leak 4.3)	HAT 1.4	-,72,-,-	-,73,-,-	1.4
O'Neill 2014	Medline, Embase, Cochrane	1993–2011	Meta-analysis (25 studies), $n = 2478$	Donor age, recipient age, MELD, CIT	–	26 (IC 16)	–	-,73,-,-	-,82,-,-	–
Blok 2016	Belgium and the Netherlands	2003–2007	Retrospective $n = 126$	DWIT >25 min	3.2	(IC 6.3)	HAT 0.8	74.8,-,54.4,44.2	87.8,-,68.1,55.9	14.3
Laing 2016	Birmingham, UK	2004–2014	Retrospective $n = 234$, propensity matched ($n = 187$)	–	–	32.6 (AS 14.4, IC 9.1)	HAT 4.8 HAS 2.7	82.7,-,-,-	87.6,-,-,-	3.4
Kalisvaart 2017	Rotterdam, the Netherlands	2001–2015	Retrospective $n = 115$	–	3.5	34 (AS 18, IC 11)	-	-,-,60,-	-,-,75,-	15

(continued)

Table 10.1 (continued)

Author and year	Cohort	Time frame	Study type; no. of DCD transplants (*n*)	Risk factors ± suggested cutoff	PNF (%)	Biliary complications (%); (AS(%); IC (%))	Vascular complications (%)	Graft survival 1–3–5-10 y (%)	Patient survival 1–3–5-10 y (%)	Retransplantation (%)
Schlegel 2018	Birmingham, UK	2004–2017	Retrospective *n* = 315	Donor age > 60 y with donor BMI > 25 kg/m^2, CIT	2.9	28.9 (AS 13, IC 11.4, leak 3.3)	HAT 7	-,-,> 80,- (donor age > 60, donor BMI ≤ 25 kg/m^2)	-,-,> 88,- (donor age > 60, donor BMI ≤ 25 kg/m^2)	7
Gilbo 2019	Leuven, Belgium	2009–2015	Retrospective *n* = 78	–	–	–	–	-, 82,-,-	-, 84.6,-,-	–
Taylor 2019	UK, national	2008–2015	Retrospective *n* = 953	Donor age, recipient age, recipient status, liver appearance	3.5	–	–	83.7,-,69.1,-	91.5,-,78.1,-	–
Martinez 2019	Malaga, Spain	2013–2017	Retrospective *n* = 25§	Donor age, DWIT, CIT	0	20 (AS 4, IC 12, leak 4)	–	-,-,-,-	-,84,-,-	8

AS anastomotic strictures, *BMI* body mass index, *Can* Canada, *CIT* cold ischemia time, *D* donor, *DCD* donation after circulatory death, *DWIT* donor warm ischemia time, inconsistently defined, *UCLA* University of California Los Angeles, *DLI* Donor Liver Index, *DRI* Donor Risk Index, *DWIT* donor warm ischemia time (includes different definitions in all centers and countries), *ET-DRI* European-Donor Risk Index, *HCC* hepatocellular carcinoma, *HCV* hepatitis C virus, *HAT* hepatic artery thrombosis, *HAS* hepatic artery stenosis, *HR* hazard ratio, *IC* ischemic cholangiopathy (includes also nonanastomotic strictures – labelled as NAS, excluding HAT-related features), *ICU* intensive care unit, *MELD* model of end-stage liver disease, *PNF* primary nonfunction, *R* recipient, *UK* United Kingdom, *WIT* warm ischemia time, *1 y* one year. § includes distant bile duct strictures. - means not reported, 0 is none. ∗ compares donor age > 50 vs. ≤ 50 years, no outcome of entire cohort. Leak represents biliary fistula – usually anastomotic leak. Empty field with a – means no information in the paper, 0 means a frequency of zero for the complication. The table includes studies on overall or mixed cohorts. Special outcome analyses of recipients with, for example, HCC only or viral hepatitis or studies involving machine perfusion were excluded. Biliary strictures due to chronic rejection were not specifically considered here. §: four DCD livers were retrieved with normothermic regional perfusion (NRP)

overall complications are presented including suggestions on how to improve outcomes after DCD liver transplantation further in the future.

Graft and Patient Survival

The proportion of DCD donors has grown in recent years and ranges presently between 5% and 50% of the total deceased donors (Fig. 10.1). Leading countries are, for example, Spain, the UK, Belgium, and the Netherlands, where DCD donors represented more than 50% of all deceased donors in 2018 (Fig. 10.1) [42, 52]. The higher overall number of DCD transplantations was mainly found due to an increased number of available donors, while the utilization rate remained largely stable in the last few years. Although experienced centers have improved their outcomes in DCD liver transplantation with modified techniques and a strict selection policy, the overall results have however plateaued within the last years, without further reduction of DCD-specific complications in context of standard cold storage liver preservation (Table 10.1) [74, 85].

Most studies are of retrospective, single-center design and report 3-year outcomes (Table 10.1) [85]. The reported 5-year overall graft and recipient survival fluctuated between 54.4–79.5% and 68–88%, respectively (Table 10.1, Figs. 10.2, 10.3, and 10.4). Although most studies, which used pooled registry data, showed a generally inferior survival with DCD livers compared to DBD transplants, single-center analyses have also demonstrated comparable outcomes (Table 10.1) [22, 29, 34, 39, 40, 62, 111]. Such different results are largely based on the heterogeneity of risk among centers "pooled together" in large databases and the individual donor and graft risk accepted in each center and country. Specialized, large volume centers, for example, achieved excellent outcomes with a 5-year graft survival of almost 80% already in earlier years [22, 75].

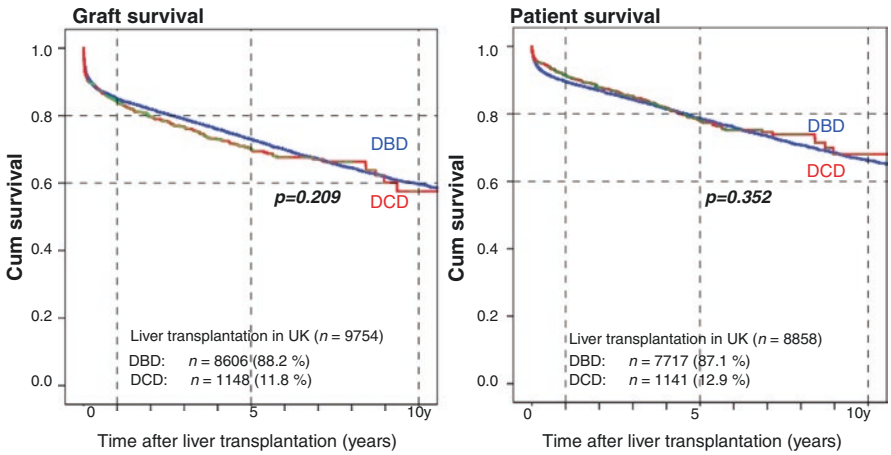

Fig. 10.2 Ten-year graft and patient survival comparing adult DBD and DCD liver transplantation in the UK. DBD donation after brain death, DCD donation after circulatory death, UK United Kingdom. (Data source: NHS Blood and Transplant Registry)

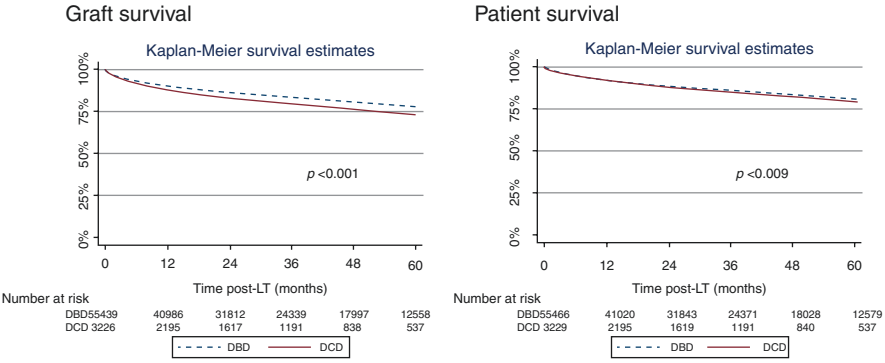

Fig. 10.3 Five-year graft and patient survival comparing adult DBD and DCD liver transplantation in the USA. DBD donation after brain death, DCD donation after circulatory death, USA United States of America. (Data source: Scientific Registry of Transplant Recipients)

The limitation of donor risk factors and a standardized organ retrieval practice with, for example, a short donor hepatectomy time and cold storage have contributed to such good outcomes [9, 22, 26, 55, 59]. The introduction of national guidelines has led to an increased utilization of livers from "good" DCD donors and subsequent excellent graft and patient survival rates, for example, in the UK or the United States of America (USA) (Figs. 10.2 and 10.3) [2, 8, 18, 26, 33, 83, 111].

In context of the rather inhomogeneous follow-up in most studies together with the gradual loss of liver recipients at risk after transplant surgery, the literature information on 10-year survival rates are limited (Table 10.1). Only two retrospective, cohort studies reported on long-term graft and patient survivals of 43–44% and 54–56% after 10 years, respectively [5, 7]. Despite the difficulties to generally interpret various outcomes found in multiple studies, the higher adjusted odds ratio (OR) consistently reported for graft loss following DCD liver transplantation remains, considering a well-mixed donor and recipient risks combination as summarized in a recent meta-analysis [72, 85, 116].

In order to identify unfavorable donor-recipient risk combinations, the UCLA group was the first to suggest a prognostic scoring system with the aim to define cutoff values for risk factors to enable clinicians to decide whether to accept a certain donor and recipient combination [38]. Further scores were developed in the UK, for example, based on the King's College DCD transplant cohort or the national DCD liver transplant cohort [55, 104]. Such models identified low-risk or "good quality" DCD livers, which led to excellent graft survival rates of more than 80% after 5 years, when respecting a balance between donor and recipient risk factors [10, 81, 82].

Pediatric DCD Recipients

Utilization of DCD liver grafts in the pediatric recipient population remains controversial, with a limited number of outcome studies available [3]. However, in context

of a strict selection policy, current data support the use of pediatric DCD grafts in children. Experience with DCD donors appears crucial to achieve good results in this cohort, as demonstrated by excellent results from single centers [95]. The team from UCLA has demonstrated equivalent long-term results comparing pediatric DCD grafts and other variants in children, including partial grafts (Segment II and III) from living or deceased donors in 2009 [37]. Such earlier results were recently supported by a UNOS database analysis, where 57 pediatric DCD liver recipients achieved comparable survival rates as with DBD grafts [41].

Liver Function

Through risk minimization, the primary nonfunction (PNF) rate has significantly reduced in recent years and ranges between 0% and 6.5% following controlled DCD liver transplants (Table 10.1, Fig. 10.4) [7, 23, 24, 27, 30, 73, 92]. Although no clear cutoff when to decline a certain donor-recipient risk combination is available, there is a general consensus to limit the donor warm ischemia and the cold storage for DCD liver grafts [18, 63, 74]. Please see also Chap. 7.

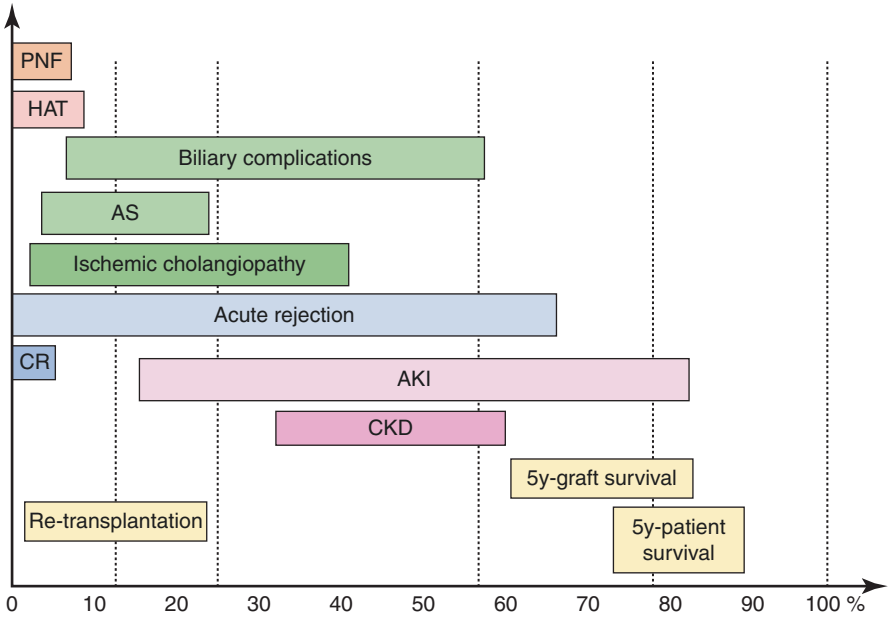

Fig. 10.4 Reported frequency of complications and survival rates after adult liver transplantation from controlled DCD donors. AKI acute kidney injury (overall mix of all severities), AS anastomotic stricture, CKD chronic kidney disease (overall rate reported, majority within 5 years), CR chronic rejection, DCD donation after circulatory death, HAT hepatic artery thrombosis, IC ischemic cholangiopathy (includes also nonanastomotic strictures, excluding HAT-related features), PNF primary nonfunction, 5 y five years. The frequency is reported as range and based on the most recent literature from the past 10 years

In contrast to the clear PNF definition, the occurrence of any sort of impaired liver function or dysfunction is more difficult to capture and frequently found in DCD liver recipients. Olthoff et al. have therefore developed the formula for early allograft dysfunction (EAD) – which includes parameters for graft injury (quantified by liver enzyme release: alanine or aspartate aminotransferase of >2000 U/L) and elevated liver function tests assessed on day 7 after transplantation, including the coagulation parameter INR (≥1.6) and bilirubin (≥10 mg/dl) [64, 88, 98]. EAD following DCD liver transplantation is covered in Chap. 11.

Biliary Complications

Despite the improved medical treatment and surgical technique with a better awareness of risk transmitted with a DCD liver, one main cause of graft loss and subsequent patient death remains with biliary complications. The reported rate of 18–51% overall biliary complications depends on the follow-up duration and includes anastomotic strictures (AS), ischemic cholangiopathy (IC), bile leaks, and other types, such as biliary casts and stones found in the biliary tree [4, 12, 45, 53, 122]. IC is covered in detail in Chap. 12. While the majority of anastomotic strictures can be addressed through endoscopic ballooning and stent placement by an expert endoscopist, hilar strictures and intrahepatic abscesses appear more difficult to treat successfully with a conservative approach [1, 54]. Enormous variations have been reported regarding the type, location, and clinical impact of ICs (Table 10.1) [12, 31, 89]. Additionally, the clinical picture of IC appears very different and may range individually from episodes of elevated parameters of cholestasis to repeat diagnostic procedures including endoscopic retrograde cholangiopancreatography (ERCP) and percutaneous transhepatic cholangiography (PTC) with stent or drain placement to rotating antibiotics and retransplantation. The clinical consideration and reporting of ICs differ significantly in the literature with the lack of a uniform clinical classification, which could provide an overview of clinically relevant ischemic strictures and link different levels of donor, graft, and recipient risk profiles [85]. The IC rate following controlled DCD liver transplantation has been reported between 2.6% and 34% in the past decade (Table 10.1) [21, 22, 30, 33, 46, 62, 99].

Multiple factors were nominated to contribute to the development of biliary complications and include the entire spectrum of donor and graft parameters, procurement surgery, preservation, and implantation [52, 85, 104]. The majority of risk factors are simply given by the donor situation, which has led to a selective policy on how to allocate DCD livers best to a certain recipient, which is one main policy clinically applied to reduce biliary complications in context of standard cold storage preservation (Table 10.1) [22, 32, 59]. An increasing body of literature is available to understand the multifactorial pathogenesis of such ischemic strictures [53]. Several factors, including vessel patency, cumulative donor risk with subsequent level of ischemia reperfusion injury, potential cytomegaly virus infection, chronic rejection, ABO incompatibility, and other toxic factors, have

been discussed as contributors [74]. The level of reperfusion injury in the large compound of hepatocytes in the liver triggers a toxic composition of the early bile, initially produced after reperfusion, which injures the vulnerable biliary epithelium further, enhancing the reperfusion injury in such sensitive cells [12, 84, 106, 122]. In this context, any additional episode of warm hepatic ischemia throughout the liver pathway from the donor to implantation will contribute to harmful damage [74]. The duration of donor hepatectomy time and implantation time has therefore been assessed with impact on complication rates following DCD liver transplantation [11, 26, 44, 55, 94]. Another "wheel to adjust" is the liver preservation, and novel perfusion concepts are currently evaluated with their potential impact on the occurrence of biliary complication and subsequent graft loss [36, 61, 79, 105, 120].

Vascular Complications

Posttransplant issues with vascular structures are frequently underreported in the field of DCD liver transplantation, because most analyses focus on biliary complications and graft or patient survival (Table 10.1) [8, 19, 21, 25, 27, 62, 102]. In context of advanced reperfusion injury with subsequent higher inotrope requirements, DCD liver grafts may have a higher degree of stiffness which promotes the development of arterial complications further, including hepatic artery thrombosis (HAT) [19, 20, 109]. Data on such additional issues appear scarce, and the reported HAT rate is found between 0% and 7.7% (Table 10.1) [8, 21, 24, 25, 28, 33, 59, 62, 110].

Despite the general lack of information in the literature, recipients with an unfavorable underlying disease may be exposed to an even higher risk of vascular complications, for example, primary sclerosing cholangitis (PSC) or autoimmune hepatitis, where the additional pro-coagulative status and higher immune system activation contribute further to arterial complications [113]. The rate of later hepatic artery stenosis (HAS) appears with 2.7–10% similarity when compared to the HAT rate in the currently available literature (Table 10.1) [19, 62, 115].

Relevant portal or hepatic vein occlusions are very rare and therefore often not reported. For example, only two retrospective studies showed the rate of venous complications, including portal vein thrombosis or hepatic vein obstruction, which ranged between 1.1% and 2.6% (Table 10.1) [25, 27, 115].

Acute and Chronic Kidney Injury

Acute kidney injury (AKI) following liver transplantation is inconsistently reported as all other outcome measures. The increased use of riskier DCD livers is paralleled by a relatively high overall AKI rate between 12% and 81% [24, 48, 49, 62, 64, 67, 112]. Of particular impact on the reported rate of renal complications are, for example, various criteria applied to define AKI, the severity, and the indication to

implement renal replacement therapy (RRT) comparing different transplant centers [57, 66, 86]. The occurrence of AKI was recently linked with a higher risk of mortality after liver transplantation in a meta-analysis [112].

The interest in a more specific analysis of AKI and underlying causes has recently evolved, and reports identified about 15–40% DCD recipients with severe AKI grade 2 and 3, where between 16% and 40% require RRT [24, 51, 62, 67, 92, 102]. The AKI rate is also significantly higher in DCD liver transplants when compared to good DBD liver grafts [24, 67]. However, implantation of extended DBD livers (ECD) with, for example, advanced donor age, donor BMI, cold storage, or steatosis was also shown to induce higher AKI rates [66, 101]. Such findings parallel other publications, in which more severe liver reperfusion injury has been shown to be a driver of development of AKI [65, 93]. A higher rate of post-reperfusion syndrome with lower mean arterial pressures (MAP) and higher cardiovascular support was also shown to be related to the severity of AKI [47]. Wadei et al. have finally demonstrated the link between reperfusion injury-related EAD development and the presence of AKI in context of DCD liver transplantation [117, 118]. And human kidneys significantly contribute to the clearance of reperfusion injury-related circulating cytokines, following liver transplantation as shown by many [80, 93]. The higher AKI frequency in DCD transplantation with the link to an impaired outcome has further supported the selective policy with regard to donor and recipient risk factors and the early introduction of medical preventive treatment in the early posttransplant phase [43, 50, 66]. Centers ideally aim to limit the duration of donor warm ischemia time and allocate DCD grafts to rather fit recipients without hepatorenal syndrome and able to cope with potential reperfusion injury [49, 50]. Moreover, renal-sparing immunosuppression is the preferred regimen in many centers and includes, for example, induction therapy with basiliximab in combination with a delayed introduction of calcineurin inhibitors (CNI) to protect kidneys following liver transplantation [13, 49].

In context of an overall longer recipient follow-up today with improved survival, chronic and long-term complications are more in focus. The cumulative incidence of severe CKD with end-stage renal failure (ESRF) was shown to increase up to almost 25% within 10 years after liver transplantation. This was, however, in earlier days when traditional immunosuppressive regiments with higher through levels were used [87].

The severity of AKI was recently found to predict the later development of chronic kidney disease (CKD) [50]. Five years after liver transplantation, more than one-third of recipients present with signs of CKD (25–54%), while severe CKD with ESRF remains rare with only 1–2% [50, 66, 67].

In addition to the initial development of severe AKI, which was shown to predict later CKD (1.8-fold increased risk), other factors have impact on impaired kidney function 5–10 years after LT, including immunosuppression and cardiovascular or renal diseases. This was further underlined by the fact that most liver recipients with AKI recover from the initial renal hit, and Kalisvaart et al. did not find any differences in the development of CKD comparing different grafts types, such as good or marginal DBD and DCD livers [50]. Very high plasma through

levels of calcineurin inhibitors were shown to impact on the early development of CKD [97]. Please see further information regarding renal complications after DCD liver transplantation in Chap. 11.

Acute and Chronic Rejection

Immunosuppression (IS) regimens have changed enormously within the last 20 years, not only based on renal complications but also cancer development and infections. The higher awareness of such drug-related long-term complications has led to an overall decrease in through levels and the introduction of new combinations of different drugs. Despite such modifications, the overall incidence of acute cellular rejection (ACR) following liver transplantation has steadily decreased and is currently reported with 10% [13, 58].

Pronounced reperfusion injury has been previously linked to a higher rejection rate in solid organ transplantation. Results comparing DCD and DBD liver transplants remain therefore controversial, and some studies reported higher ACR rates when DCD livers are utilized [29, 105]. The overall rate of ACR episodes is currently reported between 0% and 61% in the setting of DCD liver transplantation (Table 10.1, Fig. 10.4) [13, 24, 59, 75, 91, 102]. However, as seen with any other complications, such a wide range of frequencies is based on multiple contributing factors, including donor risk, level of reperfusion injury, type of immunosuppression, and other parameters related to center practice and the time window of observation after transplantation.

Some authors, for example, highlight exclusively the number of treated rejections, where the type and dosage of medical treatment appear difficult to identify [102] and true rates of ACR remain underreported. Younger recipients with an active immune system or transplant candidates with autoimmune liver disease are more prone to experience ACR episodes. Such increased immune response seems to be even more evident in DCD transplants and further increased through an elevated reperfusion injury [6, 13, 100]. The majority of DCD liver recipients are effectively treated with a dual or triple combination today [13, 15]. By far, not all experienced transplant centers add an induction therapy routinely [13, 62]. Halldorson et al. have assessed the impact of basiliximab compared to ATG induction and found similar acute rejection rates of 21% and 22% in a small DCD liver cohort [35].

Compared to other solid organs, ACR in liver transplantation is of less importance, because some studies showed a protective effect of ACR episodes with regard to graft survival [96]. Future research will identify more tailored immunosuppressive regimen with the aim for a significant drug reduction to achieve operational tolerance and complete withdrawal.

Chronic rejections with subsequent graft loss were reported with an equally low rate of 0.8–3.1% following DCD liver transplants when compared to DBD grafts [8, 24, 26, 34, 73, 75, 91]. And with today's immunosuppressive regimen, very limited chronic rejection rates are seen in children receiving DCD liver transplants, as shown by a recent report from the Netherlands [95].

Tumor Recurrence in Context of DCD Liver Transplantation

With regard to recurrence rates of underlying recipient diseases or hepatocellular carcinoma (HCC), the available literature remains limited. The overall HCC recurrence rate was found between 10% and 15% [16, 17, 56]. Such results from experienced centers and the variation in recurrence rates seen point to other factors with impact, including the cumulative donor and graft risk, the tumor load and activity, and the vascular invasion. The recurrence risk after DCD liver transplantation has been presented based on subgroup analyses, where the initial tumor load in the recipient was inside Milan criteria [17, 70]. Many centers are currently extending their acceptance criteria for HCC. The reported impact of DCD livers on outcomes in this cohort appears therefore inconsistent and may require new analysis in the future. Studies on the HCC recurrence following DCD liver transplantation with similar donor and recipient risk have demonstrated different results. For example, in 2013, Croome et al. have demonstrated inferior survival rates found in DCD liver recipients with an HCC in the large UNOS database until 2011. This report was followed by another study 2 years later from Mayo Clinic, Florida, with opposite findings and similar recurrence rates found in DCD compared to DBD liver recipients [16, 17]. Such results were however paralleled by a paper from King's College, London, where authors showed similar survivals in HCC candidates transplanted with DBD or DCD livers [56]. Both studies included a rather low cumulative donor risk with an overall good recipient survival. Another recent assessment of the impact of graft quality on recurrence rate in the UK did not support earlier results, where, for example, Nagai et al. showed a higher recurrence rate in liver transplantations with prolonged cold ischemia times [78, 119]. Others reported a link between reperfusion injury and higher recurrence rates also triggered by an inflammatory milieu in the gut [60, 90]. The Hongkong group has provided a summary on underlying mechanisms leading to the perfect environment for cancer cells to migrate and regrow in the newly implanted liver, which include all features of reperfusion injury [68]. Such limitation of donor risk and reperfusion injury through new preservation technology may mitigate the HCC recurrence, where future studies are urgently required.

Assessment of Cumulative Complications

Reported frequencies of single complications appear somewhat difficult to interpret and should always be seen in context of the overall donor and recipient risk. The majority of complications as summarized in Table 10.1 and Fig. 10.4 are routinely presented in percent and with several confounding factors. Slankamenac et al. have therefore developed a new metric system to better quantify complications. Authors present this new tool, the comprehensive complication index (CCI), which serves as novelty to assess the median of complications following any type of surgical procedure. Such model was recently applied in DBD and DCD liver transplants and demonstrated an overall median CCI during hospital stay and at 6 months of 38.2 and 53.4 points, respectively, on an overall scale between 0 and 100, where 100 points

represent recipient death [46, 108]. During hospital stay, the CCI was comparable to DBD liver transplantations, while through further follow-up, the DCD cohort experienced more complications, summarized by a higher CCI at 6 months [46]. Other reports from Canada demonstrated similar in-hospital complication rates with a mean CCI of 28.2 points, which was slightly higher compared to transplants from living donors or other DBD grafts [59]. This new tool has been recently used in multiple surgical disciplines to assess outcomes and enables comparative analyses between surgical procedures, centers, national cohorts, and even single surgeons [14].

How to Report and Improve Outcomes Further?

The majority of outcome reports rely on retrospective analyses from single center or national cohort studies, with either specific risk profiles or large volumes of missing data in pooled cohorts. In this context, future analyses should aim for international data collection with inclusion of most relevant outcomes and the CCI. A benchmarking-type analysis with DCD liver transplants is therefore currently performed, where results from most cases transplanted in all Western countries are included. Such benchmarking concept appears not new but has previously defined valid reference values for most outcome measures in DBD liver transplantation, where the impact of new technology and the results from large randomized controlled trials can be compared with [76].

The overall donor and recipient risk a specific country, center, or surgeon is willing to accept depends also on national regulations and the internal and external support a center receives. A more uniform donor and recipient risk factor application with subsequent development of general thresholds would be of importance to compare results, and the consensus conference planned for 2020 will possibly develop some guidelines.

Novel machine perfusion technology is currently improved and tested in the clinical setting of liver transplantation and in other solid organs. Results expected from various randomized controlled trials are awaited and will possibly impact on future applications. Importantly, viability criteria are currently developed for various types of cold and warm in situ and ex situ perfusion strategies to increase the generally poor utilization rate and safety of extended DBD and DCD donor liver transplants [71, 77, 121]. Future prediction models will therefore retain not only donor and recipient risk factors but also capture the metabolic liver assessment to more accurately predict outcomes and the risk for certain complications prior to decision-making whether to utilize a graft or not.

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Non-biliary Complications Associated with Liver Grafts from Donation After Circulatory Death Donors

11

Shelly Wilson, David Goldberg, and Peter Abt

Liver transplantation using grafts from donation after circulatory death (DCD) donors is an evolving mechanism to augment the pool of deceased donor grafts. However, each new modality to mitigate the organ shortage ushers in its own unique complications, and this certainly applies to DCD liver transplantation. While biliary complications are likely the most prevalent and tenacious issue with respect to DCD liver transplantation and are discussed elsewhere in this text, less understood or appreciated are the non-biliary complications. These include: post-reperfusion syndrome (PPS), early allograft dysfunction (EAD), graft primary non-function (PNF), acute kidney injury (AKI) and end-stage renal disease (ESRD), and vascular complications (Table 11.1). To what extent these as well as biliary complications are interrelated are unknown; however, it is likely they reflect and arise along a spectrum of ischemia reperfusion injury.

Post-reperfusion Syndrome

Post-reperfusion syndrome (PRS) is defined as hypotension with a 30% decrease in blood pressure from baseline in the first 5 minutes after reperfusion, lasting at least 1 minute. In a large retrospective analysis with a propensity-matched donation after brain death (DBD) population, both the rates of PRS and hyperkalemia were nearly

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Table 11.1 Incidence of non-biliary complications in DCD liver transplantation

Non-biliary complication	Incidence
Post-reperfusion syndrome	25.7–26%
Early allograft dysfunction	37.3–68.4%
Primary non-function	3–12%
Acute kidney injury	32.6–65%
Hepatic artery thrombosis	2.3–11.1%

doubled in liver transplants using DCD grafts. However, the pressor requirements immediately after reperfusion, pressor requirements at the end of the case, rates of AKI, and cardiac events were not statistically different between the two groups [20]. The main risk factor for the cardiac events observed was actually pre-reperfusion hyperkalemia [20]. Moreover, macrosteatosis (>20%) in DCD liver grafts is an independent risk factor for the development of PRS and post-reperfusion hyperkalemia, with a 14-fold increase in in the odds of developing PRS compared to non-steatotic DCD grafts [25]. In another large single-center study, no difference in PRS was seen between DCD and DBD liver transplant recipients (26% vs 24.7%, respectively); however in the DCD group, there was a significant increase in the amount of total intraoperative and postreperfusion blood products utilized, significant differences in postreperfusion thromboelastography parameters, as well as inotropes and vasopressors used [4].

Early Allograft Dysfunction

Early allograft dysfunction (EAD) and graft primary non-function (PNF) are both on the spectrum of graft dysfunction within the first several days post transplantation, with both having derangements in liver enzymes (AST and ALT) and elevated bilirubin, INR, acidosis, or increased lactic acid level, although absolute numbers vary per study [18, 19]. Among DCD liver transplant recipients, the incidence of EAD has been reported in various studies as 37.3%, 39.5%, 54%, 60%, and 68.4% [3, 5, 12, 13, 16]. While a broad range, all are higher than previously reported rates for DBD liver transplantations in general at ~25%, although individual studies did have an incidence as high as 36% for DBD liver transplant recipients [9]. Interestingly, the incidence of EAD in DCD liver transplants was associated with decreased patient and graft survival compared to those that did not develop EAD but appears independent of biliary complications [16]. Conversely, in the study with the highest rate of EAD in recipients of DCD grafts at 68%, the authors found no association between EAD rates in DCD allografts and graft or patient survival at 6 months, but an increase in INR was predictive of worse outcomes [5]. It is possible that the difference in correlation between EAD in DCD grafts and graft and patient survival would have been similar if patients had been followed for a longer period post transplantation. Regardless, the data suggest that EAD rate is indeed elevated in DCD grafts and associated with worse long-term outcomes even if not usable as a predictor of early failure within the first 6 months post transplantation.

The variable impact of EAD following DCD liver transplantation has led several groups to attempt to develop other models with slight modifications. In 2015, the Model for Early Allograft Function Scoring (MEAF) was proposed to determine the severity of early liver dysfunction rather than the simple frequency [21]. This model provides a more accurate graft function assessment and was shown to be superior in terms of graft and recipient survival prediction [1, 21]. Another new tool, the L-GraFT model, aims to more accurately predict early graft failure and was shown to be superior to the EAD model at predicting 3-month failure free graft survival after liver transplantation (c-statistic 0.85) [1]. Although superior at first glance, most tools lack validation in other large cohorts today.

Primary Non-Function

When EAD is not recoverable and the recipient requires re-transplantation to insure survival, the complication is primary non-function (PNF). Comparing DCD allograft recipients to DBD, the rate of PNF was increased in DCD recipients in at least three separate studies (12% to 3%, 3.2% to 0.7%, and 3% to 1%), and found to be 3% in analysis of PNF rates in DCD allografts alone [2, 3, 7, 11, 12]. Increased rates of PNF by definition results in higher rates of re-transplantation in those recipients of DCD allografts compared to DBD [11–13].

Acute Kidney Injury

Acute kidney injury (AKI) is one of the more common non-biliary complication following DCD liver transplantation. Although several definitions exist, studies commonly define this phenomenon by one of two sets of criteria: (1) an increase in serum creatinine greater than or equal two times baseline or (2) an increase in serum creatinine by greater than or equal to 26.5micromol/L within 48 hours post transplantation or by greater than or equal to one and a half times baseline within the first 7 days post transplant. In a retrospective analysis of 44 consecutive DCD transplants compared to equivalent DBD recipients, the rate of AKI was significantly higher in the DCD group (53.4% vs 31.8%) and was associated with higher frequency of renal replacement therapy, prolonged duration of renal injury, and longer stays in an intensive care unit. While those who did have AKI had an increased likelihood of developing chronic kidney disease at 3 years, the overall rates of chronic kidney disease between DCD and DBD recipients were not different at 3 years post transplantation [17]. In one large, single-center study comprised 234 DCD liver recipients compared with 739 recipients of DBD livers, the rate of AKI in the first 90 days was significantly higher in those receiving DCD livers, although kidney function had equalized between the two groups by 1 year post transplantation [14]. This pattern of increased AKI in DCD liver allografts which does not translate to an increased rate of chronic kidney disease in the long term when compared to DBD allografts has been recapitulated when extended to longer duration of

post-transplant follow-up [13]. While there are several studies indicating higher rates of AKI in DCD liver transplantation compared to DBD, not all studies support this finding. A large retrospective study with propensity matching failed to detect a difference in AKI rates between the liver transplantations using DBD or DCD grafts [20]. Although several studies have failed to demonstrate an increased risk of CKD among recipients of DCD liver grafts, a study utilizing national data from the United States suggested that among liver transplant recipients that progressed to chronic dialysis or received a renal transplant, the strongest risk factor amongst donor characteristics was DCD status [22].

Vascular Complications

Vascular complications have been reported and theorized to be associated with DCD liver grafts, including hepatic artery thrombosis, hepatic artery stenosis, portal vein thrombosis, and increased microthrombi formation. The incidence of hepatic artery thrombosis among liver grafts from DCD donors has been reported between 2.3–11.1% [3, 6, 7, 14, 23]. While there was a trend to increased hepatic artery thrombosis in DCD compared to propensity-matched DBD donors in a large retrospective analysis (4.8% vs 3.2%), it did not reach statistical significance. This study and others have not found an increased incidence of hepatic artery stenosis [7, 11, 14, 15]. One large single-center study from the United States did not find an increased incidence of hepatic artery thrombosis between DCD and DBD liver recipients but did identify an increased rate of hepatic artery stenosis of 16.6% compared to 5.4% [8]. Several studies have assessed for differences in portal vein thrombosis rates but have not found statistically significant differences between DCD and DBD allografts despite trends toward increased thrombosis in DCD allografts [8, 11].

Given the relative slow flow state and low blood pressure during the agonal phase of DCD donation, variation in the administration of heparin to the donor prior to withdrawal of care, and variation in length of stand-down time between declaration of death and incision time, concern has arisen about the potential for the formation of microthrombi in the capillaries of the hepatic arteries, particularly in the peribiliary plexus. However, pathological examination of the liver microenvironment after cold storage of discarded DCD allografts demonstrated no difference in microthrombi formation compared with DBD allografts, nor was there increased microthrombi in those recipients that did develop early hepatic artery thrombosis [24]. Despite the lack of a demonstration of microthrombi, attempts to improve outcomes by decreasing microthrombi have been made. One such modality is the infusion of tissue plasminogen activator (tPA) into the hepatic artery on the back bench or at the time of liver implantation with the intent of inducing lysis of potential microthrombi. A large metaanalysis evaluating the use of tPA infusion demonstrated comparable rates of hepatic artery thrombosis but improved one-year patient survival. [10].

To what extent ischemic reperfusion injury influences these vascular complications is unknown and a physiologic mechanism remains speculative at present. Interestingly, there has been a documented correlation between the rapidity of liver

extraction during DCD donation, which is necessarily more expedient than during DBD donation, and vascular injury, although reportedly none of these injuries precluded transplantation of the liver [3].

There are real difficulties and challenges when attempting to expand the liver donor pool to address the rising number of patients who would benefit from liver transplantation and subsequently perish on the list or become too sick for transplant. As discussed above, many of these complications are attributable to the DCD state and will hopefully improve with advancements in the donor process and ex vivo perfusion techniques.

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Ischemic Cholangiopathy

12

Kristopher P. Croome and C. Burcin Taner

Ischemic cholangiopathy (IC) has been described as the Achilles heel of donation after circulatory death (DCD) liver transplantation. Alternative names for IC include ischemic type biliary lesions (ITBL), nonanastomotic strictures (NAS), and post-transplant cholangiopathy. While no universally accepted definition of IC exists, a consensus survey by the Improving DCDD Outcomes in Liver Transplantation (IDOL) Consortium [1] defined it as the following:

- Ischemic cholangiopathy is defined as diffuse nonanastomotic biliary strictures that occur in a spectrum of clinical and radiologic severity following liver transplantation.
- Ischemic cholangiopathy must present within 12 months following liver transplantation.
- Ischemic cholangiopathy must be documented by endoscopic retrograde cholangiopancreatography (ERCP), percutaneous transhepatic cholangiography (PTC), surgically placed biliary catheter or magnetic resonance cholangiopancreatography (MRCP).
- Exclusion criteria include isolated anastomotic strictures and strictures in the presence of hepatic artery thrombosis.

Prior to knowledge of the association between DCD liver transplantation and IC, diffuse ischemic nonanastomotic lesions of the biliary tree had been described in the setting of hepatic artery thrombosis and ABO blood group–incompatible grafts [2–5]. The first descriptions of IC in the absence of these risk factors were published by Sanchez-Urdazpal et al from Mayo Clinic in 1992 and 1993 [6, 7]. The association between DCD liver transplant and IC was first described by Abt et al. in 2003 [8].

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Presentation

While many publications describe IC as presenting 1–6 months after liver transplant [8–10], some would argue that most patients display early signs of IC within the first 3–4 weeks after transplant . In our program, we routinely place a transcystic biliary catheter in all of our patients undergoing liver transplantation and perform a protocol cholangiogram on all patients on POD #21. This involves the placement of a 4 or 5Fr ureteral catheter secured with absorbable suture and a hemorrhoidal band placed on the cystic duct stump (Fig. 12.1). In our experience, even in patients who are clinical asymptomatic on POD#21, radiologic signs of early IC can be seen in most patients that will go on to develop clinically significant IC. In addition by 3–4 weeks following liver transplantation most patients who ultimately develop radiologic IC have significantly higher levels of alkaline phosphatase (AlkP) and bilirubin than patients who do not develop IC [11].

In most transplant programs where routine cholangiograms are not performed, patients will often be clinically asymptomatic during the initial post-transplant period. The diagnosis is made when abnormal biochemical liver tests such as elevated alkaline phosphatase and bilirubin are discovered [9]. A previous study demonstrated that two-month post–liver transplant serum alkaline phosphatase and bilirubin proved to have strong associations with the development of IC in a cohort of 89 DCD liver transplants at a single center. Inflection points for association with IC were alkaline phosphatase >300 U/L and bilirubin >2.5 mg/dL at 2 months following liver transplantation [12].

As IC progresses, patients frequently develop jaundice, cholestasis, and pruritis. Patients with milder forms of IC may remain relatively asymptomatic. Patients with severe IC may ultimately develop hepatocellular failure. Typically development of IC is accompanied by the formation of biliary casts, prestenotic dilations, and intrahepatic biloma formation. Patients with IC may be admitted to hospital multiple times for acute cholangitis and require the endoscopic or percutaneous placement of biliary drains.

Several distinct radiologic patterns of IC have been described, which are associated with different clinical courses [11, 13]:

- Diffuse Necrosis (Fig. 12.2).

These severe abnormalities of nearly the entire biliary system are identified soon after transplant. In our experience ischemic changes were detected 2–36 days following transplant. The 1-year graft survival in this group was 36% with all patients ultimately either undergoing re-transplantation or resulting in a patient death from IC-related complications [11].

- Bilateral multifocal/multifocal progressive (Fig. 12.3).

These patients begin with mild–to-moderate stenosis of the second-order and peripheral ducts and progressively worsen over time. Ischemic changes within this group are initially detected 14–60 days following transplant [11]. These patients may frequently languish with pruritus and recurrent cholangitis. A reasonable number of these patients may ultimately be listed for retransplant.

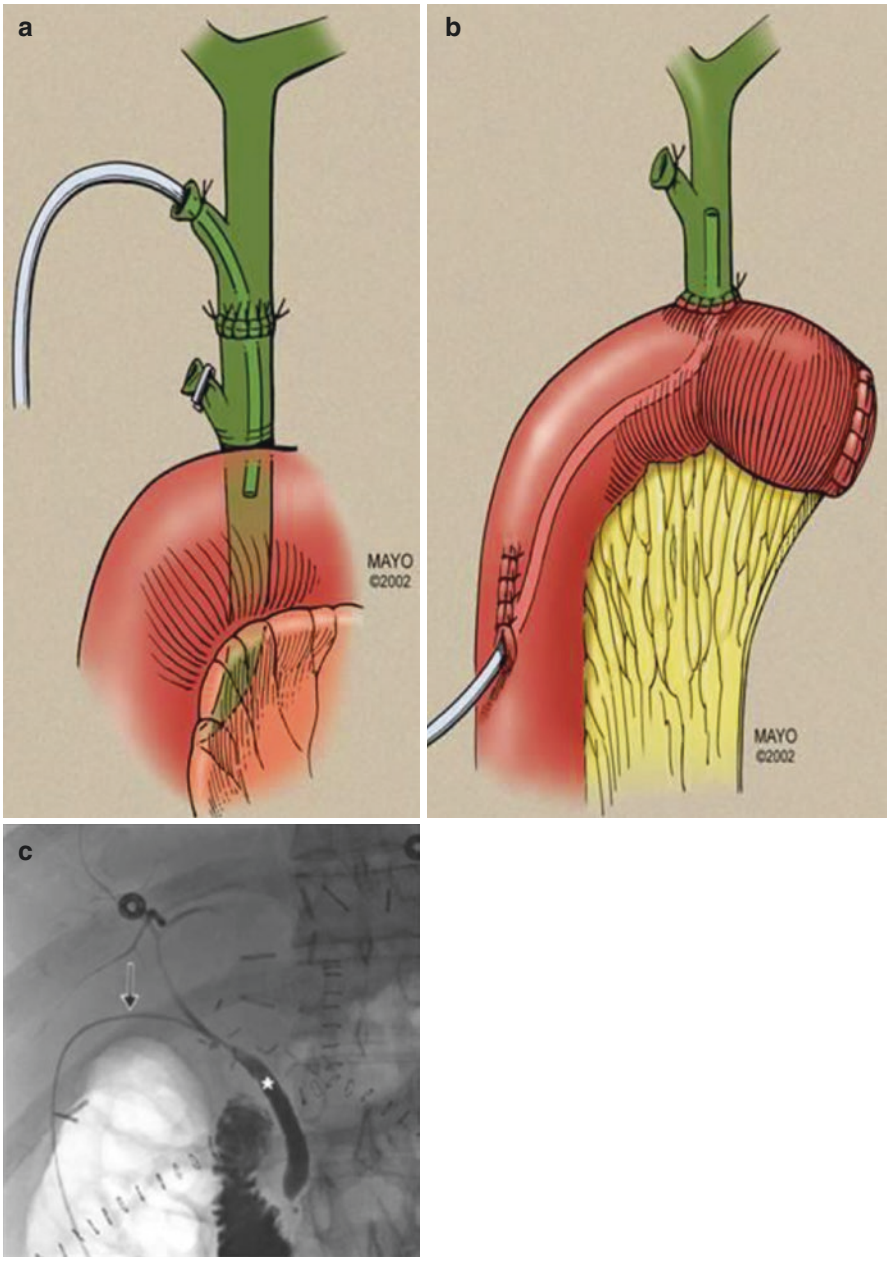
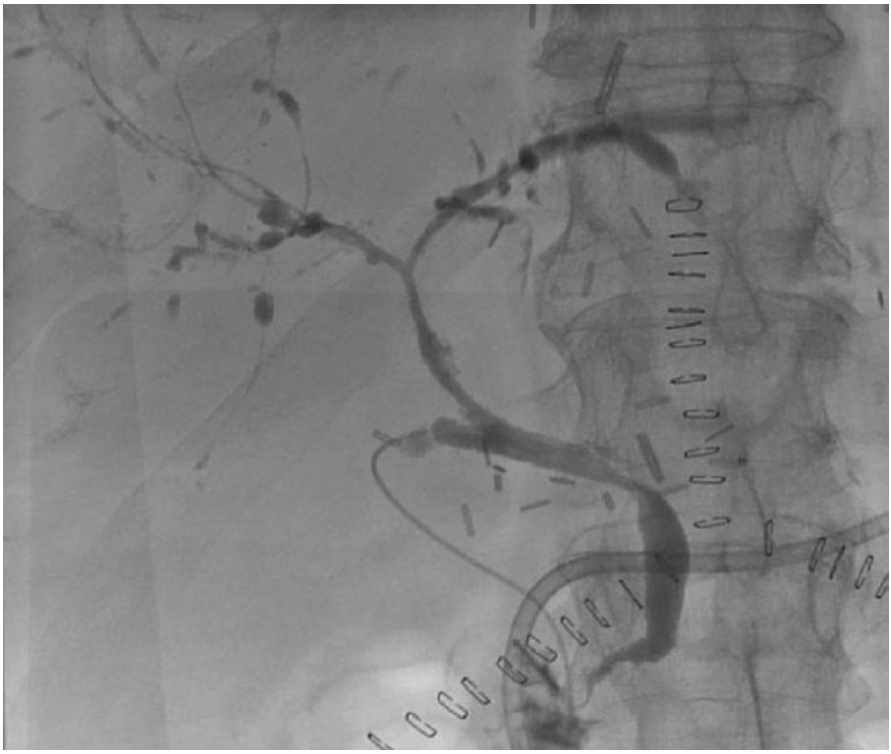


Fig. 12.1 Biliary tube placement. (**a**) and (**b**): Drawings show biliary tube placement (arrow) in duct-to-duct (**a**) and Roux-en-Y biliary-enteric (**b**) reconstruction. (**c**): Cholangiogram obtained through transcystic biliary tube (arrow) according to protocol on postoperative day 21. (**a**, **b**: Used with permission of Mayo Foundation for Medical Education and Research, all rights reserved)

The intrahepatic bile ducts are diffusely narrowed. The irregularities and filling defects suggest diffuse necrosis



14 days

Bilirubin 1.8
Alk phos 560

Fig. 12.2 Diffuse necrosis ischemic cholangiopathy

- Confluence dominant (Fig. 12.4).

These patients develop strictures confined to the biliary confluence, with relative preservation of the second-order and peripheral ducts. In this pattern, biliary abnormalities progress in severity over time but geographically never expand beyond the hilar confluence. Radiologic changes in this group are identified 20–178 days following transplant [11]. Many of these patients can be successfully managed long term with ERCP and stenting and frequently do not go on to need retransplantation.

- Minor Form (Fig. 12.5).

These patients may display mild radiologic abnormalities consistent with early IC but never go on to develop more extensive strictures. They may also demonstrate

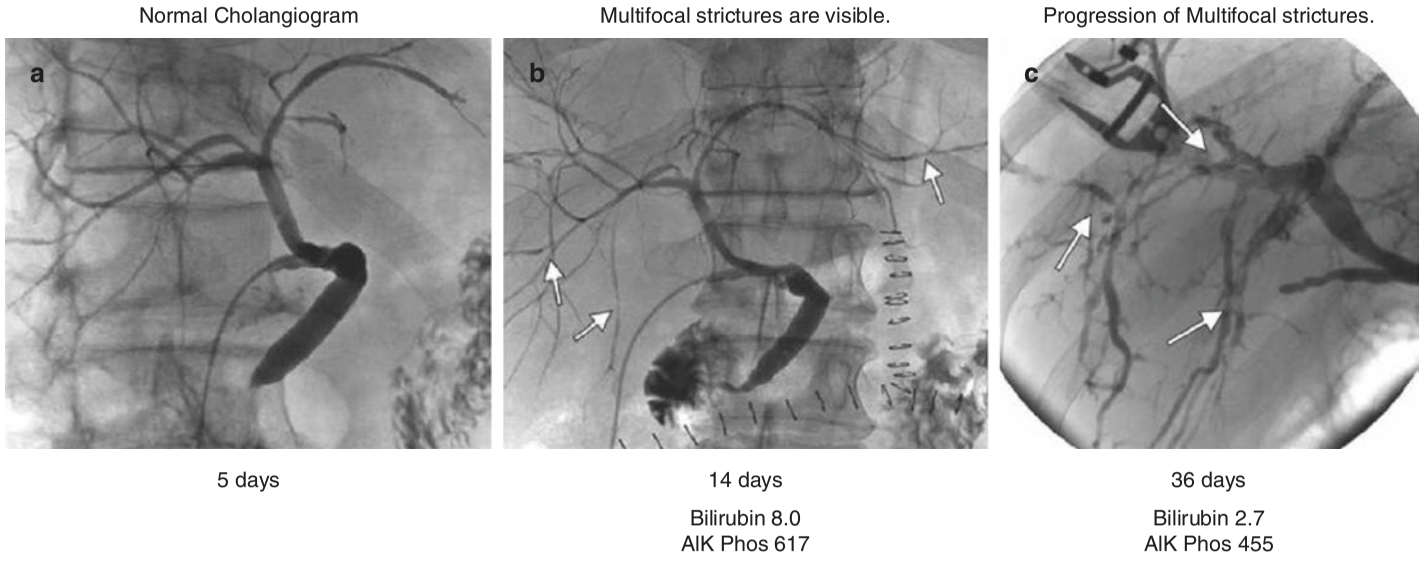


Fig. 12.3 Bilateral multifocal/multifocal progressive ischemic cholangiopathy

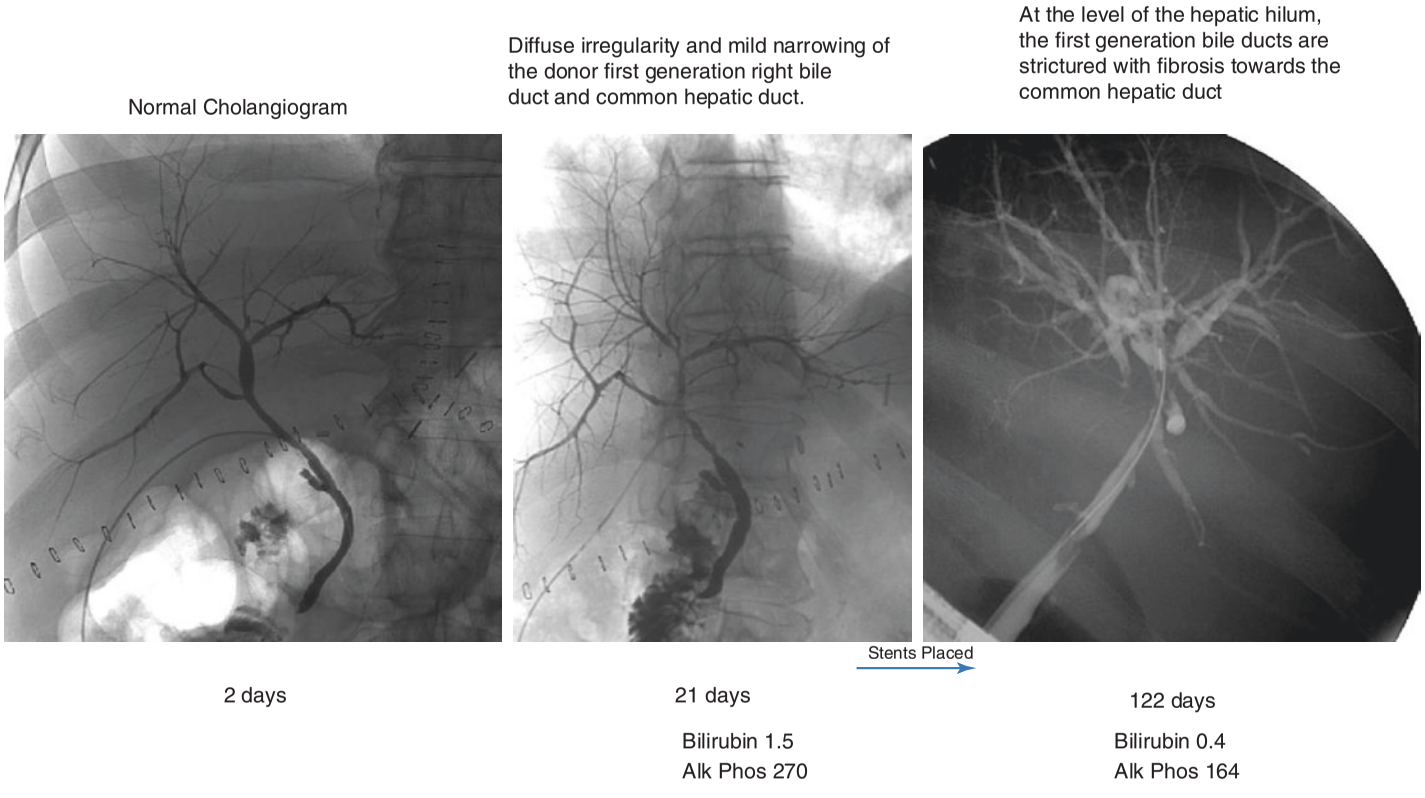
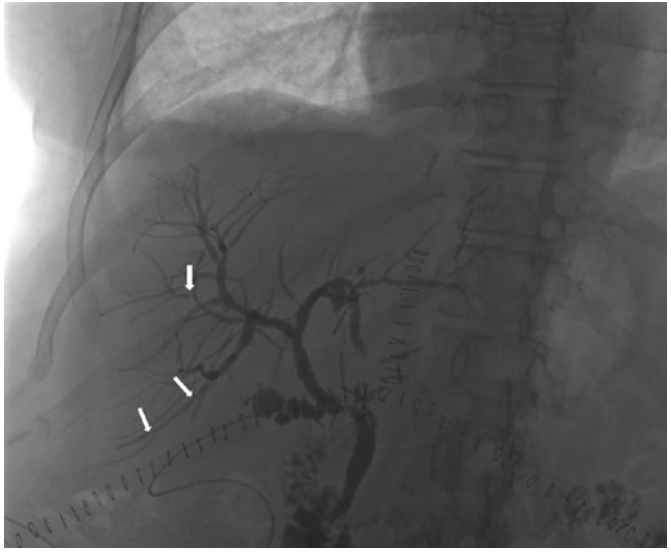


Fig. 12.4 Confluence-dominant ischemic cholangiopathy

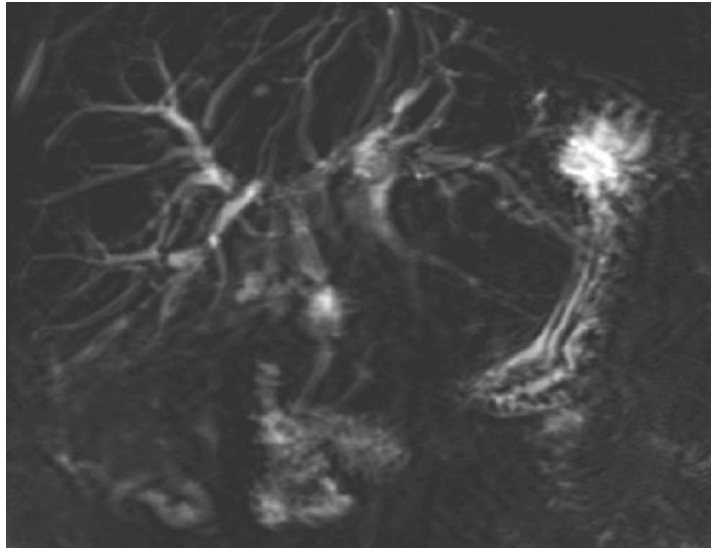
Mild irregularity in the peripheral ducts



21 days

Bilirubin 0.4
Alk Phos 132

Mild irregularity in the peripheral ducts



210 days

Bilirubin 0.4
Alk Phos 125

Fig. 12.5 Minor form ischemic cholangiopathy

a transient elevation of alkaline phosphatase but do not go on to develop cholestasis, pruritus, or cholangitis. These patients typically will not require long-term stent placement or retransplantation.

Alternatively Buis et al suggested a classification of biliary strictures based on location involved that divided the liver into zones A to D. The extrahepatic common bile duct, including the hilar bifurcation (zone A), the bile ducts between first- and second-order branches (zone B), the bile ducts between second- and third-order branches (zone C), and bile ducts in the periphery of the liver (zone D). In addition, the location of the strictures was categorized as left-sided, right-sided, or bilateral [14].

Frequency

The frequency of which IC is seen with DCD liver transplantation has varied in many previous publications. A meta-analysis investigating studies published up until 2009 demonstrated an IC rate of 8–38% for recipients of liver grafts from DCD donors compared to 0–8% for recipients of grafts from donation after brain-death (DBD) donors [15]. The studies included in this analysis were likely early in the learning curve of DCD liver transplant, as demonstrated by the low number of DCD grafts used in each of the studies [8, 10, 16–18]. Looking at IC rate in previously published studies with more than 50 grafts from DCD donors, IC rates range from 3–34% in recipients of DCD grafts and 0–7.9% in recipients of DBD grafts (Table 12.1) [17, 19–27]. A study examining waitlist outcomes of patients re-listed for IC using scientific registry of transplant recipients (SRTR) data, found that the number of patients receiving a DCD liver transplant that were listed for retransplantation decreased between 2002–2016 [28]. In this study 9.5% of patients who initially underwent a liver transplant with DCD liver grafts were relisted for biliary-related complications >14 days after transplant. These findings along with other studies [29] highlight that rates of IC have decreased over time. Looking at large single-center studies in which data is divided by era, IC rates have been reported in the range of 0–4% since 2012 (Table 12.2) [19, 23, 26, 30, 31].

Mechanism

Ischemia Reperfusion Injury

The association between ischemia reperfusion injury and IC is well established [32]. In contrast to blood supply of the liver parenchyma which is derived from both the portal vein and hepatic artery, blood supply to the biliary tree is mainly provided by the hepatic artery. This is demonstrated by necrosis and IC that is seen with hepatic artery thrombosis (HAT) following liver transplantation. The strong similarities between IC seen in the setting of HAT and IC seen in DCD liver transplantation support the role of ischemia in the development of IC. A whole chapter in the present book has been dedicated to ischemia reperfusion injury (Chap. 6).

Table 12.1 Frequency of IC in DCD and DBD recipients

			DCD LT			DBD LT		
Author	Center	Pub. year	Total (*N*=)	IC (*N*=)	% IC	Total (*N*=)	IC (*N*=)	% IC
Croome	Mayo Clinic, Florida	2017	300	35	11.7	300	6	2.0
Laing	Birmingham, UK	2016	187	17	9.1	187	2	1.1
DeOliveira	King's College, London, UK	2011	167	4	2.4	333	0	0.0
de Vera	Pittsburgh	2009	141	23	16.3	282	2	0.7
Bohorquez	Ochsner, New Orleans	2017	100	3	3.0	435	2	0.5
Firl	Cleavland Clinic	2015	92	6	6.5	92	0	0.0
Foley	University of Wisconsin	2011	87	30	34.5	1157	12	1.0
Kollman	University of Toronto	2018	77	2	2.6	706	13	1.8
Dubbeld	Rotterdam, the Netherlands	2010	55	13	23.6	471	37	7.9
Chan	University of Washington	2008	51	7	13.7	334	4	1.2

Table 12.2 Frequency of IC in DCD Recipients in the most Recent Era

Center	Era	Total (*N*=)	IC (*N*=)	IC
Mayo Clinic Florida	2010–2015	100	4	4%
Oschsner Clinic	2010–2015	100	3	3%
University of Toronto	2009–2017	77	2	2.6%
University of Western Ontario	2011–2016	38	1	2.6%
Indiana University	2011–2015	38	2	5.3%

Several mechanisms have been proposed including direct ischemic damage to the biliary epithelium, increased susceptibility of the biliary epithelium to reoxygenation injury, and peribiliary microcirculation disturbance. Direct ischemic damage may occur during the donor withdrawal phase prior to cold flush or during cold storage prior to reperfusion in the recipient. Multiple studies have shown that the length of donor warm ischemia time (DWIT) is a significant predictor of the outcomes in DCD liver transplantation [25, 29, 33, 34].

Previous authors have demonstrated that the rate of toxic reactive oxygen species formation by bile duct cells was five-fold greater than for hepatocytes during reoxygenation [35]. During cold storage, cellular metabolism and the need for oxygen, although reduced, never reaches a complete standstill. This results in mitochondrial derangements such as intracellular depletion of adenosine triphosphatase (ATP). During the first 10 min of reperfusion, hypoxic mitochondria are known to excessively consume oxygen with the release of ROS due to electron leakage within the electron transport chain [36]. This may lead to danger-associated molecular patters (DAMPs) that activate the immune system, leading to cell death and apoptosis [37, 38]. Advocates of hypothermic machine perfusion have suggested that oxygenation of the mitochondrial electron chain prior to exposure to blood is possibly a key element for protection against injury [39].

Microthrombi

When endothelial cells of the small arteries are damaged due to ischemia or coagulation activation microthrombi may occur [40, 41]. The obligatory acirculatory wait time during donor warm ischemia time (DWIT) promotes stasis of blood and theoretical microthrombi formation in the peribiliary microcirculation which could lead to ischemia, fibrosis, and stricture formation [23, 24]. Microthrombi formation has therefore been described as one of the potential mechanisms leading to the development of IC. Despite this representing a potential mechanism for IC, a previous study has shown no difference in microthrombi formation between liver grafts coming from DCD and DBD donors [42]. Other studies have found no association between microvascular thrombosis and IC [43, 44]. The role of microthrombi formation in the development of IC is still not entirely known at this time, and controversy exists on the utility of tPA for DCD liver transplantation. The topic of tPA in DCD transplantation is discussed in Chap. 8.

Immunologic

Immune-mediated injury to the biliary epithelium has been proposed to play a role in the development of IC. A high incidence of IC has been demonstrated in ABO-incompatible grafts [45]. Blood group–related antigens are expressed on bile duct epithelium; therefore, these antigens may be susceptible to immune-mediated pathogenesis. Bile ducts have also been shown to be involved in chronic rejection with many studies showing a significant association between rejection and IC. Additional evidence for this mechanism is demonstrated by the higher incidence of IC in patients who have undergone transplantation for primary sclerosing cholangitis (PSC) and autoimmune hepatitis [14].

Bile Salt Toxicity

Hydrophobic bile salts are cytotoxic due to their detergent properties toward cellular membranes of biliary epithelial cells [46]. The long recognized toxic effects of bile have led to flushing of the biliary tree becoming standard practice during liver procurement. No good studies have investigated the optimal solution to flush the biliary tree as many surgeons used cold saline while others use organ preservation fluids.

Infection

Persistent cytomegalovirus (CMV) infection has been demonstrated in liver bile ducts that developed vanishing bile duct syndrome and chronic rejection [47]. Previous authors have postulated that CMV infection increases alloantigen expression, making bile ducts more susceptible to immunologic attack [48]. Other studies have demonstrated no association between CMV infection and

IC [49]. Therefore the role, if any, of CMV infection in the pathogenesis of IC remains unknown.

Associated Factors

Many studies have described factors associated with graft loss following DCD liver transplantation. While many of these studies do not specifically look at the risk of IC, IC likely represents one of the leading causes of graft loss in DCD liver transplantation. Few studies have an adequate number of cases of IC to perform statistically reliable prediction models. Nonetheless, several factors associated with IC are routinely described.

Cold Ischemic Time

From the first descriptions of IC in DBD liver grafts, prolonged cold ischemia time (CIT) was demonstrated to be a predictive factor [6, 7]. A single-center study on DCD liver transplantation demonstrated CIT ≥ 9 h to be predictive of the development of IC [17]. A large registry study demonstrated that each hour of CIT was associated with a 6% increase in the relative rate of graft failure when analyzed continuously. When analyzed categorically, even moderate CIT (6–10 h) was associated with a significant 64% higher graft failure risk (compared to those less than 6 h). Compared to those with CIT less than 6 h, CITs greater than 10 h were associated with at least a twofold risk of graft failure and this hazard ratio approached a fourfold increase when CIT was greater than 13 h [33]. In light of this data, efforts to minimize CIT as much as possible when utilizing DCD liver grafts should be made.

Donor Warm Ischemia Time (DWIT)

Perhaps, one of the most widely accepted negative predictor of outcome with DCD LT is prolonged donor warm ischemia time (DWIT) [25, 29, 33, 34]. Since DWIT is unique to DCD grafts, this has been implicated as one of the primary contributors to the increase in IC seen with DCD liver transplantation [50, 51]. A previous registry study demonstrated that DCD liver grafts with DWIT 35 minutes or greater had a significant 1.8-fold higher graft loss rate compared to those with DWIT less than 15 min [33]. A study that showed improved results with DCD liver transplantation in the US over time found a concomitant decrease in the proportion of donors with DWIT longer than 30 minutes in the modern era. That study speculated that this was one of the contributing factors to the improved graft survival seen in the modern era [29]. Since DWIT is somewhat of a crude variable, many authors have tried to differentiate DWIT based on various parameters such as oxygen saturation and mean arterial pressure (MAP). The time from a drop below a certain threshold for hemodynamic parameters (systolic blood pressure (sBP) or oxygen saturation (O2 sat)) until cold organ flush/cross clamp in the donor is known as functional DWIT (f-DWIT).

One previous study identified a period of MAP <60 mm Hg before circulatory arrest longer than 20 minutes increased the risk for graft loss [52]. Another study suggested that a drop in SpO2 < 80% for >13 minutes was associated with higher graft loss [53]. A large single-center study found that the time from asystole to cross clamp was the only significant f-DWIT predictor of IC [50]. On multivariate analysis each-minute increase in asystole–cross clamp duration was associated with a 16% increase in odds for the development of IC. This manuscript advocated hesitancy in accepting DCD livers with asystole–cross clamp period greater than 10 minutes. In our center we will accept Total DWIT of up to 50 minutes but place a stronger emphasis on asystole–cross clamp time. An entire chapter in the present book is dedicated to WIT in DCD liver transplantation (Chap. 5).

Donor Age

Despite recent single-center reports that have shown excellent results with older DCD donors [53, 54], advanced donor age appears to have some association to the development of IC. Previous studies looking at DBD donors found that advanced donor age was a risk factor for IC development [55, 56]. Early DCD series described a significantly increased risk for IC using livers from DCD donors >40–45 years [10, 25]. Another study showed increased risk of IC when using livers from DCD donors >60 years [22]. Multiple previous reports have suggested that donors 50 years or older are a risk factor for graft loss after DCD LT [33, 57]. A large registry study found that older donor age (>50 years) was associated with a 39%–88% higher adjusted risk of graft failure compared to donors age 18–50 years (donor age 50–60 years, HR1.39, donor age ≥ 60 years, HR 1.88) [33]. A large multicenter study found a slight trend of higher IC rates in DCD donors ≥50 years of age (11.6%) compared to DCD donors <50 years (7.6%). Despite this, graft survival was not significantly different between the two groups in that study [53]. Advanced donor age should be considered when evaluating a DCD donor; however in appropriately selected donors and recipients, advanced donor age unto itself should not be used as an absolute contraindication to the usage of these grafts.

Donor Liver Steatosis

The usage of liver grafts from DCD donors with macrosteatosis (≥ 30%) has generally been avoided given the additive or potentially multiplicative risk from using donor livers that are both steatotic and from a DCD donor [58]. Several previous reports have suggested that brain death donors with mild–to-moderate macrosteatosis may be at an increased risk of IC [59, 60]. Given the inherent concerns with IC development in all DCD liver grafts, it seems reasonable that there has been a reluctance to potentiate this risk with the addition of donor macrosteatosis [19].

A multicenter study was recently published that examined the effects of donor graft macrosteatosis on both peri-operative and long-term outcomes following DCD LT [61]. In that study, patients undergoing DCD LT with a moderate macrosteatosis

(30–60%) donor liver had a higher rate of post-reperfusion syndrome (PRS) (53.9% vs. 26.2%; $p = 0.002$), post-reperfusion cardiac arrest (7.7% vs.0.3%; $p < 0.001$), primary non-function (PNF) (7.7%vs.1.0%; $p = 0.003$), early allograft dysfunction (EAD) (70.8%vs.45.6% and 8.3%; $p = 0.02$), and acute kidney injury (AKI) (39.1%vs.19.4%; $p = 0.02$) than patients undergoing DCD LT with a no-steatosis donor liver. No difference in any of the above-mentioned peri-operative complications was seen between patients undergoing DCD LT with a mild macrosteatosis (5–29%) donor liver and those undergoing DCD LT with a no-steatosis donor liver except for a higher rate of EAD (56.8% vs. 45.6%; $p = 0.04$). No difference in the rate of IC or graft survival was seen when comparing the moderate macrosteatosis, mild macrosteatosis, and no-steatosis groups. An abstract has also previously been published investigating 27 recipients of DCD LTs with 30% ≥ steatosis (combined micro and macro). In that analysis patient and graft 1-yr survival rates were 91.8% and 90.4% for DCD livers with <30% steatosis vs. 92.6% and 92.6% for those with ≥30% combined micro−/macrosteatosis ($p = 0.47$) [62]. A single-center study from the United Kingdom evaluated histology reports from 233 DCD LT for steatosis [63]. In their multivariate analysis, macrosteatosis and microsteatosis were not found to impact graft survival. Only 5/233 DCD LT had moderate macrosteatosis; therefore the analysis was largely based on mild macrosteatosis (94/233). This study therefore does not provide data on the impact of moderate macrosteatosis in DCD LT. Another study demonstrated that macrosteatosis ≥20% was associated with a 2.97 fold increase rate of graft loss [64]. In general, most programs avoid moderately steatotic DCD livers; however given the limited data available, definitive conclusions about the implications of steatosis on IC are lacking.

Donor Weight

The impact of donor weight on the development of IC was first described in a study that showed a connection between donor weights >100kg and IC [17]. Another large registry study demonstrated that DCD donors with a weight > 100 kg had a hazard ratio of mortality of 1.39 (CI 1.02–1.89) compared to lower weight DCD donors [33]. High BMI in these studies has been shown to be an important predictor even in the absence of liver steatosis. It has been hypothesized that larger donor weight may lead to an inadequate flush of the preservation solution in the biliary tree. For less-experienced DCD procurement teams, higher BMI DCD donors may also be more technically challenging, resulting in longer time from incision until cold perfusion of the liver.

Roux en Y Hepatoicojejunostomy

A previous multicenter study identified a higher risk of intrahepatic biliary strictures in DCD recipients who underwent a Roux-en-Y hepaticojejunostomy for the biliary reconstruction. The authors of this study hypothesized that increased exposure of ischemic bile ducts to enteric bacteria and toxins in the setting of a

Roux-en-Y may predispose to the development of IC [1]. Moreover several previous studies of patients undergoing living donor or DBD liver transplant have shown increased risk of biliary strictures with the use of Roux-en-Y hepaticojejunostomy [65, 66].

Recipient Factors

While donor factors are of extreme importance, recipient factors also likely contribute to the development of IC. Since an entire chapter of the present book is dedicated to recipient selection (Chap. 9), this will not be covered in depth here. In general most authors would suggest that DCD livers should be used for recipients with low surgical difficulty so that CIT and blood loss can be minimized. Also, recipients in the ICU at the time with higher end-stage liver disease (MELD) scores or on vasopressors are likely more prone to developing IC. The transplant centers described above (Table 12.2), that have achieved lower IC rates, all preferentially utilize DCD livers in patients with lower biologic MELD scores and lower surgical difficulty such as those patients needing liver transplantation with HCC.

Treatment

Treatment of IC can be difficult given the often diffuse multifocal lesions of the biliary tree. Initial therapy primarily focuses on addressing biliary obstruction and treatment of infection (cholangitis). While milder cases of IC can sometimes be successfully managed with percutaneous or endoscopic drainage and stenting; more severe cases will often ultimately require retransplantation.

Ursodeoxycholic Acid

Ursodeoxycholic acid (UDCA) is established in the treatment of primary biliary cirrhosis (PBC) and has been demonstrated in several randomized trials to improve biochemical liver function as well as improve long-term survival [67, 68]. It has also been described as an adjunct treatment in addition to ERCP therapy in the setting of common bile duct stones/casts [69]. While it has been used in the setting of IC, there are no trials that have demonstrated its benefit in this capacity.

ERCP

The majority of studies describing biliary strictures following DCD liver transplantation utilize ERCP interventions. ERCP is useful in removing biliary sludge and casts from the biliary tree. Balloon dilation of accessible strictures and placement of plastic stents with stent exchange every 3 months is also frequently performed [70, 71]. Data concerning endoscopic treatment of IC is inconsistent, possibly because

of the small patient numbers published and the different endoscopic therapeutic approaches. Success rates vary in the range of 0–70% [72, 73]. In cases of confluence dominant or the minor form of IC, endoscopic therapy may be a definitive solution; however in many cases of IC, it is frequently used for symptom management and as a bridge to retransplantation [28].

High Hepaticojejunostomy

A previous report demonstrated that resection of the extrahepatic ducts and high hepaticojejunostomy was an effective approach for select patients with confluence dominant IC limited to the hepatic bifurcation [74]. This study demonstrated persistent improvement in 14 of 16 (88%) of patients. In patients with confluence dominant IC who are stent dependent, this may be a reasonable approach. High hepaticojejunostomy has no role for patients with bilateral multifocal/multifocal progressive or diffuse necrosis IC.

Retransplantation

While non-surgical management such as ERCP and stenting can be effective for some patients with confluence dominant or the minor form of IC, a proportion of patients with IC will ultimately require consideration for retransplantation. In patients who develop IC and who may require retransplantation, there is currently no standardized paradigm for expedited access to retransplantation in the United States. Unlike patients who develop primary non-function, who often have higher calculated model for end-stage liver disease (MELD) scores, or patients with early hepatic artery thrombosis, who receive MELD exception points, patients with IC often languish on the waiting list once relisted due to lower MELD scores. These patients may receive non-standard MELD exceptions in the UNOS system, through the national review board (or previously through regional review boards). The current UNOS guidelines for non-standard MELD exception for IC give the following guidance [75]:

Patients with a prior DCD transplant who develop IC and that demonstrated two or more of the following criteria within 12 months of transplant should be considered for MELD exception:

- Persistent cholestasis as defined by abnormal bilirubin (greater than 2 mg/dl).
- Two or more episodes of cholangitis with an associated bacteremia requiring hospital admission.
- Evidence of nonanastomotic biliary strictures not responsive to further treatment.

A previous study demonstrated that patients re-listed for IC following DCD liver transplant had higher waitlist mortality than patients with exceptions for hepatocellular carcinoma and hepatopulmonary syndrome [28]. This study demonstrated a 16.2% mortality for patients listed for retransplantation for IC at 24 months following listing. In addition, it has been shown in previous work that patients relisted

following DCD LT who receive MELD exception scores have superior waitlist survival compared with both patients who do not receive exception scores and relisted patients who did not apply for exception scores [76].

Outcomes

While the outcomes of DCD liver transplant have substantially improved over time, patients who develop IC undoubtedly have inferior survival. Chap. 10 of the present book looks at overall outcomes following DCD liver transplantation. Few studies exist with large enough cohorts of patients receiving DCD liver transplant and ergo patients who developed IC to provide a meaningful survival analysis following development of IC. A large single-center study demonstrated graft survival of 59.4%, 37.4%, and 27.2% in recipients of DCD liver transplant that developed IC at 1, 3, and 5 years, respectively [19]. This study found that recipients of DCD liver grafts who developed IC had inferior graft survival compared with both the recipients of DCD liver grafts who did not develop IC and the propensity-matched cohort of DBD liver graft recipients; no difference in graft survival was seen between the recipients of DCD who did not develop IC and the recipients of DBD liver grafts (Fig. 12.6). Of the 35 patients who developed IC,

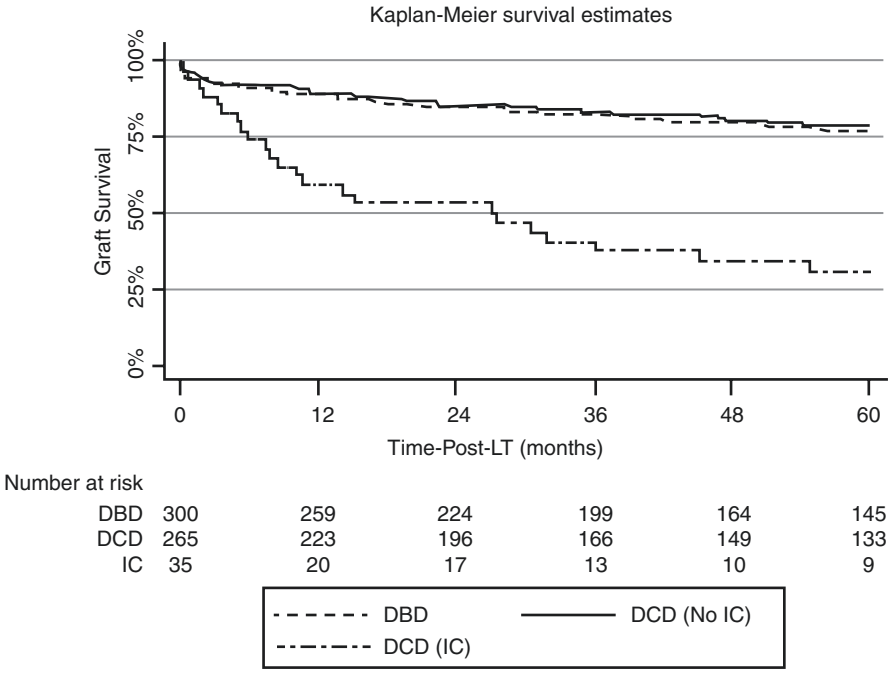


Fig. 12.6 Graft survival comparison in DCD LT patients who developed IC compared to DCD LT patients who did not develop IC and DBD LT matched cohort

16 were retransplanted while 8 patients died between 1–68 months following the diagnosis of IC. These data highlights the fact that IC is the leading cause of graft loss in DCD LT.

Quality of Life

Quality of life following DCD liver transplant has previously been evaluated in two single-center studies [18, 77]. In the larger of these studies looking at 300 DCD liver transplants, quality of life based on SF-12 questionnaire was not significantly different between DCD and DBD groups, nor was there any difference in pruritus score, need for antibiotics, or requirement of ERCP >6 months following liver transplant. In this study there was a low rate of IC (11.7%). These results are in contrast to the second study that found inferior QOL in 30 patients undergoing DCD liver transplant compared to 60 patients undergoing DBD transplant. That study found that patients receiving a DCD liver transplant who developed IC had a significantly lower QOL than the group of patients receiving a DCD that did not develop IC.

Economic Impact

The economic impact of DCD liver transplantation is obviously linked to outcomes including the frequency of problems such as IC**.** A study by Jay et al. demonstrated that post-transplantation costs were 25.2% higher for DCD recipients compared to DBD recipients after adjusting for recipient characteristics [78]. It should be noted that in that study a very high rate of IC was observed (44%). One-year costs were increased for recipients with IC or retransplantation by 53% and 107%, respectively. In subsequent studies that have demonstrated low rates of IC, the economic cost of DCD transplants may be similar to DBD transplant. Regardless, there is likely little debate that in patients who develop IC, costs are substantially increased even if they do not ultimately require retransplantation. One facet that is often ignored in many cost analyses is the costs for patient on the waiting list prior to transplant. Since the utilization of DCD livers has the potential to significantly expand the donor pool and thus decrease wait time for transplant, a low rate of IC may be more than offset by cost savings by timelier transplant of patients on the waiting list.

Prevention

tPA

While the exact mechanism for the higher rate of IC in DCD donors is not clearly defined, microthrombi formation within the biliary ductal circulation has been suggested as a one potential mechanism. Various tPA protocols have been employed

that differ in both the timing and type of thrombolytic flush given. Despite the enthusiasm surrounding the utilization of tPA in DCD donors, the actual benefits are debated [79]. A study performing liver biopsies at different time points during graft preservation showed no difference in microthrombi between liver grafts coming from DCD and DBD donors [42]. In addition, the authors showed no correlation between microthrombi formation and the development of IC. Despite these findings, several publications have shown significant reduction in the incidence of IC in LT using DCD livers after adopting protocols involving tPA compared to historical cohorts. A recent systemic review identified three published retrospective studies (two from the same institution) and one conference abstract with a prospective randomized/non-randomized study, all of which described tPA protocols [80]. Two of these retrospective studies demonstrated a reduction in the incidence of IC/ITBL following the adoption of a tPA protocol while the other retrospective study and the randomized study demonstrated no difference [81–83]. Although the authors of the two positive studies showed a significant reduction in the incidence of IC, they acknowledged that other changes in both procurement technique and patient selection occurred between the two compared era cohorts. The value of tPA therefore remains somewhat debated and likely additional studies are needed before ubiquitous adoption of tPA use in DCD LT can be recommended. A full chapter of the present book is dedicated to the role of tPA and DCD liver transplant (Chap. 8).

Backtable Flush

At our center we strongly believe in the importance of backtable flush for all DCD liver grafts. We routinely flush the liver graft on the back table at the time of procurement until there is no visible blood in the effluent. In some grafts this may take 4–5 additional liters of flush. We also routinely flush the liver with an additional liter containing heparin prior to implantation. Previous authors have suggested that additional arterial backtable pressure perfusion may reduce the development of IC [84].

UW Versus HTK Solution

Several studies have suggested the superiority of low-viscosity HTK for flush in preventing biliary complications [84, 85]. Despite this, an analysis of United Network for Organ Sharing data on >17,000 liver transplants demonstrated a significantly increased risk of graft loss in livers preserved with HTK, particularly among those arising from DCD donors [86]. An analysis of eurotransplant data evaluating >42,000 liver recipients found similar findings [87]. Given large registry studies, it seems unlikely that low-viscosity HTK provides better preservation of the biliary tree.

Machine Perfusion

Hypothermic machine perfusion, normothermic regional perfusion, and ex vivo normothermic machine perfusion may have benefits in the reduction of IC. Several chapters (Chaps. 13, 14, and 15) of the present book are dedicated to the role of machine perfusion and DCD liver transplant and so it will not be discussed here.

N-Acetylcysteine (NAC)

NAC is a rich source of sulfhydryl (SH) groups which are important for replenishing glutathione (GSH) stores. GSH acts as a free radical scavenger to decrease damage caused by toxic-free radicals. While no study exists describing the use of NAC specifically in DCD liver transplantation, it has been used in some clinical trials in patients receiving liver transplant to improve the function of the liver graft [88, 89]. Our center routinely uses a NAC infusion for DCD liver transplant. Our protocol involves a bolus of 150 mg/kg given over 1 hour prior to reperfusion followed by an infusion of 150 mg/kg given for 72 hours. Our current rate of IC is less than 4%; however whether NAC provides any benefit in the reduction of IC remains unknown.

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Hypothermic Machine Perfusion in Liver Transplantation Using Grafts From Donation After Circulatory Death Donors

13

Andrea Schlegel, Matteo Mueller, and Philipp Dutkowski

Introduction

Machine perfusion of organs before transplantation is currently a hot topic, as many organs are declined due to the lack of methods ensuring graft quality, for example, steatotic grafts or livers donated after circulatory death (DCD) [34, 69]. The utilization rate of marginal livers is therefore highly different between centers and countries and is influenced by donation rates, risk strategies, and transplanting surgeon's experience [9, 34]. Often, however, the decision to reject livers is not based on objective parameters, but rather on gut feeling [69]. In contrast, machine perfusion concepts would potentially offer the advantage to test organ function before transplantation and to optimize metabolic deficiencies. Despite numerous research efforts in this field during the last 20 years, it remains unclear which perfusion procedures and which ex vivo viability tests are most reliable and also practical today.

This chapter provides an overview of current machine liver perfusion techniques and focuses on different achievements through hypothermic perfusion of liver grafts from DCD donors.

Machine Liver Perfusion Concepts

Two perfusion approaches for liver grafts have been recently introduced in clinical practice, which differ fundamentally in terms of their logistic efforts and protective mechanism. Firstly, an upfront machine perfusion, immediately after standard procurement, with the aim to replace conventional cold storage [45]. For this purpose,

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the organ is placed directly after procurement on a transportable device and undergoes continuous perfusion until implantation in the recipient center [16, 45]. Sophisticated and expensive systems are used for this approach, mostly at normothermic (NMP) or subnormothermic (SMP) temperatures, with a blood-based perfusate (Organox®, Transmedics®, Liver Assist®) [6, 7, 16, 21, 37, 45]. A modification of this technique involves an even earlier start of machine liver perfusion already in the donor, e.g., normothermic regional perfusion (NRP), instead of the routine super rapid cannulation and cold in situ organ flush [24, 66, 67]. A logical extreme would be the combination of NRP and NMP, in order to keep the perfused organ without any intermittent cooling and therefore preventing interruption of normothermic perfusion until implantation. This concept leads to complete abundance of cold ischemia and has been introduced as "ischemia free organ transplantation" (IFOT) in a few human livers [23]. Although such procedure avoids repeated temperature changes during liver preservation, the enormous technical complexity appears as a clear hurdle for a broad clinical introduction. Additionally, the IFOT technique should be compared to other perfusion techniques.

An alternative machine liver perfusion approach is applied endischemically, after initial cold storage and liver transport to the recipient center (repair centers) [36, 57, 71]. Subsequently, organs are perfused for a relatively short period prior to implantation. Such endischemic perfusion techniques have been applied at various temperatures, including normothermic and hypothermic temperatures or by a combination of both conditions, defined as controlled oxygenated rewarming (COR) [41, 64]. Although these techniques are logistically easier and cheaper, because a device transport is not necessary, the initial period of cold ischemia induces severe metabolic depletion before perfusion is started, particularly in high-risk grafts, such as steatotic livers or livers from DCD donors [4, 38, 69].

Besides the timing of machine perfusion, the perfusate composition varies substantially among techniques at all temperatures [7, 56]. While normothermic or subnormothermic perfusions require the presence of red blood cells or artificial oxygen carriers, cold perfusion technologies rely on the presence of dissolved oxygen in the perfusate [7, 58]. Accordingly, hypothermic oxygenated perfusion (HOPE) is performed with high oxygen concentrations (>80 kPa) at low temperatures between 8–12 degrees (Fig. 13.1) [11, 49, 58, 59].

Of note, as liver architecture always implies sinusoidal fusion of both the portal and the arterial system, perfusion of human or pig livers through the portal system reaches every single liver cell (Fig. 13.1), including the tip of the extrahepatic bile duct and all epithelial cell layers [52]. The benefit of dual perfusion in the cold appears therefore unclear. While a direct clinical comparison of hypothermic single vs. dual perfusion has not been performed yet (HOPE vs. D-HOPE), recent experimental studies showed no difference between single and dual liver perfusion even under subnormothermic conditions in rats [5]. An additional often underestimated but important factor is the much lower perfusion pressure needed during hypothermic liver perfusion to avoid sinusoidal shear stress at low temperatures. Therefore, perfusion flow should be approximately ten-fold reduced during hypothermic liver perfusion compared to normothermic perfusion [49].

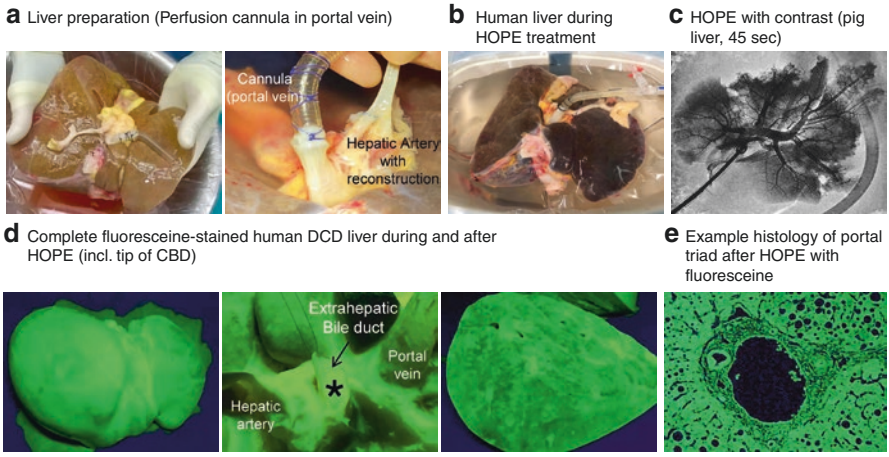

Fig. 13.1 Example of hypothermic oxygenated perfusion (HOPE) of DCD livers prior to transplantation: (**a**, **b**): Preparation (**a**) of human livers and hypothermic oxygenated perfusion (HOPE) (**b**), performed with UW gluconate (Belzer Machine perfusion solution) at 10 °C with a high oxygen concentration of 80–100 kPa and a perfusion pressure limited to 3 mmHg. (**c**) Angiograpy confirmed rapid and complete liver imaging through single portal vein perfusion of pig DCD liver example with the HOPE technique. (**d**) The entire liver including the tip of the extrahepatic bile duct is entirely stained by fluorescein during early HOPE through the portal vein alone. HOPE with fluorescein was performed in discarded human DCD liver (concentration: 0.5 g/5 ml) through the portal vein. Images obtained under dark light confirmed complete perfusion of liver graft by macroscopy and microscopic assessment of portal triad (**e**)

Protective Mechanism of Cold Liver Perfusion

Ischemic cells, regardless of the organ type, experience a rapid loss of nucleotides, and most adenosine triphosphate (ATP)-dependent processes are subsequently on hold [39, 61]. This phenomenon is paralleled by a massive accumulation of nicotine adenine dinucleotide (NADH), citric acid cycle- and purine-metabolites, mainly succinate, hypoxanthine, and xanthine (Fig. 13.2) [14, 40, 60]. Upon normothermic liver reperfusion, accumulated electron donors, such as NADH and succinate, deliver high amounts of electrons to mitochondrial complex I and II, while ADP is not yet available for ATP synthetase, due to previous nucleotide breakdown during ischemia [14, 63]. This results in over-reduction of complex I, either through electron back flow through complex II (reverse electron transfer, RET) or by accumulation of NADH. Both modes lead to a dissociation of reduced flavin mononucleotide ($FMNH_2$) from mitochondrial complex I, with sudden oxidation to FMN and reactive oxygen species (ROS) release [19, 40, 44] (Fig. 13.2). Of note, RET supports the highest rate of ROS generation in mitochondria [15, 29], and complex I has been identified as the main site of ROS production [44, 62]. Any machine perfusion with an oxygenated perfusate after ischemia will therefore induce reperfusion injury to some extent. Such mitochondrial ROS release occurs within the first minutes of reintroduction of oxygen to

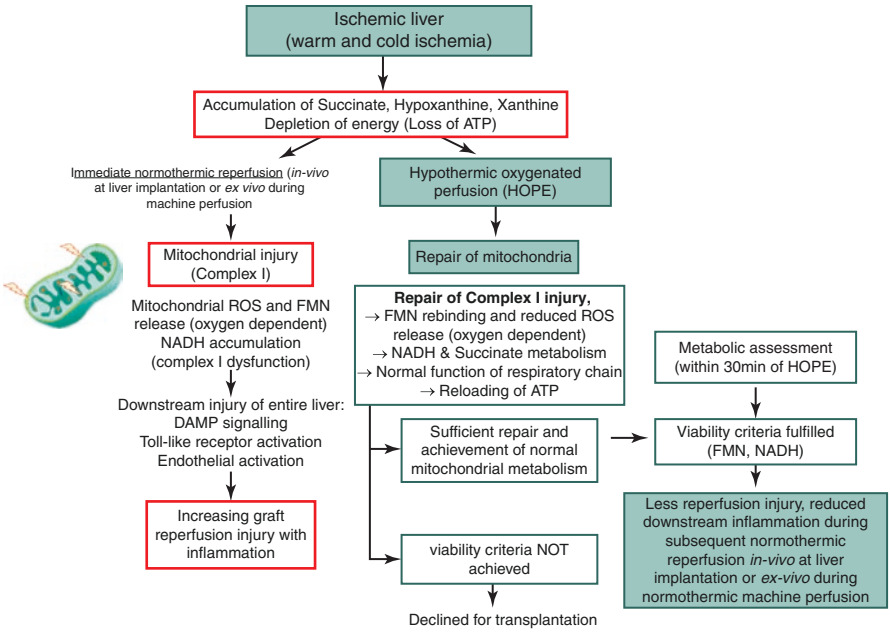

Fig. 13.2 Mechanism of liver protection and viability assessment through hypothermic oxygenated perfusion. This chart presents the underlying mechanisms of liver injury during warm and cold ischemia, which subsequently becomes evident at oxygenated reperfusion under normothermic conditions. Initial ROS and FMNH2 release from complex 1 presents the instigators of the entire reperfusion injury cascade with downstream DAMPs and cytokine release with increasing inflammation throughout continuous normothermic reperfusion in vivo after graft implantation or ex vivo on a perfusion device. Endischemic HOPE perfusion has been shown to protect mitochondria from this initial injury and such cold oxygenated perfusion induces a complex 1 repair with subsequent improved function of the respiratory chain, which lead to recharging of ATP at complex V and metabolism of metabolites which accumulate during warm and cold ischemia. When livers become rewarmed at implantation or normothermic perfusion on a device, the injury is significantly less, due to such improvement of mitochondrial function during previous HOPE treatment. Furthermore, the entire metabolism of the liver can be captured by fluorometric analysis of mitochondrial function (NADH) and injury ($FMNH_2$) using the auto-fluorescent properties of such two molecules, representing complex I behavior during reoxygenation in the cold. Importantly, the quantification of $FMNH_2$ and NADH predicts liver function and further outcomes after transplantation and therefore guides surgeons to decide, if a high-risk DCD liver with prolonged warm ischemia is metabolically "good enough" to become utilized or not

ischemic tissues and triggers an opening of the mitochondrial membrane pore with further release of mitochondrial DNA together with other DAMPs and multiple cytokines [31, 32, 44, 50]. Accordingly, the release of signaling proteins has been recently confirmed during endischemic normothermic perfusion of several organs, including kidneys, lungs and also livers [4, 22, 25, 26, 30, 51].

In contrast, a newly recognized but decisive option to minimize upfront mitochondrial injury during re-oxygenation is cooling of mitochondria below the Arrhenius breakpoint temperature of 15 °C [1, 2, 17], thereby inducing significant

changes in the reactivity of mitochondrial transfer processes, as seen in hibernating animals or plants [18, 33]. Consistently, $FMNH_2$ release and injury of mitochondrial complex I occur less frequently during cold oxygenated reperfusion when compared to normothermic oxygenated reperfusion [4] (Fig. 13.2).

Likewise and surprisingly, mitochondria work more effectively at hypothermic temperatures in uploading cellular ATP, when consuming processes are significantly reduced [4, 8, 51, 70]. A similar central role of attenuating mitochondria-derived oxidative injury has currently also been recognized in other biological fields, such as aging and cancer development [3, 28, 65]. Hypothermic oxygenated perfusion (HOPE) after ischemia protects therefore, first, from significant mitochondrial ROS release and, secondly, provides uploaded cellular energy reserves before implantation [19, 31, 51]. Both effects depend, however, on the number of accumulating metabolites during ischemia, which in principle may also lead to an oxidative injury during HOPE. Of note, the changes in mitochondrial metabolism during HOPE are detectable by perfusate analysis during cold perfusion, which will likewise be available as viability parameters in the future (see paragraph on viability assessment [31, 58]).

The clinical effect of the hypothermic perfusion approach has been demonstrated in recent observational studies in Maastricht III DCD livers [48, 55]. Accordingly, despite extended donor warm ischemia, HOPE-treated DCD liver transplants achieved similar overall graft survival, compared to standard DBD liver transplants. Particularly, graft loss due to non-tumor-related causes occurred in 8% (4/50) of cases. In contrast, one-third of untreated DCD livers (16/50) were lost due to non-tumor-related graft failure, despite significantly shorter functional donor warm ischemia time ($p < 0.0001$) [55]. Five-year graft survival, censored for tumor death, was 94% for HOPE-treated DCD liver transplants vs. 78% in untreated DCD liver transplants ($p = 0.024$). Similar results were recently presented by a group from Milan, where Maastricht II and III DCD livers are routinely transplanted with a combination of NRP, cold storage, and endischemic HOPE treatment [10–13] (Fig. 13.3). These results have been achieved despite the use of extended DCD liver grafts and are strikingly different from recent outcomes after endischemic normothermic perfusion of human livers [68, 69]. The findings by the Italian groups suggest that a simple endischemic perfusion approach is very effective and may open the field for safe utilization of extended DCD liver grafts. Recent clinical studies on hypothermic liver perfusion are summarized in Fig. 13.3. Results of most randomized controlled trials in DBD and DCD livers are awaited.

Which Livers Benefit from Cold Machine Perfusion?

Current benchmark analysis suggests that ideal liver transplants, defined as primary low risk DBD transplants, show excellent outcome by conventional cold storage [42]. This has also been confirmed for low-risk DCD liver transplants, defined by the recent UK DCD risk score [54]. Importantly, the former criteria for extended criteria donors, based on donor age > 65 years, hepatitis C core antigen positivity, donor

Author	Year	Country/Region	Liver type	Perfusion duration	Implantation	n	Active oxygenation	Modified Belzer MPS	Status
Clinical studies (matched or case series)									
Guarrera JV et al	2010	USA	DBD	3-7h	yes	20	-	+	-
Dutkowski P et al	2014	Switzerland	DCD	1-2h	yes	8*	+	-	-
Guarrera JV et al	2015	USA	DBD/DCD	3-7h	yes	31	-	+	-
Dutkowski P et al	2016	Switzerland	DCD	1-2h	yes	25*	+	-	-
van Rijn, R et al	2017	The Netherlands	DCD	2h	yes	10	+	-	-
De Carlis R et al	2017	Italy	DCD	8-10h	yes	2	+	-	-
De Carlis R et al	2017	Italy	DCD	8-10h	yes	7	+	-	-
Patrono D et al	2018	Italy	DBD/ECD	1-2h	yes	4	+	-	-
Patrono D et al	2019	Italy	DBD/ECD	1-2h	yes	25	+	-	-
Schlegel A et al	2019	Switzerland	DCD	1-2h	yes	50*	+	-	-
Randomized controlled trials									
RCT HOPE NCT01317342	2018	Europe	DBD/ECD	1-2h	yes	85		-	Recruitment completed
RCT D-HOPE NCT02584283	2018	Europe	DCD	1-2h	yes	78	+	+	Recruitment completed
Guarrera JV	2019	USA	DBD/ECD	3-7h	yes	18§	+	+	Recruiting
Lesurtel M	2019	France	DBD/ECD	1-2h	yes	?§	+	-	Recruiting
Lurje G	2019	Europe	DBD/ECD	1-2h	yes	?§	+	-	Recruiting
Total perfused livers	2019			1-10h	yes	>300	+/-	+/-	-

Fig. 13.3 Overview of clinical studies with hypothermic oxygenated perfusion with implantation. HOPE Hypothermic oxygenated perfusion, ATP Adenosine triphosphate, ROS Reactive oxygen species, 8-OHdG Hydroxydesoxyguanosin, DAMPs Danger-associated molecular pattern, HMGB-1 High-mobility-group-box-protein-1, HSC Hepatic stellate cells, SEC Sinusoidal endothelia cells, KC Kupffer cells, PNF Primary non-function, RET Retrograde electron transport CI Complex I, ∗ same series 50 DCD include the earlier reports of 25 and 8, § continue to recruit

BMI > 30 kg/m^2, elevated sodium >165 mmol/l, ICU stay >7 days and hepatic steatosis >40% [20], require an urgent refinement, because such grafts are frequently considered by many transplant programs today [34, 58]. For example, several reports have demonstrated safe utilization of DBD livers with advanced donor age, elevated sodium, prolonged ICU stay, high donor BMI, or elevated liver enzymes [53, 27]. Graft optimization by any sort of machine perfusion is therefore likely to be reserved for marginal DBD and extended DCD livers, with, for example, advanced donor age and expected severely prolonged cold ischemia (more than 12 h for DBD, or more than 6 h for DCD), or increased donor warm ischemia (more than 30 minutes functional warm ischemia), or for livers with significant macrosteatotic livers (more than 30%), in contrast to only microsteatotic livers [11, 31, 46] (Fig. 13.4).

Viability Assessment During Hypothermic Liver Perfusion

Measuring graft function before clinical use has been a dream of many transplant surgeons. Normothermic physiologic liver or kidney perfusion appears logical to determine visible signs of liver or kidney function. Yet, the current set of parameters used for the determination of viability during ex vivo normothermic liver perfusion failed to predict function or irreversible injury [38, 66, 67, 69]. For example, lactate clearance, bile production, and liver enzyme release were identified to be weak predictors. In addition, bile glucose and pH have been suggested to be more informative for post-transplant biliary injury; however, validation of this data set remains awaited [35].

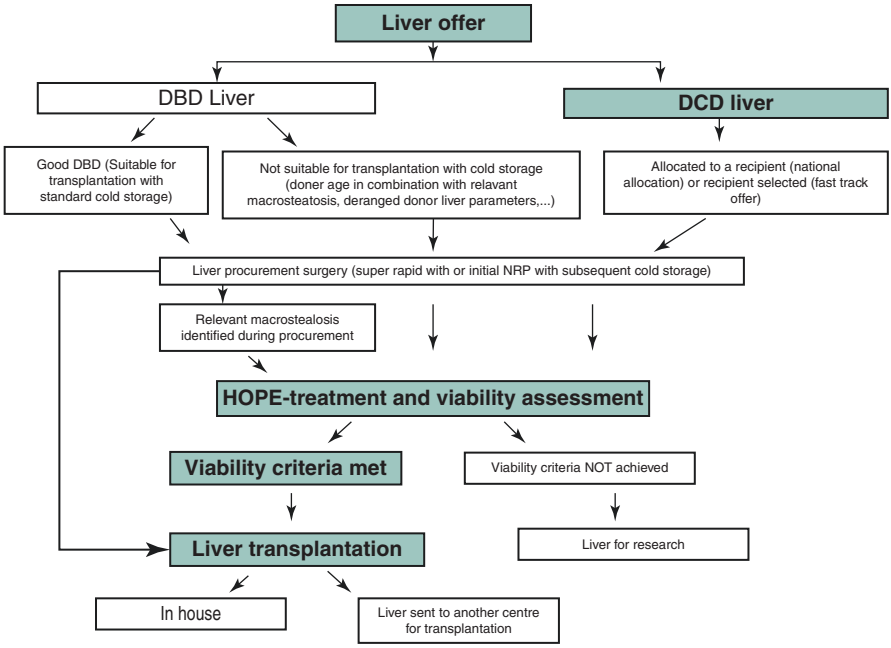

Fig. 13.4 Clinical application of hypothermic oxygenated perfusion in liver transplantation. This chart represents current clinical application of the HOPE technique in liver transplantation. Hypothermic perfusion is used to improve high-risk DCD livers or steatotic grafts. Additionally, this technique is routinely applied to use such high-risk livers for sick recipients to also improve safety and to confirm liver function before transplantation of high MELD recipients, even when ventilated on intensive care unit before transplantation. Finally, the HOPE approach is of great importance to bridge potential prolonged cold ischemia times when recipients are suddenly unfit for transplantation or when logistical issues, including an exchange of recipient, are required. In Switzerland, the HOPE approach is also used to treat DCD liver grafts and confirm viability with the fluorometric analysis, prior to liver transport to other transplant centers

While normothermic perfusion appears advantageous for measuring organ function ex vivo, recent work has shown that the metabolic status of organs can also be easily monitored during hypothermic oxygenated perfusion. Especially mitochondrial injury and function can be assessed by measuring perfusate Flavin, released from complex I (flavin mononucleotide, FMN) [62]. Current data suggest, accordingly, that perfusate analysis during hypothermic oxygenated perfusion is predictive for later graft function (Fig. 13.4) [43]. These results are in clear contrast with the low predictive value of conventional perfusate parameters, including liver transaminases or perfusate lactate levels, which repeatedly failed to recognize impaired liver function after implantation [66, 67]. Instead of solely focusing on the release of cytosolic compounds, future perfusate analysis should target on real-time monitoring of mitochondrial metabolism to enable an accurate prediction of oxidative stress and downstream activation of the hepatic inflammasome upon transplantation [47, 50]. The combination of several key mitochondrial metabolites including FMN,

NADH, succinate, and purine metabolites, e.g., inosine monophosphate, xanthine and hypoxanthine, may allow future detailed assessment of mitochondrial function of any solid organ.

Ideal Hypothermic Machine Perfusion Design

An underestimated hurdle for the widespread use of machine perfusion techniques is the complicated design and application. All liver machines suffer from the need for extra man power to connect livers to the device and the need for extra support during perfusion. Even an easy perfusion approach, as, for example, single portal vein perfusion requires repeated calibration of perfusion pressure, temperature, and flow control. Device alarming leads frequently to full perfusion stop, requiring reset and additional calibration with subsequent repeat liver connection. Although transport of livers on machines has been reported, most centers try to avoid continuous perfusion from donor center to transplant center with device transport, due to the additional need of travelling perfusion experts. From our point of view, instead, perfusion at recipient centers has clear advantages and should be performed by small, automatic devices, fully blue tooth connectable to, for example, smart phones or tablets, with full screen information of perfusion pressures, flow, oxygenation, temperature, and mitochondrial metabolism. Calibration should be as easy as possible with automatic perfusion start and stop. All perfusion machines should work with minimal heat or noise effects, and the liver basin should be either designed to cope with all possible liver sizes or the device should be connected to a simple metal liver bench bowl, routinely in use. Disposables should be kept as cheap as possible, e.g., less than approximately 1500 € per perfusion. We may envision that liver perfusion machine design will substantially improve and adapt according to the clinical need in the next years. The hypothermic LifePort Liver Transporter machine by Organ Recover Systems can be seen in Figure 13.5a. The VitaSmart hypothermic oxygenated machine perfusion platform by Bridge to Life can be seen in Figure 13.5b. Such two devices are currently avaible to provide hypothermic oxygenated perfusion only.

Summary

Hypothermic liver perfusion (HOPE) achieves excellent clinical outcome in extended DCD liver transplantations, despite an endischemic application, e.g., perfusion after organ procurement and organ transport. This technique is currently the cheapest and easiest perfusion concept, requiring no transport of perfusion equipment to donor locations, and only short perfusion periods through the portal vein. Recent experimental studies have unravelled the protective mechanism of cold re-oxygenation of ischemic liver tissues and have confirmed a novel and unique mitochondrial response compared to any form of re-oxygenation under normothermic conditions. Based on these results, the assessment of mitochondrial function and injury is possible during the initial first 30 minutes of HOPE and

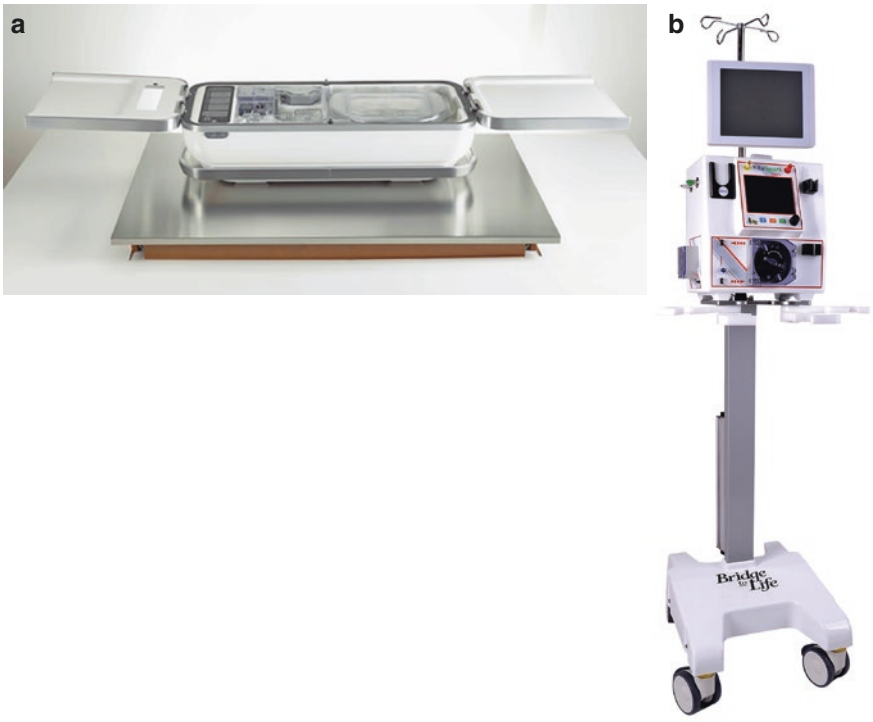

Fig. 13.5 (**a**) Hypothermic LifePort Liver Transporter machine by Organ Recover Systems. (**b**) The VitaSmart hypothermic oxygenated machine perfusion platform by Bridge to Life

allows recognition of later graft function already before implantation. This will likewise have an effect on the future safe utilization of extended DCD and steatotic liver grafts.

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Normothermic Regional Perfusion

14

Christopher J. E. Watson

Background

Normothermic regional perfusion (NRP), also known as normothermic recirculation, normothermic abdominal recirculation and normothermic extracorporeal membrane oxygenation (NECMO), was developed by Garcia-Valdecasas and colleagues in Barcelona from initial animal research [1]. At the time of their experimental work a case was reported from the United States of a patient who was on ECMO when he donated, with successful transplantation of the liver [2]. The Barcelona group went on to demonstrate that NRP improved primary graft function in kidney transplantation from DCD donors [3] and subsequently that it facilitated liver transplantation from uncontrolled DCD donors [4]. The technique was also described in Taiwan for the recovery of kidneys from controlled DCD donors [5], following which the Michigan group reported their experience first with renal transplantation using NRP in controlled DCD donors [6], and latterly with liver transplantation [7, 8].

In the last few years NRP has taken off across Europe as the method of choice for many centres for the retrieval of DCD livers for transplantation, with experiences reported from France, Italy, Russia, Spain, Norway and the United Kingdom [9–16].

This chapter will describe the technical details of NRP and then review the results.

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Technique

NRP involves circulating the donor's blood through an extracorporeal device to oxygenate the blood, maintain normothermia and circulate it back to the abdominal organs in situ. This is achieved by cannulating the inferior vena cava and abdominal aorta, either directly or remotely, while occluding the descending thoracic aorta to prevent perfusion of the brain.

Cannulation and Heparinisation

Cannulation techniques and the timing of heparin administration vary depending on the prevailing laws and surgical preferences (Table 14.1).

In France, NRP is established in the intensive care unit (ICU). Heparin is given at the withdrawal of treatment and small cannulae are placed in the femoral artery and vein and, upon verification of death, these are rewired and replaced with large bore perfusion cannulae. In the opposite groin a balloon catheter is passed to occlude the thoracic aorta. The patient is established on NRP in the ICU, and the donor's family is invited back to be with the donor until the retrieval team are ready at which point the donor is transferred to the operating room.

Table 14.1 Different NRP practices

	France[a]	Spain[b]	Norway[c]	UK	Michigan, USA [8]
Who runs NRP	Intensivist	Transplant coordinators	Cardiopulmonary bypass perfusionists	Transplant perfusionists	
Premortem cannulation	Yes	Yes	Yes	No	Yes
Duration	Target 120 min	Target 120 min Minimum 60 min	Target 120 mins	Target 120 min	Mean 83 min
Leucocyte filter	No	No	No	Yes	No
Prime	Saline or hemosol ormultibic	83 mMol $NaHCO_3$ 50 g mannitol 500 ml plasmalyte 500 ml colloid	1300 ml ringers acetate 500 ml mannitol 200 ml 3.3 M THAM	1 mMol/kg $NaHCO_3$ 1.5 L Hartmann's solution Meropenem & fluconazole	50 mMol $NaHCO_3$ 50 g mannitol 1 L normosol-R
FiO_2 at start PaO_2	50–100% 10–20 kPa	40%; 20 kPa	50%, sweep 2–3 L/min $SVO_2 > 60\%$	21%, sweep 2 L/min $SVO_2 > 60\%$	
Flow rate		2–2.5 L/min	3–3.5 L/min	2 - 3 L/min	Mean 3.4 L/min

[a]French data courtesy of Corinne Antoine
[b]Spanish data courtesy of Amelia Hessheimer
[c]Norwegian data courtesy of Stein Foss

In Italy, where 20 minutes must pass after cessation of electrical activity before surgery can commence, femoral wires can be placed once the systolic blood pressure is below 50 mmHg or haemoglobin oxygen saturations are below 75%. These can then be used to pass cannulas and an aortic occlusion balloon.

In Spain, heparinisation and cannulation depend on the ethical committee in the donor hospital, but can often be done ahead of treatment withdrawal, with a similar practice reported from Norway [17]. In the United States there are different rules for different states. Early reports from Michigan describe prior cannulation and heparinisation [7].

In the United Kingdom, no prior donor intervention is permissible. The donor is brought into the operating room after verification of death whereupon a rapid laparotomy is performed and cannulae placed in the aorta and inferior vena cava, either directly or via the right common iliac artery and vein (Fig. 14.1). This is preferred to femoral access since it is believed to be quicker, with more confidence in thoracic aortic occlusion when performed under direct vision. 50,000 units (100 mg) heparin is added to the perfusate to achieve heparinisation as perfusion begins.

Whichever technique is used, it is important to ensure that flow cranially beyond the descending thoracic aorta is prevented. We do this by placing a clear 24G cannula in the ascending aorta open to atmosphere which allows us to see if there is any blood flow and to determine the pressure in the ascending aorta (and by extrapolation the carotid arteries) – there should be no flow/pressure if the thoracic aortic clamp has been correctly placed.

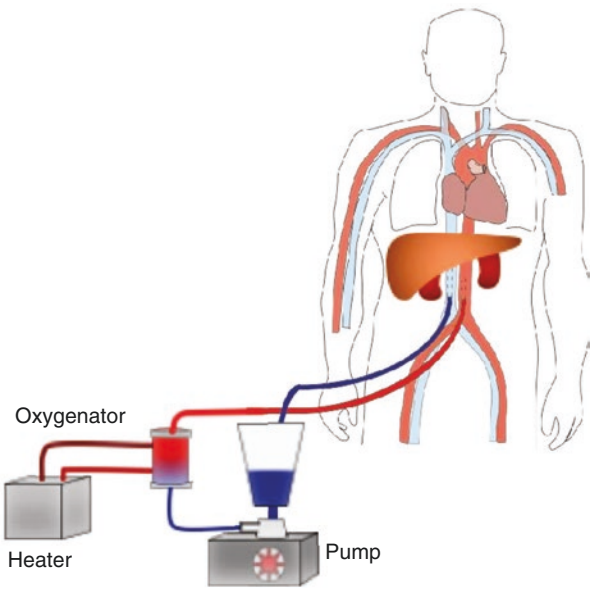

Fig. 14.1 The normothermic regional perfusion circuit

The Circuit

The NRP perfusion circuit comprises an oxygenator, heat exchanger and pump. The circuit may be closed, in which case there is a soft-shell reservoir, or open and containing a hard shell reservoir; there are arguments in favour of both which are beyond discussion here. Some perfusion equipment, such as the Donor Assist (Organ Assist, Groningen, Netherlands) (Fig. 14.2) has specifically designed circuits, while many groups use bespoke circuits and cardiopulmonary bypass pumps or portable pumps designed to support extracorporeal membrane oxygenation (ECMO).

Typically, the circuit is packed sterile with an enclosed length of tubing that has an additional sterile cover, and which is handed to the surgeon (the "sash") and a non-enclosed portion containing the pump-head, oxygenator and heat-exchanger that can be handled by the perfusionist while setting up NRP. The sash is divided by the surgeon, and one end connected to an arterial inflow cannula, while the other is connected to the venous outflow cannula.

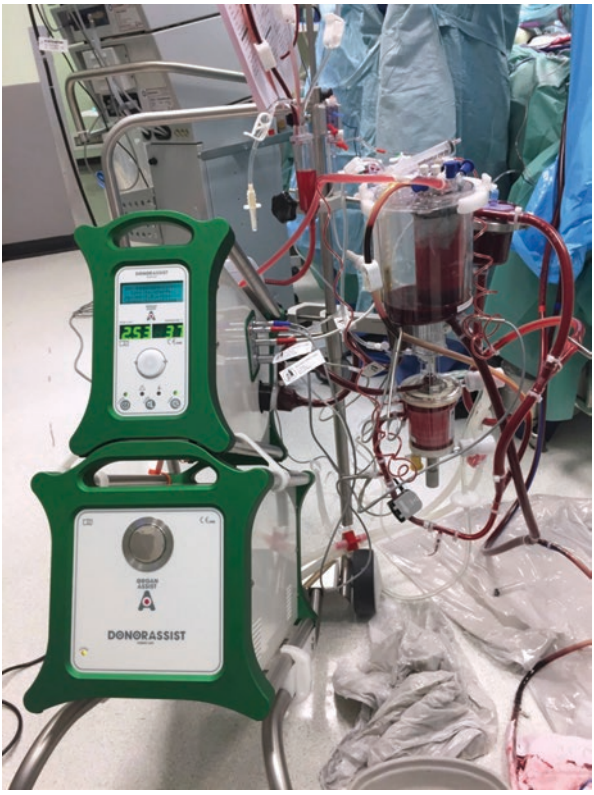

Fig. 14.2 The Donor Assist device for normothermic regional perfusion
Note the hard shell reservoir sitting above the oxygenator, with brighter red blood leaving that and entering a leucocyte filter just behind the reservoir

Perfusate

The composition of the perfusate varies from centre to centre but needs to contain the following:

- *Heparin:* Whether or not the donor is pre-heparinised, it is important to add heparin to the perfusate before connecting the circuit. Non-heparinised fluid will cause thrombus formation.
- *Sodium bicarbonate*: It is added to partially correct the acidosis that occurs in the withdrawal and asystolic periods. Amounts vary from a total volume of 50 mmol (50mls of 8.4% solution) to 1 mmol/kg.
- *Electrolyte solution:* The choice of fluid varies; we use Hartmann's solution since it is readily available, and we can add drugs to it without risk of precipitation, but any balanced electrolyte solution would suffice. Plasma-Lyte is commonly used in Europe.
- *Colloid/impermeant:* Some centres add a colloid (e.g. gelatin) or mannitol to the perfusate. Mannitol may also be used as a free radical scavenger, but the evidence for its ability to do this is poor. Some plasma expanders may cause certain antibiotics to precipitate out of solution, so care needs to be taken with additives.
- *Blood:* If the donor is a child, or the donor's haemoglobin concentration low (e.g. less than 60gm/L), then adding third-party packed red cells to the perfusate is sensible and avoids further diluting the haemoglobin.
- *Antimicrobials:* Blood cultures during NRP have indicated that candida and enteric organisms are common, probably originating from translocation across the large bowel mucosa. Therefore broad-spectrum anti-bacterial and anti-candidal agents (e.g. meropenem and fluconazole) are used routinely in the United Kingdom and are added to the prime before NRP commences. The choice of antibiotics should also take into account any prevailing infection in the donor.

The volume of perfusate varies depending upon the circuit, with longer tubing and greater diameters demanding bigger volumes. Typically it would be around 1.5 L.

Withdrawal Period

The period from withdrawal to arrest is characterised by reduced perfusion of tissues and worsening haemoglobin oxygen saturations [18]. For standard cold perfusion retrievals, the concept of functional donor warm ischaemic time (f-DWIT) has been introduced to represent the point at which tissue perfusion is thought to be suboptimal, and beyond which the organs are experiencing warm ischaemia. Thresholds for functional donor warm ischemia vary internationally, reflecting a lack of agreement regarding the point at which a liver ceases to be a safe and viable organ to transplant, or the risk of cholangiopathy becomes unacceptable. Given that NRP allows functional testing of the liver *in situ* after the withdrawal and asystolic periods, the utility of f-DWIT thresholds is questionable.

While the duration of the withdrawal period may no longer be important, knowledge of its physiology is. Several pieces of animal work have shown that withdrawal of treatment is followed by a catecholamine release which aims to preserve blood flow to the brain at the expense of other organs [18, 19]. The vasospastic effects of these catecholamines can be alleviated with an alpha-adrenergic blocker administered before withdrawal where that is permitted [19, 20] and should result in improved organ perfusion during NRP.

Perfusion

During cannulation it is important to avoid introducing air into the circuit. Air in the arterial side may stop perfusion of the organs to which the air embolus passes; on the venous side air may stop venous return to the reservoir in an open circuit, or block the pump head in a closed circuit. Following successful cannulation of the aorta and vena cava, perfusion is started aiming for flows of around 3 L/min for abdominal NRP, or greater for thoraco-abdominal NRP. Hyperoxaemia should be avoided during the restoration of the circulation as this may promote free radical production and worsen reperfusion injury, but the delivered oxygen can be increased once NRP is established. Oxygen delivery is best adjusted to achieve a venous haemoglobin oxygen saturation of 60–80% in the returning blood.

There is no good evidence as to the optimum duration of perfusion. It is likely that regeneration of ATP in the liver takes some time, but maintaining the liver in the donor for a long time is likely to be harmful. Prolonged periods of cardiopulonary bypass are recognised as being deleterious to renal function and to be associated with acute pancreatitis, so by extrapolation prolonged NRP may not be beneficial. Most centres aim for 2 hours, with 30 minutes probably being a minimum to achieve a reasonable resuscitation of the organs. Experimental studies on NRP tend not to replicate the donor circulatory collapse and catecholamine production before the asystolic period, and instead study only the effects of NRP after an asystolic warm period; with this proviso 4 hours appears to be the maximum duration [21].

Cooling

At the end of perfusion, it is possible to start to gradually cool the donor, either by using a heater cooler in the circuit or by stopping warming the blood and placing ice-slush in the abdomen. In animal models, even a modest cooling to 34 °C has been shown to reduce reperfusion injury, and pre-retrieval hypothermia in brain dead donors has been shown to reduce delayed graft function in renal transplantation [22].

Monitoring

Maintaining Safe Perfusion

During NRP it is important to monitor the donor to ensure adequate oxygenation and to enable adjustment of gas flow and gas mixture to the oxygenator. In most cases judicious adjustment of these parameters can correct any acid/base imbalance without resort to additional bicarbonate in the presence of a functioning liver. Measuring venous blood gases every 30 minutes should suffice, aiming for a venous haemoglobin oxygen saturation of 60–80%. The blood gas estimation will also indicate haemoglobin, which should be supplemented if it falls below 60 g/L.

Viability Markers

One of the benefits of NRP is that it allows monitoring of the liver following the withdrawal and asystolic periods and should allow identification of livers that have suffered irreversible damage, and which should not be used.

Damage

Transaminase levels measured in the perfusate have been used to determine the degree of hepatocellular injury. Typically they are done just after starting NRP, and after 60 and 120 minutes. In most controlled DCD NRP cases the transaminase levels remain within the normal range. The Spanish group describe a threshold 4 times the upper limit of normal in uncontrolled DCD donor livers; we have used up to 10 times the upper limit of normal provided the transaminase is not continuing to rise and other markers are satisfactory.

Function

While transaminase is an indicator of damage, the ability to metabolise lactate gives an indication of function. In most DCD donors, where Hartmann's solution has been used for the perfusate, the lactate is over 10 mmol/L at the start of NRP since Hartmann's contains 29 mmol/L of lactate. Over the course of the next 120 minutes, the lactate concentration falls but does not reach zero as lactate continues to enter the circuit from the non-perfused head, neck, upper, and lower limbs. We would expect a fall over 4 mmol/L in the first 2 hours in a normal-size adult.

Bile

Early during NRP the bile duct can be divided and cannulated and bile collected. Bile production suggests the liver is working. An alkali bile (pH > 7.5) with low glucose concentration relative to perfusate concentration suggests that the cholangiocytes of the small bile ducts are functioning and not irreparably damaged during the dying process.

Problems/Solutions

Loss of Volume

Loss of volume in the circuit can be due to one of two reasons, either bleeding or the normal vasodilation that occurs as the effects of the catecholamine surge at death wear off. It is important to have cross-matched blood available before starting NRP and not to use a lactate containing fluid such as Hartmann's to replace fluid losses, since this will negate the ability to use perfusate lactate concentrations as a marker of function.

Hypoxaemia

Low haemoglobin oxygen saturations in the return venous blood can be corrected in one of three ways: if the haemoglobin concentration is low (<60 g/L) additional packed red cells should be added to the circuit; if the haemoglobin is OK, then increased oxygen delivery can be achieved by either increasing the flow rate of blood or increasing the fraction of oxygen (FiO_2) being delivered to the oxygenator.

Thoracic Organ Retrieval

The heart and lungs may be retrieved either directly by cold flushing while the descending thoracic aorta is clamped (termed "Direct Procurement") [23], or as part of a thoraco-abdominal NRP (TA-NRP) whereby a circulation is restored to the heart and lungs as well as the abdomen [24]. In either case it is essential that the cardiothoracic team ensure haemostasis in the chest; otherwise the extracorporeal circulation will fail. One of the major sources of blood loss is the Azygos vein which drains into the posterior aspect of the SVC and which should be clamped or oversewn.

In order to prevent reperfusion of the brain in TA-NRP, it is necessary to clamp the brachiocephalic artery on the right and the left common carotid and left subclavian arteries. There remains the possibility of collateral flow, particularly from the supreme intercostal arteries, which arise from the cranial end of the descending thoracic aorta and form anastomoses with branches of the costocervical trunk of the subclavian artery, which itself gives off the vertebral artery. One solution is to cannulate the three arterial trunks and drain them into the venous circuit, thus removing any brain perfusion pressure. Since cannulation of the arteries is time consuming, the heart can be flushed with cold cardioplegia before this is done, reducing ischaemic damage before perfusion is restored.

Ethics

Concerns have been expressed with the concept of restoring a circulation to a donor who has been certified dead by the absence of a circulation to the brain [25]. The precautions described above should ensure that brain perfusion does not occur during NRP and should be followed in all cases.

Results

There are several large series that have reported results of NRP in DCD liver donors. All show that NRP offers superior graft survival with a reduction in ischaemic cholangiopathy. The results are particularly impressive for controlled DCD donors. Table 14.2 shows the results of larger series of liver transplants from controlled DCD donors.

In our own analysis NRP minimised post-transplant cholangiopathy, reduced anastomotic stricture rate, improved graft survival [16], and reduced the time spent in hospital in the first year by 11 days compared to non-NRP DCD recipients. NRP was also associated with less acute kidney injury post-transplant compared to normal DCD liver transplants. NRP has enabled DCD livers to be used for difficult transplants such retransplants and those with portal vein thrombosis, something usually associated with poor outcomes [26].

Table 14.2 Reports of series of controlled DCD donor liver transplants with NRP

Report	Spain (controlled DCD) [13]		Cambridge and Edinburgh, UK [16]		Oslo, Norway [14]	Milan, Italy[a] [11]
	NRP cases	Comparators	NRP cases	Comparators	NRP	NRP
Numbers	95	117	43	187	8	20
Donor age	57 (45–65)	56 (47–64)	41 (33–57)	50 (37–58)	50 (23–63)[b]	51 (46–61)
Duration of NRP (min)	120 (76–136)		123 (103–130)		94 (73–221)[b]	352 (308–434)
Total "DWIT"	18 (13–23)	22 (19–26)	30 (26–36)	27 (22–32)	29 (16–96)[b]	125 (72–143)
Cold ischaemic time	315 (265–365)	340 (285–383)	382 (303–502)	444 (395–493)	428 (206–573)[b]	480 (360–540)#
Recipient age	56 (52–61)	59 (53–63)	60 (51–64)	57 (51–63)		56 (54–63)
Recipient MELD	15 (11–19)	13 (9–18)	15 (12–23)	15 (11–20)	26 (6–40)[b]	10 (8–13)
Early allograft dysfunction	21 (22%)	32 (27%)	5 (12%)	55 (32%)	0	4 (24%)
Primary non function	2 (2%)	3 (3%)	0	13 (7%)	0	2 (10%)
ITBL	2 (2%)	15 (13%)	0	41 (27%)		2 (10%)
Graft survival at 1 year	88%	76%	98%	87%	100	85%
Patient survival at 1 year	93%	88%	98%	94%	100	95%

Comparators were DCD liver produced by rapid recovery technique with in situ cold flush. Numbers are median (interquartile range) or numbers and percentages

DWIT Withdrawal of treatment to cold in situ perfusion or start of NRP, *MELD* Laboratory model for end-stage liver disease score, *ITBL* Ischaemic-type biliary lesions (ischaemic cholangiopathy). Early allograft dysfunction defined by the Olthoff criteria [30]

[a]Uncontrolled (14) and controlled (6) DCD livers, preserved with a combination of NRP and hypothermic ex situ machine perfusion. Reported as hours

[b]Range, not IQR

Mechanism

It is not clear way NRP has the beneficial effect it does. In 1908 Pringle described being able to safely interrupt the inflow to the liver for a period of time to facilitate surgery, provided the circulation was restored in a timely manner [27]. This is essentially what is happening with NRP, with the restoration of a blood supply to reverse the changes of warm ischaemia without imposing an immediate period of cold ischaemia. The NRP allows replenishment of ATP [28], which allows the liver to recover and tolerate subsequent cold ischaemia better. It has also been suggested that the period of asystole before NRP may act as a preconditioning stimulus, allowing the liver and other organs to better tolerate subsequent cold ischaemia [29].

Conclusions

Normothermic regional perfusion is becoming adopted throughout Europe and in parts of the United States to improve the preservation of livers donated after circulatory death, being associated with fewer of the side effects normally attributed to DCD livers procured by rapid recovery in the cold. These effects include a reduction in primary non function and delayed graft function, minimisation of non-anastomotic strictures, reduction of anastomotic strictures and less acute kidney in the liver recipients.

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Ex Vivo Normothermic Machine Perfusion

15

Daniele Pezzati, Qiang Liu, and Cristiano Quintini

Historical Background

Since the first human liver transplant by Thomas Starzl in 1963, liver transplantation (LT) has become the standard therapy for end-stage liver disease, but organ preservation methods have remained largely unchanged. The graft is flushed and cooled with preservation fluid, then stored in an icebox [1]. Static cold storage (SCS), still the gold standard for organ preservation, inevitably produces ischemia/reperfusion injury (IRI) [2, 3]. Fortunately, most grafts can tolerate the injury, but severe IRI can lead to major complications and death.

The detrimental effects of SCS are magnified in marginal organs, and particularly in organs from donors after circulatory death (DCD). The increasing use of marginal organs has spurred interest in improving organ preservation techniques and tools for determining the suitability of marginal organs for transplantation [4, 5].

The concept of machine perfusion (MP) was introduced by Alexis Carrel and Charles Lindberg in 1935 in their work "The Culture of Organs." As early as 1970, Thomas Starzl described the potential benefits of hypothermic oxygenated ex-vivo machine perfusion. He wrote: "After excision of the liver, it can be transplanted immediately or placed in a conservation chamber employing low-flow perfusion, hyperbaric oxygenation, and hypothermia. Using the latter method, the organ can be kept in good conditions for as long as eight hours" [6]. At the time, however, given the reliability of SCS for standard criteria grafts, the logistical and financial challenges of MP led to temporary discontinuation of research on this approach.

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More recently, as technology has advanced and the use of marginal organs has increased, preclinical and clinical studies testing MP have spread from kidney grafts to liver grafts. Currently, several machines are available for clinical use, and ex-situ perfusion of donor livers can be performed at four different temperature ranges: 0–12 °C (hypothermic machine perfusion; HMP); 13–24 °C (mid-thermic machine perfusion; MMP); 25–33 °C (subnormothermic machine perfusion; SMP), and 35–38 °C (normothermic machine perfusion; NMP) [7]. Published reports of MP for liver grafts include results from hundreds of patients worldwide, but several controversies are yet to be solved, including identification of grafts and recipients who might benefit the most from MP.

Rationale

In solid organ transplantation, grafts are exposed to ischemia from the time of cross-clamping in the donor until reperfusion in the recipient. During procurement the graft is abruptly deprived of oxygen, cooled at 4 °C with preservation fluids and slush ice, and its metabolism is slowed but not completely stopped.

Oxygen is essential for cellular activity and production of ATP. As soon as blood flow ceases, the supply of nutrients and oxygen stops. ATP levels rapidly drop, anaerobic metabolism begins, and metabolic waste products accumulate. ATP loss leads to disabling of membrane pumps and membrane integrity damage. This causes edema, influx of calcium, phospholipase activation, inflammation, and cellular death [7, 8].

Furthermore, in an ischemic environment, xanthine dehydrogenase is converted to xanthine oxidase which, during reperfusion in the presence of oxygen, converts accumulated products into free radicals.

When the liver is reperfused, there is massive production of reactive oxygen species (ROS) and cytokines, neutrophil infiltration and impaired hepatic microcirculation leading to inflammation, cellular death (cholangiocytes are most susceptible), and loss of functioning parenchyma. The resulting clinical scenarios can range from silent damage to early graft dysfunction (EGD), primary nonfunction (PNF), and ischemic-type biliary lesions (ITBL) [7, 9–11].

SCS is based on the concept that cooling diminishes cellular metabolism and minimizes ATP depletion. With every 10 °C drop in temperature, metabolism is slowed twofold, but it is never completely stopped, as ATP consumption continues at 1 °C [7].

The ideal method of preservation should mimic the physiological conditions as much as possible in order to reduce IRI-related damage, prolong preservation time, reduce post-LT complications, allow organ viability assessment, and facilitate extended use of marginal organs.

SCS fails to accomplish the majority of these targets.

NMP, on the other hand, perfuses the graft with normothermic, blood-based solutions that recreate the physiological environment, thereby tending to decrease the detrimental effects seen with SCS. NMP should enable prolonged preservation, allow the organ to recover from injuries incurred during retrieval, permit evaluation of organ function before implantation, and minimize IRI injury by reducing the cold ischemic time.

However, the precise mechanism that underlies the beneficial effects of NMP is not completely clear. Probably, normothermic perfusion helps to maintain a healthy endothelium and replenish adenosine triphosphate (ATP). The importance of increasing hepatic ATP in LT has already been demonstrated, with a direct correlation between high hepatic ATP content and good post-transplant outcome [4]. The role of NMP in ATP regeneration has been confirmed in porcine models, where initiation of NMP has been followed by rapid recovery of ATP as well as mitochondrial ATP-ase activity [11]. More recently, human studies have proved histological evidence of glycogen depletion during NMP.

Glycogen preserves hepatocellular integrity and function by supplying glucose for ATP generation. Once glycogen is consumed, ATP depletion ensues, leading to irreversible cell injury and necrosis.

Difference in gene expression between transplanted human NMP and SCS livers has also been shown [4]. When gene expression was compared between pre- and post-reperfusion biopsies, the genes upregulated after NMP were mainly those involved in the control of inflammation. In contrast, the upregulated genes in SCS were mainly those implicated in inflammation, apoptosis, and activation of coagulation [12].

Further, NMP has been shown to reduce injury to liver parenchyma and improve epithelial regeneration in extrahepatic bile ducts, thus preventing the development of ischemic cholangiopathy [13].

Technology

Several NMP circuits have been described that use components developed for cardiopulmonary bypass. Main elements are: a blood reservoir, a pump (some circuits consist of two pumps, one for the portal vein and one for the hepatic artery), an oxygenator, and a heat exchanger. The devices currently used in clinical trials are OrganOx Metra® (OrganOx Ltd., Oxford, UK), Liver Assist®(Organ Assist, Gronigen, the Netherlands), OCS Liver System® (Transmedics, Andover, MA, USA), and the Cleveland NMP circuit (Cleveland Clinic, Cleveland, OH, USA). The machines differ in the type of circuit (closed circuit vs open drainage), type of arterial flow (pulsatile vs continuous), portability vs not, and degrees of automation (regulation of vascular pressures, flows, and blood gases).

Most published clinical trials have tested the OrganOx Metra® device. This machine provides automated pumping, oxygen/air delivery, and heat exchange in order to preserve the perfusate at normal temperature, within physiological ranges for pO_2, pCO_2, pH and at physiological pressures in the vascular hepatic inflow and outflow (hepatic artery pressure from 60 to 75 mmHg; inferior vena cava pressure from 1 to 2 mmHg). Portal flow is continuously measured, but portal pressure is not. The perfusate is pumped out of the inferior vena cava using a centrifugal pump, then heated, and oxygenated. It is subsequently diverted to the hepatic artery through a high-pressure, low-flow system or to the soft-shell reservoir which feeds the portal vein via a low-pressure, high-flow system. Bile production is monitored through duct cannulation. Bile salt, insulin, heparin, and prostacyclin are automatically infused;

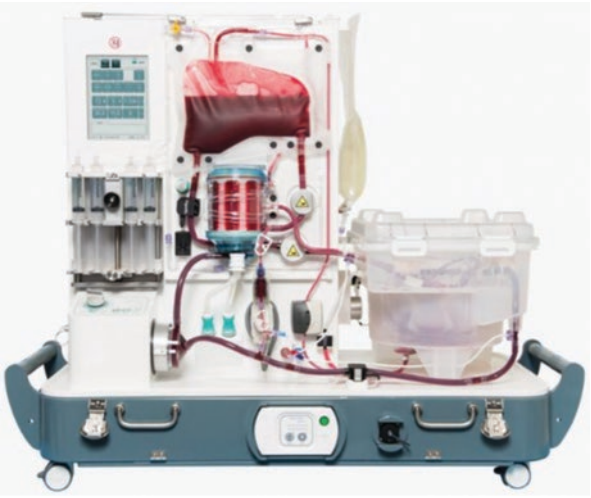

Fig. 15.1 Organ Ox Metra®

glucose and amino acid infusion can be manually regulated. The perfusate comprises 3 units of packed red blood cells cross-matched to the donor, one unit of colloid solution, calcium gluconate, heparin, cefuroxime, and 30 mL of sodium bicarbonate. During priming, the perfusate should reach operating conditions: 37 °C, a pO_2 of 12 kPa, a pCO_2 of 5 kPa, and a pH of 7.35. Acid-base homeostasis is reached by constant blood gas analysis and monitoring and control of pO_2 and pCO_2 levels. Continuous infusions ensure sufficient vasodilatation, protection against coagulation, and an environment with near-physiological metabolic and synthetic liver function (Fig. 15.1).

The Liver Assist® is a pressure-controlled device that provides pulsatile arterial flow and continuous non-pulsatile portal flow via two independent rotary pump circuits. Perfusate is not standardized but is generally made of 3 units of ABO-compatible blood plus a variable quantity of succinylated gelatin. Several other components may be added. Operative conditions are generally set up at 37 °C. Target pressures in the hepatic artery and portal vein are 60 mmHg and 8 mmHg, respectively. Bile can be collected after cannulation of the common bile duct. In the report of a liver recipient who underwent the first ischemia-free organ transplant (IFOT), a Chinese team describes how they manipulated the circuit by adding components to make the connection of the machine to the donor and recipient possible (Fig. 15.2).

OCS Liver System is a device providing pulsatile arterial flow and continuous non-pulsatile venous flow. The perfusate is provided by the company.

The Cleveland NMP circuit initially consisted of two separate pumps, an oxygenator and a heater; it uses a combination of air and oxygen that can be mixed and regulated. Subsequently it was converted to a single pump design where hepatic artery and portal vein flows can be regulated through a C-clamp application to the circuit. Perfusate includes blood and fresh frozen plasma. The only “home-grown” device, the Cleveland NMP is FDA-approved for use in clinical trials but is not yet commercially available. The device is transportable (Fig. 15.3).

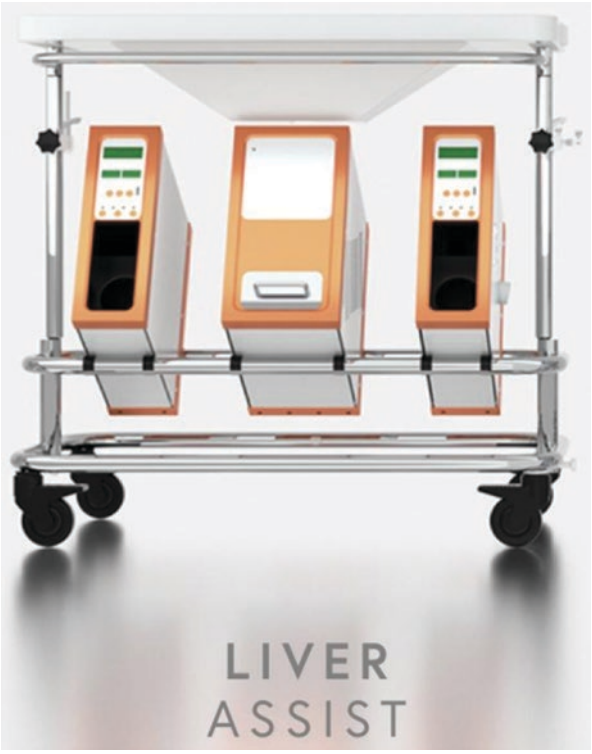

Fig. 15.2 Liver Assist®

Pre-clinical Studies

Pre-clinical studies of NMP were mainly in pigs, which provide appropriate size at reasonable cost. Still, anatomical differences obliged surgeons to alter the LT procedure. Moreover, for immunological reasons, pigs need to be sacrificed early, so late complications such as ischemic-type biliary lesions (ITBL) cannot be studied.

Schon et al. [14] studied the effect of NMP on grafts with an extended warm ischemia time (WIT) of 1 hour. All six animals transplanted with NMP usage survived versus none of the four transplanted after SCS.

Foley at al [15] mimicked an NMP circuit by connecting the liver to an anesthetized pig with an extracorporeal circuit. They found that single perfused livers were completely unable to increase biliary cholesterol in response to bile acid.

Brockmann et al. [16] compared liver transplant outcomes in pigs following either conventional cold preservation or warm preservation. After 20 hours of preservation without warm ischemia, posttransplant survival was improved in NMP livers. With the addition of 40 min of warm ischemia, the differences were even more marked. The authors concluded that organ preservation by warm perfusion, maintaining physiological pressure and flow parameters, enables prolonged preservation and successful transplantation both of normal livers and those with substantial ischemic damage.

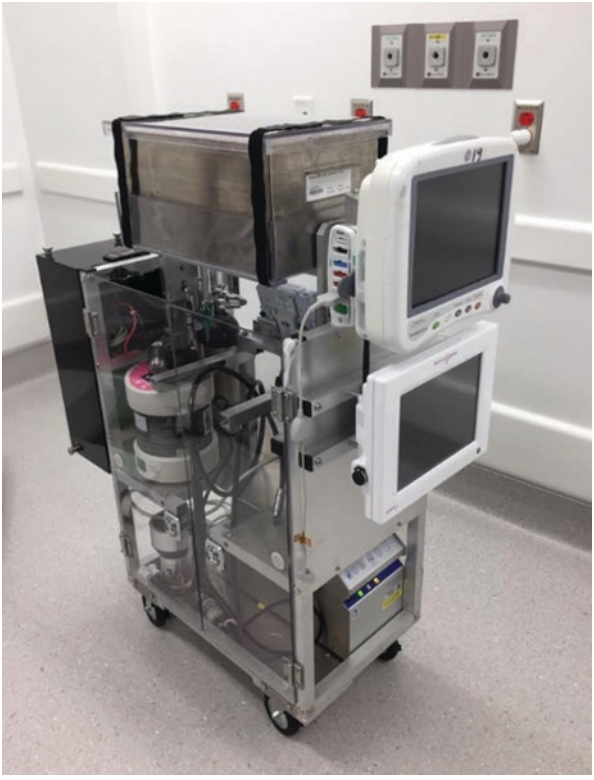

Fig. 15.3 Cleveland NMP

Fondevilla et al. [17] studied the effect of NMP in combination with regional perfusion. Donor pigs underwent 90-min cardiac arrest and were divided into 3 groups. In one group, livers were preserved immediately with cold storage. In the other 2 groups, donors underwent 60-min of normothermic regional perfusion followed by SCS or NMP. Five-day survival was 0 with immediate cold storage, 83% with normothermic regional perfusion+SCS, and 100% in normothermic regional perfusion+NMP. The authors concluded although 60 min recuperative normothermic regional perfusion is better than SCS alone, NMP further improves results and may have a role in preserving DCD livers in the clinical setting.

Boehnert et al. [18] compared cold static with acellular normothermic ex vivo liver perfusion (NEVLP) in a pig model of DCD liver injury. DCD livers (60 min warm ischemia) were cold stored for 4 hours or treated with 4 hours cold storage plus 8 hours NEVLP. Compared to the NEVLP grafts, the cold-stored grafts had higher ALT levels, decreased oxygen extraction, and increased hepatocyte necrosis. Furthermore, in the cold-stored grafts, levels of bilirubin, phospholipids, and bile salts were decreased fivefold, while LDH was sixfold higher and bile duct necrosis was increased. Following transplantation, mean serum AST level was

higher in cold-stored versus NEVLP livers with similar bile production. NEVLP improved hepatic artery perfusion and decreased markers of liver duct injury in DCD grafts.

St. Peter et al. [19] also studied the effect of NMP on DCD pig livers, subjecting grafts to 60 min of in vivo total warm ischaemia before flushing, after which they were preserved for 24 hours either by SCS with the University of Wisconsin (UW) solution or via oxygenated autologous blood perfusion on an extracorporeal circuit. During a 24-hour reperfusion phase, SCS livers showed no evidence of viability, with no bile production or glucose utilization; they also displayed massive necrosis. NMP livers demonstrated recovery of function by synthetic function, substrate utilization, and perfusion hemodynamics.

To address a debate over the possible deleterious effect of brief SCS before NMP, Reddy et al. [20] subjected porcine livers to 60 min of warm ischemia, after which the livers were either cold-preserved in UW solution for 4 hours followed by 20 hours of NMP or preserved with NMP for 24 hours. The NMP group had superior bile production, metabolic activity, and less evidence of hepatocellular damage and sinusoidal endothelial cell dysfunction, leading the authors to conclude that even a short period of cold ischemia significantly compounds the dysfunction of ischemically damaged livers.

Also working with pigs, Liu et al. [13] investigated the effect of NMP on hemodynamics and biliary epithelial regeneration; they reported that it improves biliary regeneration after a major ischemic event and may prevent the development of ischemic cholangiopathy in clinical transplantation. The same group also investigated the role of different perfusates on graft and bile duct viability in NMP porcine DCD livers, concluding that perfusate containing an oxygen carrier is most effective. Specifically, whole-blood perfused livers showed a trend toward better outcomes compared with perfusion with Steen solution plus red blood cells [21].

Clinical Series

Starting in 2016, reports of NMP in clinical scenarios began to emerge. Ravikumar et al. [22] reported the first-in-human phase 1 trial testing safety and feasibility. Twenty patients underwent liver transplantation after NMP. Organs were retrieved using standard techniques, attached to the perfusion device Organox® at the donor hospital, and transported to the implanting center in a functioning state. When NMP livers were matched 1:2 to cold-stored livers, 30-day graft survival was similar (100% NMP vs. 97.5% control, $p = 1.00$). Median peak aspartate aminotransferase (AST) in the first 7 days was significantly lower in the NMP group (417 IU [84–4681]) versus (902 IU [218–8786], $p = 0.03$).

Angelico et al. [23] reported that post-reperfusion syndrome developed in 2 of 12 patients who received cold-stored livers but in none of 6 patients who received NMP livers. The NMP group also had better intraoperative mean arterial pressure at 90 min post-reperfusion, achieved with significantly lower vasopressor requirements and fewer blood products compared with the SCS group.

Mergental et al. investigated the potential of NMP to increase the use of high-risk graftsby, allowing more accurate functional evaluation [24]. Following viability assessment by NMP, five originally rejected livers were transplanted. To be considered viable, livers had to meet the following criteria: the perfusate lactate level had to be less than 2.5 mmol/L or the liver had to produce bile, in combination with at least 2 of the following 3 criteria: (1) perfusate pH greater than 7.30, (2) stable arterial flow of more than 150 mL/min and portal venous flow more than 500 mL/min, and (3) homogeneous graft perfusion with soft consistency of the parenchyma.

Four of the organs had been rejected due to prolonged warm ischemic times in DCDs. The authors reported an uneventful transplant procedure in every recipient, with immediate function in all grafts. Notably, this was the first series to provide specific parameters for graft viability assessment during NMP.

Watson et al. transplanted 12 discarded livers following NMP [25]. The first 6 were perfused at high perfusate oxygen tensions, and the subsequent 6 at near-physiologic oxygen tensions. The authors found that avoidance of hyperoxia during perfusion may prevent postreperfusion syndrome and vasoplegia, and monitoring biliary pH, rather than absolute bile production, may be important in determining the likelihood of posttransplant cholangiopathy. The same group [26] also investigated which parameters could predict graft viability during 47 liver perfusions, of which 22 resulted in transplants. They concluded liver viability during normothermic perfusion can be assessed using a combination of transaminase release, glucose metabolism, lactate clearance, and maintenance of acid-base balance. The evaluation of bile pH may offer a valuable insight into bile duct integrity and risk of post-transplant ischemic cholangiopathy.

Selzner et al. reported the first North American series of LT with NMP using Steen solution in the perfusate [27], concluding that outcomes were comparable to results with SCS. Ten patients who received livers that had been perfused on the Metra device at 37 °C with Steen solution plus 3 units of erythrocytes were compared with a matched historical control group of 30 patients who received SCS grafts. There were no significant differences in aspartate aminotransferase and alanine aminotransferase levels on postoperative days 1–3, graft function by day 7 as assessed by international normalized ratio and bilirubin, duration of intensive care unit stay or hospital length of stay. No graft loss or patient death was observed in either group.

The group from Edmonton [28] reported on 10 grafts preserved with NMP, of which 9 were transplanted. Transplanted NMP grafts were matched 1:3 with transplanted SCS livers. All transplanted livers had good function, similar to controls, and graft survival at 30 days was not statistically different between groups. Intensive care and hospital stays were significantly more prolonged in the NMP group. Authors were criticized because of non-homogenous preservation times that reached

22.5 hours in one case and because NMP was also used as a tool to face logistical problems. Notably authors also reported a graft loss during NMP due to an unnoticed portal vein twisting.

The same group also investigated the effect of transient SCS before NMP [29]. As transportation of the machine to donor's hospital increases costs, prolongs retrieval time, and requires the presence of an experienced surgeon, the authors investigated whether a more practical back-to-base approach after initial SCS would compromise results. They compared outcomes of 26 back-to-base livers and 17 livers procured locally that underwent immediate NMP. The primary outcome measure (safety) was defined as 30-day patient and graft survival. Despite significantly prolonged mean cold ischemia time, the back-to-base livers demonstrated no difference in graft function, incidence of complications, or graft and patient survival.

Ceresa et al. also investigated the safety of a period of SCS before NMP [30], concluding that it was safe. Thirty-one livers were transplanted in the prospective multicenter study. The 30-day graft survival rate was 94%. Median peak serum AST in the first 7 days was 457 U/L, and 4 patients developed early allograft dysfunction (EAD). Postrepefusion syndrome (PRS) was observed in 3 livers. The median duration of initial critical care stay was 3 days, and median hospital stay was 13 days.

The first report of a randomized clinical trial comparing NMP to SCS came from Nasralla et al. [31]. With results from 220 liver transplantations, NMP was associated with a 50% lower level of graft injury as measured by hepatocellular enzyme release. Rates of bile duct complications, graft survival, and patient survival were statistically similar with the two approaches. The authors reported a 50% lower rate of organ discard but did not disclose viability parameters.

Ghinolfi et al. reported another pilot randomized clinical trial [32] on the use of NMP with very old donors. Results did not show any significant difference. This study has a main limitation in the small number of cases so that its results have to be carefully evaluated.

Van Leeuwen et al. investigated a combination of dual hypothermic oxygenated machine perfusion (DHOPE) with NMP in 16 discarded DCD livers [33]. Ex situ NMP (viability assessment phase) was preceded by 1-hour DHOPE (resuscitation phase) and 1 hour of controlled oxygenated rewarming (COR). During the first 2.5hours of NMP, hepatobiliary viability was assessed, using predefined criteria: perfusate lactate <1.7 mmol/L, pH 7.35–7.45, bile production >10mL, and bile pH >7.45. All of the livers cleared lactate and produced sufficient bile volume, but 5 livers were discarded due to low bile pH. The remaining 11 livers (69%) were successfully transplanted, with 100% patient and graft survival at 6 months. The authors concluded that sequential DHOPE-COR-NMP enabled resuscitation and safe selection of initially declined high-risk donor livers, thereby increasing the number of transplantable livers (Table 15.1).

Table 15.1 Clinical studies reporting LT with both DBD/DCD grafts perfused with NMP

Author	N	DBD/DCD	Recipient age	Recipient MELD	Machine	Hospital stay (days)	FU (months)	Graft loss causes	6 months Pt Survival	6 months graft survival	PNF	DGF	PRS	ITBL	Vascular complications
Nasralla et al. [31]	121	87/34	55 (48–62)	13 (10–18)	Organox	15(10–24)	12	2 HAT 1 ITBL 1 non-thrombotic infarction 1 inferior vena cava occlusion 1 PNF	/	/	1	3	15	1	2 HAT 5 hepatic artery stenosis 1 hepatic vein trombosis 1 portal vein trombosis
Mergental et al. [24]	5	1/4	56 (47–66)	10 (7–17)	Organox/ liver assist	10(6–15)	7(6–9)	0	100%	100%	0	0	0	0	0
Bral et al. [28]	9	6/3	54 (43–69)	17 (9–32)	Organox	45(13–114)	6	1 HCV relapse	89%	90%	0	0	0	0	0
Ravikumar et al. [22]	20	16/4	54(33–66)	12 (7–27)	Organox	12 (6–34)	9	1 alcohol relapse	95%	95%	0	0	0	4	0
Selzner et al. [27]	10	8/2	56(45–71)	21 (8–40)	Organox	11(8–17)	3	0	/	/	0	0	0	0	0
Watson et al. [26]	22	6/16		/	Liver assist	/	/	0	94%	75%	1	0	5	4	0
Ghinolfi et al. [32]	10	10/0	57(46–61)	12 (9–16)	Liver assist	12	7–18	1 HAT	100%	90%	0	0	3	3	1 HAT

Author	N	DBD/ DCD	Recipient age	Recipient MELD	Machine	Hospital stay (days)	FU (months)	Graft loss causes	6 months Pt Survival	6 months graft survival	PNF	DGF	PRS	ITBL	Vascular complications
Liu et al. [21]	15	10/5	/	/	Cleveland clinic	17(14–22)	/	1	/	/	0	0	0	1	1 HAT
Angelico et al. [23]	6	4/2	55(34–66)	12 (9–18)	Organox	9(5–14)	/	1	/	/	/	/	/	/	/
Watson et al. [25]	12	3/9	57(46–65)	17 (10–26)	Liver assist	/	9–24	1 PNF	92%	92%	1	0	/	3	/
Bral et al. [29]	43	33/10	57 (40–63) 59 (50–63)	22 (17–24) 25 (21–32)	Organox	16 (12–20) 43 (22–61)	6	Biliary stricture Cholestatic hepatitis	94% 93%	100% 88%	0	11	/	0	0
Ceresa et al. [30]	31	23/8	58 (25–73)	14 (7–24)	Organox	13 (7–31)	12	2 HAT	100%	84%	/	4	3	0	2 HAT
Van Leeuwen et al. [33]	11	11/0	61 (55–66)	14 (13–15)	Liver assist	/	12	0	100	100	0	/	/	1	0

Viability Parameters

Transplant surgeons are called on daily to decide whether or not to use a graft. Historically, the assessment of a liver graft involved a review of the donor's medical history, biochemical and instrumental analysis followed by visual inspection during retrieval and eventually biopsy. Recently some prognostic models have been created to give an estimation of risk of graft failure [34–36]. These models help to reduce uncertainty about graft viability but do not completely eliminate it.

Viability assessment should be directed toward analysis of hepatocellular compartment and cholangiocyte compartment [37].

Hepatocellular Compartment

Liver lobule is divided into 3 zones. Zone 1 is the closest to portal triad and is exposed to higher concentration of oxygen, hormones, and metabolic substrates. Zone 3 hepatocytes include metabolic processes that are less dependent on oxygen.

Gluoconeogenesis from lactate and aminoacids takes part mainly in Zone 1 while glycolysis in Zone 3. Glycogen synthesis from generated glucose happens mainly in Zone 1 while glycogen synthesis from circulating glucose in Zone 3.

During hypothermia, liver faces an oxygen-independent glycogen breakdown [38, 39] that continues during the early phase of NMP.

Shortly after, the high levels of glucose should stimulate glycogenesis, thus causing a glucose fall in the perfusate.

Should the glucose not rise, this could mean there has been a glycogen depletion or panlobular injury [37] (Fig. 15.4).

Lactate metabolism occurs mainly in Zone 1; as this is the last zone to be deprived of oxygen, impaired lactate clearance could mean panlobular injury.

As Zones 2 and 3 do not take part in lactate clearance, their injury cannot be detected by this marker.

Transaminases give an indication of damage but are of a limited function to assess viability.

As the liver has a remarkable regenerative potential, it is unclear what threshold of all of these markers should be adopted to warrantee a complete post-LT functional recovery.

Cholangiocyte Compartment

Ischemic cholangiopathy (IC) is a main concern in LT as its development cannot be predicted.

The possibility to assess bile ducts during NMP is of great interest as it may reduce IC incidence.

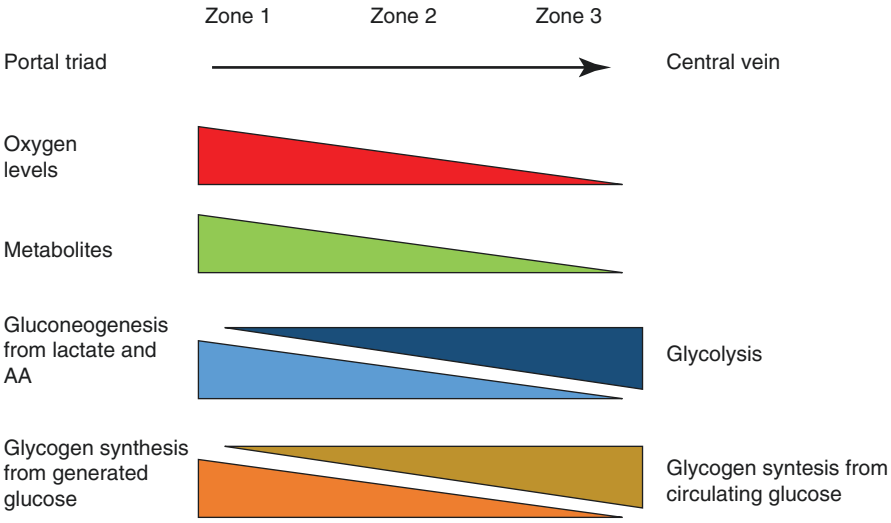

Fig. 15.4 Metabolic zonation of the liver lobule. (Adapted from Watson and Jochmans [37]. With permission from Creative Commoncs Licens 4.0: http://creativecommons.org/licenses/by/4.0/)

Bile normally undergoes deprotonation and glucose removal; deprotonation is achieved by bicarbonate secretion so that an alkali pH should be associated with viable cholangiocytes. Glucose <3 mmol/L should also represent a normal cholangiocyte function.

The amount of bile production has been proposed as a marker of viability. In a preclinical study, Sutton et al. reported their experience with 12 discarded livers. They concluded that bile production can be used as an easily assessable marker of liver graft viability during ex-vivo NMP, given that cumulative production of >30 g of bile during 6 hours NMP was associated with significantly lower release of transaminases and potassium into the perfusate and better hepatobiliary function as reflected by a normalization in glucose and lactate levels and higher secretion of bilirubin; in addition histology showed less signs of venous congestion and hepatocellular necrosis [40]. These findings, although interesting, are not conclusive, as the livers were never transplanted. In other experiences bile production did not appear to be related to post-LT function [25].

Clinically Used Viability Parameters (Table 15.2)

Some authors have proposed some viability parameters in clinical studies.

Table 15.2 Viability parameters proposed in clinical studies

Clinically used viability parameters			
Author/year	# graft	Device	Viability parameters
Mergental et al. [24]	6	Liver assist/ Organox	Lactate <2.5 or bile production plus 2 of the following: pH > 7.3 HA flow >150 ml/min and PV flow >500 ml/min Homogeneous graft perfusion
Watson et al. [25]	12	Liver assist	Lactate Glucose Transaminases pH
Bral et al. [28]	10	Organox	Perfusate biochemistry Need for bicarbonate correction Perfusion flow stability Hourly bile production
Van Leeuwen et al. [33]	11	Liver assist	Perfusate lactate <1.7 mmol/L pH 7.35–7.45 Bile production >10mL Bile pH >7.45

Mergental et al. evaluated 6 discarded grafts, 5 of which were finally transplanted [24]. Lactate had to be <2.5 or bile had to be produced in combination with at least 2 parameters between: pH > 7.3, HA flow >150 ml/min and PV flow>500 ml/min, homogeneous graft perfusion. A graft was not transplanted due to abnormal arterial anatomy, causing a lactate level rising.

Watson et al. reported a series of 12 transplants with livers potentially viable but where the ischemic time would have been unreasonably long or there was uncertainty about the quality based on the subjective evaluation of the retrieving surgeon [25]. Viability was assessed by changes in lactate, glucose, and transaminase concentration as well as on the ability of the liver to maintain pH without supplemental bicarbonate.

Bral et al. reported a series of 10 cases where they evaluated liver perfusion quality by variation in perfusate pH, lactate concentration, vascular stability, and hourly bile production. A graft was discarded due to an unnoticed portal twisting [28].

Van Leeuwen et al. proposed the following parameters to evaluate viability: perfusate lactate <1.7 mmol/L, pH 7.35–7.45, bile production >10mL, and bile pH >7.45 [33].

All of these parameters have been created and proposed based on hypotheses and have never been validated. We are unfortunately far from being sure about what graft will function or not by assessing its function during NMP. Moreover proposed parameters are somewhat restrictive and could result in discarding of livers that could be transplanted without complications.

Ghinolfi et al. [32] reported that 6 of the 10 of the NMP livers they transplanted in their pilot study presented an acidic bile pH. Based on previously proposed data

those grafts should have been discarded but in fact they were successfully transplanted and none of the recipients developed IC.

NMP undoubtedly brings the potential to assess viability of a graft on an objective basis, but more trials are needed to identify optimal markers and their applicability.

DCD and Normothermic Machine Perfusion

The global shortage of organ donors will not be resolved solely by relying on deceased donation following a brain death determination (DBD). Expansion of ECD and particularly deceased donation after circulatory death (DCD) will be needed to address the shortfall of transplantable organs.

In Europe, there are approximately 350,000 cases of cardiopulmonary resuscitation a year (1000 cases per day). Only 40% (400) of such cases are successfully resuscitated to result in a 15% hospital survival and 12% patient survival at the end of 1 year [41]. The remaining 60% that do not recover become a potential for uncontrolled DCD. Two hundred and fifty deaths each day throughout Europe in the ICU becomes an opportunity for controlled DCD at the time of the withdrawal of futile treatment.

DCD liver grafts, due to warm ischemic damage, carry higher risks for delayed graft function (DGF), primary nonfunction (PNF), and biliary complications following transplantation [42]. Because of poor results with DCD liver grafts after conventional cold storage (CS), interest in liver machine preservation was renewed. NMP allows a subjective graft evaluation, and its usage was often directed to assess viability of ECD and particularly of DCD grafts.

Ravikumar et al. reported the first series of 20 NMP perfused livers successfully transplanted. Four were DCD grafts. Results were compared to 40 SCS preserved historical LT [22].

Selzner et al. compared a series of 10 transplanted livers, of which 2 were DCDs, with a historical series of 30 SCS preserved grafts and did not find substantial differences between the two groups [27].

Mergental reported a series of 6 declined livers, 5 of which were deemed transplantable after NMP evaluation. Four were DCDs liver that have been successfully transplanted [24].

Watson et al. reported a series of 12 declined livers successfully transplanted after NMP evaluation; 9 were DCDs, and 8 were alive at 12 months [25].

Bral reported a series of 10 livers (4 DCDs) transplanted after NMP preservation. One out of four DCDs was discarded due to an unnoticed portal vein twisting [28].

Watson reported another series of 47 liver perfusion of which 22 resulted in transplants. Sixteen grafts were from DCDs; 4 IC and 1 PNF have been observed [26].

Bral reported another series in 2018 of 46 NMP livers. Outcomes of back to base livers were compared to grafts perfused at donor's hospital. Ten were DCDs livers [29].

Nasralla reported a large randomized controlled trial on NMP. Thirty-four perfused livers were from DCDs. A specific analisis on DCDs was not reported [31].

Table 15.3 Clinical studies reporting LT with DCDs graft perfused with NMP

	# DCDs	Device	Viability	Median CIT	Median NMP	Recipient median age	Median MELD	PRS	PNF	EAD	IC	Peak ALT
Ravikumar et al. [22]	4	Organox	/	/	570	61 (52–64)	11 (9–12)	/	0	1	0	/
Selzner et al. [27][a]	2	Organox	/	106	480	56	21 (8–40)	/	/	/	/	619 (55–2858)
Mergental et al. [24]	5	Liver assist/ Organox	Lactate <2.5 or bile production plus 2 of the following: pH > 7.3 HA flow >150 ml/min and PV flow >500 ml/min Homogeneous graft perfusion	428	389	56	8 (7–17)	/	0	0	0	1242 (1188–1879)
Watson et al. [25]	9	Liver assist	Lactate Glucose Transaminases Ph	427 min	284	57	17 (10–26)	5	1	/	3	1069 (187–4991)
Bral et al. [28]	4 (3 LT)	Organox		208 (108–284)	735 (196–1347)	62 (62–69)	16 (9–26)	0	0	3	0	/
Watson et al. [26]	16	Liver assist	/	386 (292–448)	/	/	/	5	1	/	4	/
Bral et al. [29][a]	10	Organox	Perfusate biochemistry Need for bicarbonate correction Perfusion flow stability Hourly bile production	4.6 Hours (1–8.4)	9 Hours (3.3–22.4)	58 (40–63)	23 (17–32)	/	0	6	0	437 (252–1536)
Nasrala et al. [31][a]	34	Organox	/	126 (106.5–143)	547.5 (372.5–710.5	55 (48–62)	13 (10–18)	15	1	12	1	/
Ceresa et al. [30][a]	8	Organox	/			58 (25–73)	14 (7–24)	3	0	4	0	/
Van Leeuwen et al. [33]	11	Liver assist	Perfusate lactate <1.7 mmol/L pH 7.35–7.45 Bile production >10mL Bile pH >7.45	/	504	61 (55–66)	14 (13–15)	/	0	/	1	683 (282–757)

[a]Data are cumulative as those on DCDs cannot be extracted

Ceresa reported a series of 31 LT with NMP. Eight were DCDs. A specific analysis on DCDs was not reported [30].

Van Leeuwen reported a series with 11 DCDs that were previously discarded as non-transplantable. Their graft and patient survival was 100% at 12 months [33] (Table 15.3).

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Liver Transplantation From Uncontrolled DCD Donors

16

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Introduction

Donation after circulatory death (DCD) donors, which are declared dead following cardiorespiratory arrest, is an increasingly more common source of organs for transplantation. They may be classified among four categories depending on events and conditions surrounding arrest:

Category I:	Dead on arrival (no attempt at resuscitation)
Category II:	Sudden, unanticipated, and (a) out-of-hospital or (b) in-hospital cardiac arrest followed by unsuccessful resuscitation
Category III:	Anticipated arrest following intentional withdrawal of life support in ventilated patient not meeting brain death criteria
Category IV:	Sudden and unanticipated cardiac arrest occurring after or during the process of declaring brain death

Categories I, II, and IV are considered uncontrolled DCD (uDCD) and category III controlled DCD (cDCD) [39].

For practical purposes, category III cDCD and, to a lesser extent, category IIa uDCD donors comprise essentially all DCD donors that are used for transplantation globally. The period of warm ischemia surrounding arrest provokes organ injury, and DCD in general yields fewer organs per donor and ones of inferior quality when compared with donation after brain death (DBD) [41]. Uncontrolled category II DCD donors in particular may suffer prolonged periods of pre-recovery warm ischemia (up to 2–2.5 hours, Fig. 16.1) due to the unexpected loss of cardiocirculatory function, repeated attempts to achieve return of spontaneous circulation (ROSC),

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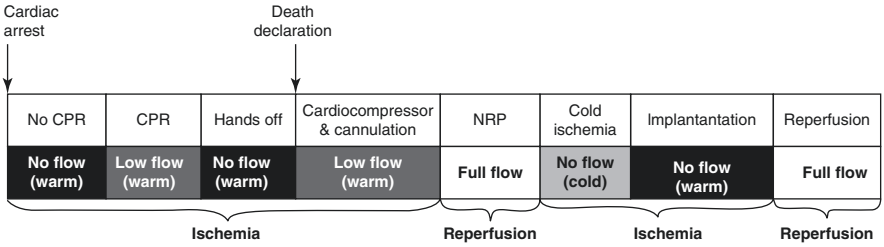

Fig. 16.1 In uDCD liver transplantation, the transplant graft is subjected to a relatively prolonged period of pre-recovery warm ischemia, which alternates between alternating low-flow and no-flow states. Under current protocols, the total length of this period can last up to 2.5 hours before full flow is restored using normothermic regional perfusion (NRP)

and lack of prior preparation for organ preservation when ROSC is finally not achieved. For this reason, recovery of viable uDCD livers for transplantation is difficult, and relatively few have been transplanted worldwide.

While liver transplantation using liver grafts from uDCD may not be a high-yield venture, accumulated experience has nonetheless offered valuable lessons regarding donor maintenance, graft selection and preservation, and recipient selection and perioperative management in what can reasonably be considered the most marginal form of human liver transplantation being performed currently. In this chapter, we discuss these and other aspects associated with uDCD liver transplantation, with the aim of demonstrating that, though complex, it does offer a viable alternative to more standard forms of transplantation.

Donor Process and Logistics

Uncontrolled DCD (uDCD) donors suffer sudden cardiac arrest, oftentimes outside of the hospital. Advanced cardio-pulmonary resuscitation (CPR) is performed according to international standards [22, 36], with the goal of achieving ROSC. When CPR is unsuccessful despite prolonged and repeated efforts and its futility has been recognized by the medical team treating the patient, the uDCD protocol may be activated and the patient routed to the nearest center performing uDCD. During transfer, chest compressions and mechanical ventilation are continued in spite of recognized futility in order to maintain flow of oxygenated blood to the organs and the possibility of their subsequent donation for transplantation.

In the hospital emergency department, death is declared based on the absence of cardiac function and spontaneous respiration during a no-touch period ranging from 5 min in most countries, including Spain and France, to 20 min in Italy and 30 min in Russia (in the latter, where category IIb uDCD kidneys have been recovered and transplanted) [1, 23, 33]. Following declaration of death, chest compressions and mechanical ventilation are reinitiated, the uDCD donor is systemically heparinized, and organ preservation maneuvers are initiated.

Abdominal preservation in uDCD may consist in rapid cooling of the organs using a double-balloon triple-lumen catheter [19] or in abdominal regional perfusion.

When abdominal regional perfusion is performed in uDCD, the abdominal circulation is isolated from the systemic circulation through the placement of cannulae in the femoral vasculature. Access to unilateral femoral vessels is achieved via open femoral cutdown and isolation of the femoral artery and vein or percutaneously using Seldinger technique [8, 12]. The contralateral femoral artery is also accessed for the placement of an aortic occlusion balloon catheter, which is advanced into the supraceliac aorta and inflated. The abdominal NRP circuit is then initiated. Proper positioning of the balloon in the supradiaphragmatic descending aorta is confirmed by chest radiograph. An in-line pump is used to recover venous blood, mix it with oxygen and other substrates, and return it to the subdiaphragmatic aorta. Abdominal regional perfusion may be performed at either hypothermic or normothermic temperatures. In hypothermic regional perfusion, the temperature of the perfusate is actively cooled to 0–20 °C, while normothermic regional perfusion (NRP) is performed without any active cooling of the perfusate. Currently, only NRP is used when uDCD liver donation is considered.

Normothermic Regional Perfusion

During warm ischemia, adenosine triphosphate degradation leads to the progressive accumulation of xanthine and hypoxanthine, important sources of superoxide radicals at organ reperfusion [13]. A period of post-ischemic NRP in DCD donors is useful to restore cellular energy substrates, [11], reduce levels of nucleotide degradation products [27], improve the concentrations of endogenous antioxidants [2], and even stimulate processes of cellular repair prior to graft recovery [17]. An experimental study demonstrates that by blocking the A2 receptors of adenosine, the beneficial effects of NRP are abolished, indicating that NRP mediates its effects in great part through adenosine [25]. Post-ischemic NRP may also be useful to reduce the vasoconstrictive effects of cold graft washout with the static cold storage solution [6].

In general, NRP is run for a minimum of 1 h and a maximum of 4 h to allow adequate reconditioning of the abdominal organs and recovery of energy substrates without provoking additional end-organ injury [10, 11, 17, 25–27]. Different centers use different criteria to assess the adequacy of uDCD livers undergoing NRP [7–9, 16, 34]. This assessment is largely based on factors related to the length of the initial warm ischemic insult and the evolution of hepatic transaminases and occasionally lactate levels during NRP. Some centers also rely on the results of hepatic biopsy to rule out moderate-to-severe macrosteatosis and/or the presence of fibrosis.

Ethical Issues

In uDCD, death is declared based on the irreversible loss of cardiorespiratory function, demonstrated after prolonged efforts to reverse it have failed. Death is typically declared in the emergency department and always by a team entirely independent of that responsible for organ recovery and preservation. More often than not, potential uDCD donors are declared dead prior to the arrival of next-of-kin. Based on a

consequentialist ethical standpoint and the principles of utility and donor autonomy, certain countries, including Spain and France, allow cannulation maneuvers to commence in this setting, even in cases where first-person consent may not have yet been obtained [1, 28]. The will of the potential donor regarding donation is always subsequently investigated in the context a family interview, where information regarding circumstances of arrest, outcome of resuscitation maneuvers, and measures taken related to the donation process, is relayed. Next-of-kin then decide, taking into consideration the potential donor's wishes, whether to proceed with donation or abort the process. Above all, it should be clear that NRP is organ maintenance and not therapy. While the technology employed is similar, terms such as "extracorporeal membrane oxygenation/ECMO" and "extracorporeal life support/ECLS" should not be used in relation to organ donation. Such terminology is confusing, especially considering the fact that it is used to describe therapeutic maneuvers that may be used to recover patients suffering sudden cardiac arrest more commonly occurring inside the hospital itself.

Graft Selection

In spite of great theoretical potential, considering the number of sudden cardiac arrests occurring in all parts of the world each day, the yield of viable livers arising through uDCD for transplantation is relatively low. In Spain, the actual utilization of uDCD livers for transplantation has ranged between 20 and 50% in recent years, based on the total number of uDCD liver donors evaluated [30]. Table 16.1 lists the current limits for accepting uDCD livers for transplantation in Spain [29]. These limits might be considered an obstacle to greater utilization of uDCD livers for transplantation, but reported uDCD liver transplant outcomes (graft survival, in particular) remain inferior to those achieved with standard DBD livers ([7, 14];Jiménez-Romero et la. 2019;[34]) (Table 16.2).

Table 16.1 Current limits for accepting an uncontrolled DCD liver for transplantation in Spain

Donor age	≤55–67 years, depending on region
Length of cardiac arrest prior to advanced life support	<20 min
Total length of warm ischemia (time from arrest to initiation of NRP)	<150 min
Length of NRP	Preferably <4 hours, though NRP can be maintained for up to 6 hours as long as biochemical, gasometric, and hematological parameters remain stable.
Transaminase evolution during NRP	Initial AST/ALT: <4× ULN Final AST/ALT: <5× ULN

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *NRP* normothermic regional perfusion, *ULN* upper limit of normal

Table 16.2 Donor and preservation conditions, acceptance criteria, and clinical outcomes of contemporary series of uncontrolled DCD liver transplantation

Study	Country	*N*	Donor age (y)	DWIT (min)	NRP (h)	CIT (h)	Acceptance criteria			PNF (%)	Overall biliary complications (%)	ITBL (%)	One-year graft survival (%)
							DWIT	Biochemistry	Biopsy				
Jímenez-Romero et al. [16]	Spain	75	42 ± 10	130 ± 22	NR	6.4 ± 1.4	Arrest to: CPR <15′, NRP <150’	AST/ALT <4x ULN	≤30% macrosteatosis No fibrosis	8	31	16	73
Hessheimer et al. [14]	Spain	43	46 (27–57)	107 (102–131)	3.3 (3.1–3.8)	6.3 (5.5–7.2)	Arrest to: CPR <15′, NRP <150’	AST/ALT <4-5x ULN	–	9	16	12	74
De Carlis et al. [7]	Italy	20 (incl. 6 cDCD)	51 (46–61)	125 (72–143)	5.9 (5.1–7.2)	8 (6–9)[a]	Arrest to NRP <160’	ALT ≤1000 IU/L Lactate declining	≤30% macrosteatosis Minimal-to-no fibrosis	10	20	10	85 (death-censored)
Savier et al. [34]	France	13	37 ± 3	137 ± 13	4.2 ± 0.6	5.8 ± 0.5	Arrest to: CPR <15′, NRP <150’	ALT <200 IU/L	<20% macrosteatosis	23	15	8	69

Continuous variables are reported as mean ± standard deviation or median (25–75% interquartile range), unless otherwise specified

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *cDCD* controlled donation after circulatory death, *CIT* cold ischemia time, *CPR* cardiopulmonary resuscitation, *DWIT* donor warm ischemia time, *ITBL* ischemic-type biliary lesions, *NR* not reported, *NRP* normothermic regional perfusion, *PNF* primary non-function, *ULN* upper limit of normal

[a]Includes a period of hypothermic oxygenated machine perfusion

Recipient Selection

Apart from tendency for more biliary complications and inferior graft survival, recipients of uDCD livers are at increased risk for the development of coagulopathy, hyperfibrinolysis, and post-reperfusion syndrome when compared with DBD liver recipients, indicating substandard immediate allograft function [3]. Greater proclivity for early dysfunction among these livers raises the issue of the appropriateness of their transplantation into recipients with a precarious pre-transplantation state. The poor tolerance of certain high-risk recipients to an ischemically injured liver is reflected in different cDCD liver transplant risk stratification scores that have determined re-transplantation and a high recipient MELD score to be factors associated with inferior post-transplant outcomes [5, 15, 18, 35]. Taking into consideration experience from both cDCD in addition to uDCD liver transplantation, it seems that avoidance of transplanting uDCD livers into recipients >60 years, undergoing repeat liver transplantation or transplantation for acute liver failure, and/or with higher biologic MELD scores (>25) is important [8, 9, 15, 16, 35].

Post-Transplantation Outcomes

Early reports of uDCD liver transplantation included organ recovery methods different from normothermic regional perfusion (NRP). In 1995, Casavilla and colleagues from the University of Pittsburgh reported on the transplantation of livers from category IV uncontrolled DCD donors. Following arrest, cardiopulmonary resuscitation (CPR) was maintained while donors were taken to the operating room, where super rapid recovery was performed. Six among a total of 10 uDCD livers recovered in this fashion over a four-year period were transplanted, but only one among the transplanted grafts survived beyond 2 months [4]. In La Coruña, Spain, livers have been be transplanted from category II uDCD donors maintained with ongoing CPR or normothermic or hypothermic perfusion. Reports on this group's experience transplanting a total of 27 livers (10 from donors maintained with simultaneous chest and abdominal compressions, 10 with NRP, and 7 with hypothermic perfusion) have described 18% primary non-function (PNF); 42% post-transplant biliary complications, including 25% non-anastomotic biliary strictures/ischemic-type biliary lesions (ITBL); and one-year graft survival of approximately 65% [31, 37].

In contrast with earlier experiences, contemporary reports on liver transplantation using livers from uDCD donors have all included the use of postmortem NRP. Series from Spain, France, and Italy have been published in recent years and have described 8–23% PNF, 8–16% ITBL, and one-year graft survival (not censored for patient death) of 69–74% following transplantation of these grafts (Table 16.2). These results are inferior to those achieved with standard DBD and even well-selected cDCD livers, though it has also been noted in these series that post-transplant results have improved from the initial to the more recent period of each group's experiences, with one-year graft survival rates in the latter periods

Table 16.3 Recommendations for the perioperative management of recipients of uDCD livers

Hemodynamic instability:
Adequate fluid management; consider the use of TEE when appropriate expertise is available.
Early vasopressor support, initiated prior to graft reperfusion.
Nephroprotection: Maintain MAP >70 mmHg, urine output >0.5 mL/kg/h.
Coagulopathy:
Maintain hemoglobin >8 g/dL.
Maintain platelets >50 × 10^9/L and fibrinogen >2 g/L prior to graft reperfusion and during closure.
Tranexamic acid:
10 mg/kg bolus before portal reperfusion.
10 mg/kg/h until completion of the biliary anastomosis.
Fibrinogen/cryoprecipitate and platelets:
EXTEM A10 < 35 mm and FIBTEM A10 < 10 mm: 2 U/10 kg cryoprecipitate (maximum 16 U) OR 50 mg/kg fibrinogen; evaluate response.
EXTEM A10 < 35 mm and FIBTEM A10 > 10 mm: 1 or 2 U of platelets; evaluate response.
Fresh frozen plasma:
EXTEM A10 > 35 mm and FIBTEM >10 mm with diffuse microvascular bleeding: 10–15 mL/kg FFP.
Abdominal packing during 48 h for diffuse microvascular bleeding.

CVP central venous pressure, *EXTEM* A10 clot amplitude at 10 min on ROTEM® EXTEM analysis, *FIBTEM* A10 clot amplitude at 10 min on ROTEM® FIBTEM analysis, *MAP* mean arterial pressure, *ROTEM*® rotational thromboelastometry, *TEE* transesophageal echocardiography
Adapted from Blasi et al. [3], With permission from John Wiley & Sons

surpassing 80% [8, 16]. Aside from meticulous donor and recipient selection (transplanting more younger recipients <60 years and with lower biologic MELD scores/more compensated liver disease), improved perioperative management of uDCD liver recipients, with aggressive correction of hemodynamic and coagulation abnormalities and prophylactic administration of tranexamic acid prior to graft reperfusion in all cases [3] (Table 16.3), has played an important role in the improvements in outcomes that have been observed over time.

Future Perspectives

Injury arising in uDCD livers is related not only to warm ischemia but also – and perhaps more importantly – reperfusion. The manner in which reperfusion is carried out may have a significant impact on the extent of injury and organ viability. Evidence from the resuscitation literature suggests that the physical conditions of reperfusion and the constitution of the reperfusion solution are critical factors in limiting reperfusion injury [20, 38]. In the context of a pilot study in which automated reperfusion was performed using high-flow, high-pressure pulsatile arterial perfusion and a solution that was (at least initially) acidotic, hyperkalemic, hyperosmolar, hypocalcemic, normoxemic (PaO2 100–200 mmHg), and subnormothermic (32–33 °C), significant neurological injury was limited and neurologically intact survival achieved in 14 consecutive patients with witnessed sudden cardiac

arrest followed by prolonged advanced CPR (51–120 min) [40]. In the future, if the use of this or other similar strategies is confirmed to be beneficial for achieving ROSC with neurologically favorable outcomes following sudden cardiac arrest, not only will more patients be recovered but those that are still unable to be recovered might be considered for uDCD with their organs, including the liver, in a theoretically less-injured state.

Ex situ machine perfusion (MP) is another technique currently under investigation to increase the number and improve the quality of livers from uDCD and DCD donors in general for transplantation. Machine perfusion provides a continuous supply of oxygen and other substrates during the ex situ preservation period, clears metabolic wastes, and offers an opportunity to assess graft function prior to transplantation [24, 42]. To date, clinical experience with fifteen uDCD livers undergoing in situ NRP followed by ex situ MP (14 hypothermic oxygenated MP – "HOPE" – and one normothermic MP) has been reported [7, 32]. While preliminary results of the aforementioned case studies have been promising, other recent reports on viability testing of marginal livers have described relatively high rates of post-transplant ITBL among cDCD recipients (25–30%) [21, 42], indicating the need for further refinement of the MP technique and/or selection criteria for marginal DCD grafts.

Final Comments

Liver transplantation using uncontrolled DCD donors is a complex form of deceased donor liver transplantation that is currently only performed at a handful of centers worldwide. The complexity of uDCD is primarily related to the process of donation, which requires coordinated efforts by numerous professionals in the field and in the emergency department, as well as the added obstacles that surgeons and anesthesiologists face on the recipient side. At present, in situ preservation with normothermic regional perfusion is considered a must if livers from uDCD donors are to be recovered for transplantation, and uDCD liver transplant programs adhere to relatively strict selection criteria in order to avoid disastrous consequences for recipients. In spite of all the added difficulties, uDCD remains a liver transplant option that has yet to reach its full potential. By optimizing out-of-hospital and in-hospital donor maintenance as well as ex situ preservation, there is hope that in the future more livers can be recovered from this large potential source of organs.

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Developing a DCD Liver Transplant Program

17

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With the growing clinical demand for liver transplantation across the world, liver transplant physicians and surgeons have searched for multiple strategies to increase access to life-saving treatment for patients with end-stage liver diseases. Donation after circulatory death (DCD) liver transplantation is a relatively untapped source of donor organs in many parts of the world. This is particularly prominent in the United States, which cumulatively has one of the largest liver transplant waiting lists in the world. In 2018, there were 2182 DCD organ donors in the United States, accounting for 22.7% of all deceased organ donors. Yet, only 537 DCD liver transplants were performed during that time, which accounted for 6.8% of deceased donor liver transplants in the country (SRTR data). Previous data indicate that excellent survival is possible with DCD liver transplantation; with high volume programs achieving equivalent graft survival compared to brain-dead donor liver transplantation, and 10–14% long-term graft loss [1, 3, 7, 8, 10]. With the significant risk of waitlist mortality in the end-stage liver disease population, DCD liver transplantation remains an important but underutilized source of deceased donor organs in many parts of the world.

The risk of graft loss and regulatory scrutiny has been a disincentive to broader utilization of DCD livers for transplantation. However, several centers in the United States have developed high volume DCD liver transplant programs [1, 3, 10]. In 2017, a single center in the United States was responsible for 10% of all US DCD liver transplant activity (SRTR data). The variation in the utilization of DCD liver transplantation in the United States suggest opportunities for further development of program expertise to increase transplant volume and reduce waitlist mortality [4]. In this chapter, we aim to review key principles that programs should consider in implementing a DCD liver transplant program. These key principles include: leadership and mentorship, team development and engagement, careful recipient

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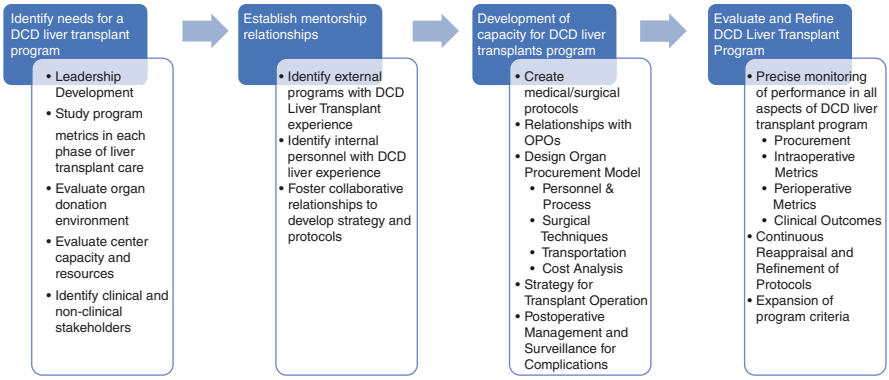

Fig. 17.1 A stepwise approach to DCD liver transplant program development

selection, utilization of data-driven protocols, relationship management with organ procurement organizations and donor hospitals, and the use of clinical quality improvement techniques to push stepwise program maturation. Figure 17.1 demonstrates a programmatic road map for developing and maturing a DCD liver transplant program in a liver transplant center. It is important to emphasize that this approach should be a part of a careful approach toward increasing the utilization of suboptimal deceased donor allografts, as many of the principles applied in DCD liver transplantation can be applied to other allograft types, including steatotic liver allografts and older age liver allografts. Through a careful and measured approach in our program, we have been able to expand the utilization of DCD liver transplant allografts to a volume of more than 60 transplants annually over a 5-year period in our institution, while maintaining excellent clinical outcomes.

Identifying the Needs for a DCD Liver Transplant Program

The Importance of Leadership Development

In the development of all new surgical programs, leadership is a critical element to successful initiation. Effective clinical program leaders must drive strategy, influence and manage change, establish buy-in with stakeholders, develop teams, identify pitfalls, barriers, and opportunities, and play a critical role in appraisal of program efficacy. These leaders should include the transplant surgical leadership and medical director of the program, as well as transplant center clinical and administrative leadership. These three or four individuals will play a critical role in the development of this program, but have several areas to develop prior to doing the first DCD liver transplant.

Once assembled, this core group of leaders must understand all aspects of the existing liver transplant landscape in the program. This will include individual and group study of program data from all phases of transplant care. These data will arise from external data sources such as those published in the program-specific reports by

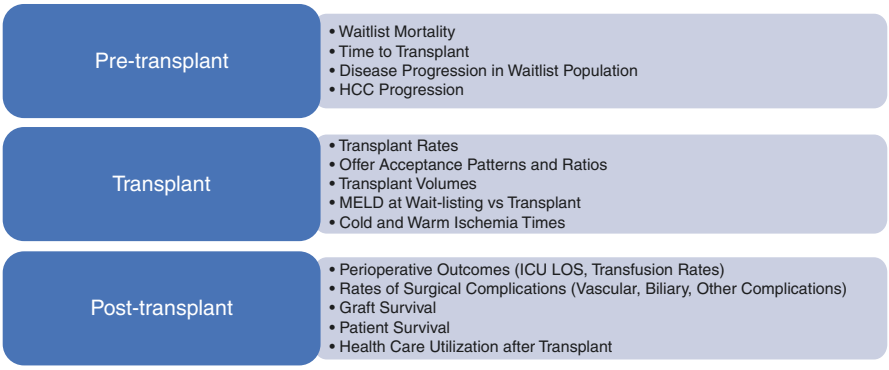

Fig. 17.2 Program metrics to assess prior to and after initiating a DCD liver transplant program

the Scientific Registry of Transplant Recipients and the Benchmark Report published by the Organ Procurement and Transplant Network. Internal data sources from program dashboards or databases may complement these sources and provide insights into the current status of transplant program performance. Metrics that should be areas of focus can be divided by phase of transplant (Fig. 17.2). Understanding these data is critical to understanding both the demand for a DCD liver transplant program and the current state of performance. Ideally, these data will also be assessed at other programs to serve as a barometer for the status of the program. This informs the core leaders as to current practice within the program, but also informs strategy development, and setting performance targets. These data can also be used to reassess program maturation once DCD liver transplant activity begins. It is also critical to understand the DCD liver transplant literature, which may inform programs on risk factors for complications, rates of complications, and other issues.

An important step before initiating DCD liver transplant program development is assessing potential sources for DCD liver allografts. Programs should have an understanding of local and regional organ procurement organization (OPO) performance and pursuit of DCD donors. The core leadership of the liver transplant program must be discerning in the desire of the OPO to pursue these cases, as well as their own surgical personnel to participate in them. Similarly, liver transplant leaders must evaluate the local resources within their centers that will play a role in the DCD liver transplant enterprise. This core group must work collaboratively to educate and inform clinical leaders in several departments that DCD liver transplantation will touch. For example, leaders must assess surgical and medical capacity, partner with nursing leaders to assess personnel capacity and preparedness, and identify champions in critical care and anesthesiology. These assessments can be challenging work, as establishing buy-in is never an automatic process. Initiation of DCD liver transplantation for the first time in any liver transplant program will be met with animosity, confusion, ignorance, and a host of other negative emotions. Leaders must help assess and educate personnel in other departments to mitigate these concerns. Clinical and non-clinical stakeholder identification and early engagement is nothing short of critical and is strongly advised.

Identifying Mentorship in DCD Liver Transplantation

An important element in the initiation of DCD liver transplantation is establishing a foundation of mentorship for the developing program. Mentorship should ideally be both external and internal. External mentorship may include partnering with an established DCD liver transplant center. This type of relationship can be formal or informal but should foster the sharing of ideas and collaboration between the two programs, based in honesty and transparency. This mentorship may include program visits, interactions between clinical personnel, and discussions. This may provide a sense of strategy and direction for the burgeoning program.

Similarly, clinical mentorship must be established within the program. Informing and educating individual providers in DCD liver transplant utilization, techniques, and post-operative management is key to a successful program; if it is not disseminated to all personnel, it simply devolves into a practice conducted by one or two personnel within a liver transplant program. Clinical mentorship should ideally come from one or more surgeons who may help to establish protocols but should also extend to hepatologists, advanced endoscopists, anesthesiologists, and critical care doctors. The appropriate mentors should bring their DCD liver transplant experience forward, have excellent communication skills, and should be open to influencing others' perspective. External and internal mentorship in this context can help shape protocols for organ procurement, surgical technique, surgical management, and post-transplant care.

Without appropriate mentorship, it is impossible to develop the village necessary to have a DCD liver transplant program.

In our experience, we sought mentorship from high volume DCD liver transplant programs. We reviewed their published data; sought out interactions; and discussed ideas related to procurement models, recipient selection, surgical techniques, post-transplant surveillance for complications, and many other issues. While our program has matured substantially, we still seek out these interactions to further refine the DCD liver transplant practice. Internally, we had multiple surgeons with at least some DCD liver transplant experience when we initiated the program and recruited others as the program grew. This led to the development of a highly collaborative environment in which to discuss ideas about DCD liver transplantation. We identified a few key strategic principles in this early experience:

- Develop a program guideline for DCD graft selection and encourage strict adherence to the protocol. Discuss organ offers with other personnel. Start slowly with "ideal" DCD liver allografts.
- Collaboration between medical and surgical personnel in the liver transplant program is key to identify patients who would benefit from DCD liver transplant listing.
- Assess and reassess program outcomes to ensure continued program viability and opportunities for program expansion.

Develop Capacity for a DCD Liver Transplant Program

Protocol Design for Recipient Selection

Programs must decide early on which patients on their waitlist would benefit from DCD liver transplantation. Multiple factors may affect recipient selection. We found that studying the dynamics of MELD score at waitlisting and at transplantation both in our center and in our region to be highly informative. We tend to target transplant candidates with relatively lower MELD scores who are devastated by their liver disease complications, such as ascites or variceal bleeding, who would otherwise have difficulty receiving a liver transplant. We also direct DCD grafts toward patients with hepatocellular carcinoma, who still continue to have low MELD scores even with the use of MELD exception points. Because DCD liver transplant grafts carry an association with post-reperfusion syndrome (PRS) during the transplant (a period of hemodynamic instability typified by hypotension, bradycardia or tachycardia, increased myocardial demand, hypothermia, and other derangements after reperfusion of the graft), we found it necessary to direct DCD liver grafts to patients who have good cardiovascular reserve [2, 11]. Additionally, recipient diagnosis is also a key consideration. We tend to avoid DCD liver grafts in patients with primary sclerosing cholangitis, as recurrent PSC and ischemic cholangiopathy can have similar phenotypes. Outcomes with DCD liver transplants are correlated with cold ischemia time, and judgment of duration of hepatectomy can be incorporated into guideline development (i.e., avoidance of DCD utilization in repeat liver transplantation or in significant prior upper abdominal surgery). Due to the risks of ischemic cholangiopathy, we avoid DCD liver transplantation in patients who will require Roux-en-Y hepaticojejunostomy to preserve access for advanced endoscopy. Importantly, we have not found portal vein thrombosis to be a contraindication as long as the portal confluence is patent. As patients are waitlisted, we determine if DCD liver transplantation should be considered for them. A detailed discussion of recipient selection can be seen in Chap. 9.

Protocol Design for Donor Graft Selection

Perhaps the greatest variation in DCD liver transplant practice surrounds graft selection protocols. Previous SRTR data from the early 2000s indicated that several factors were predictive of long-term graft loss including donor age, long donor warm ischemia time, long cold ischemia time, and high donor BMI [9]. Additionally, there is tremendous variation in program decision-making around donor warm ischemia time; specifically, there is no defined standard for what physiological parameters truly constitute the beginning of liver allograft tissue injury. Protocols defining donor warm ischemia time have been tied to systolic blood pressure thresholds, certain oxygen saturation levels, time to circulatory arrest, and time to initiation of cold perfusion. Previous registry analyses indicate that donor warm ischemia time

greater than 35 minutes is associated with higher risk of graft loss, but other programs have shown good results with donor warm ischemia time beyond 35 minutes [9]. There is a lack of consistency in definitions, namely, characterizing when ischemia begins, which makes this a difficult area for program decision-making. Programs should identify a protocol for DCD liver selection in order to provide consistency in results, based on mentorship, review of the literature, and clinical judgment. At Mayo Clinic in Arizona, we have employed a conservative definition for donor warm ischemia time in our program. We select grafts where the withdrawal of life support until cold perfusion time is ≤30 minutes without inclusion of hemodynamic parameters.

While organ recovery procedures aim to rapidly exsanguinate and cool organs down to reduce metabolism and preserve function, there is tremendous variability in practice of how DCD abdominal organ recovery is conducted. Programs should strongly consider consistent recovery approaches within the program to ensure reliability of organ quality. In the initiation of our DCD liver program, we performed all of our own recoveries with a consistent technique. This technique consisted of rapid aortic cannulation, initiation of high volume cold perfusion, exsanguination from IVC, aortic cross-clamping in the chest, and transection of the suprahepatic IVC in the pericardium and topical icing of organs. Portal venous cannulation is conducted through the SMV with a large cannula unless a pancreas is being recovered. We prefer using Custodial (Histidine-Tryptophan-Ketoglutarate) solution for preservation, but also accept organs preserved with UW solution. A major challenge for liver transplant programs is identifying whether external teams are proficient in DCD liver procurement. Programs must balance their perceptions of surgical quality and expediency in the procurement process. As we initiated our program, we were hesitant initially to utilize external teams for surgical recovery. As we have matured, however, we have developed trusted relationships with highly reputable abdominal organ procurement surgeons outside of our practice who facilitate organ recovery. The use of external procurement teams does effectively lower organ procurement costs and shields transplant team members from the sunk costs of a procurement trip that does not mature to yield a transplant.

Relationships with OPOs

No matter what protocols are used, it is necessary to partner closely with OPOs to ensure maximal utility of all available donor organs. These partnerships should focus on open discussion of what criteria should be utilized in pursuing DCD organs, efforts to interface with donor hospitals to pursue DCD donor opportunities, timely organ offers to programs, and the creation of specific protocols during DCD organ recovery. These protocols should include processes for timing of systemic heparin administration, real-time vital sign tracking after withdrawal of support, and communication to the procurement and transplant teams and should reflect donor family wishes and local hospital practices. Clear communication is also critical at each organ recovery. “Huddles” between the organ procurement staff and

transplant team are encouraged (See Chap. 2). An inevitable eventuality in the pursuit of DCD liver grafts is the donor that does not progress to death in a fashion that results in the utilization of the liver allograft after withdrawal of life support. This occurs in up to 50% of DCD donors based on our acceptance protocols. As in all organ recovery procedures, it is necessary for organ recovery teams to maintain a positive and professional approach during interactions with OPO and hospital personnel during DCD procurements. These interactions have a significant effect on perceptions of the organ donation and transplant community, and all recovery teams have a shared responsibility to maintain a professional and empathetic image. Importantly, transplant teams must avoid influencing any decisions on the end-of-life treatment of a potential DCD donor and maintaining professional interactions with any medical personnel they encounter who may be involved in the end-of-life care of the organ donor.

Relationships with Transplant Program Stakeholders

As transplant program leaders establish protocols for recipient selection, they must elicit support from key clinical personnel who will play a critical role in the management of DCD liver transplant recipients. We found it was critical to interface with several groups, which was done through daily multidisciplinary rounds, individual meetings and interactions, through transplant quality meetings. While there may be multiple groups with which to establish buy-in, we will focus the discussion on transplant anesthesiology and perioperative services personnel including nursing, critical care, advanced endoscopy, and interventional radiology providers.

Transplant anesthesiologists are at the front lines of the liver transplant procedure and must shepherd a patient through a series of massive metabolic derangements in every case. Each case includes the hepatectomy, obligatory coagulopathy, liver implantation, post-reperfusion syndrome, and correction of remaining coagulopathy, acidosis, electrolyte imbalances, and so forth. DCD liver transplantation is associated with higher rates of blood product administration, coagulopathy, and post-reperfusion syndrome [2, 11]. Engaging transplant anesthesiologists on the utilization of DCD livers is critical to assist in their preparedness for the intraoperative management of the recipient. This engagement leads to a collaborative relationship between surgeons and anesthesiologists that creates a partnership, not just across the ether screen but in programmatic initiatives at large. This partnership should explore approaches to coagulopathy management, coagulation monitoring, the use of procoagulant and anticoagulant drugs, invasive line use, the use of transesophageal echocardiography, and other issues. The increased demands on transplant anesthesiology teams during a DCD liver transplant procedure should be a subject of open discussion to create solutions and open lines of communication. Careful intraoperative management in these transplants is critical, so it is imperative that both surgeons and anethesiologists are partnered entities in each case.

As the patient transitions to the intensive care unit post-operatively, critical care specialists and nurses play a significant role in the management of the DCD liver

transplant recipient. Staffing models may differ in ICUs and so individual provider involvement in resuscitating a post-liver transplant patient may differ. In a closed ICU environment, critical care specialists will be charged managing the entirety of the resuscitation. Collaboration with liver transplant surgeons in this regard is critical, as there are distinct differences in managing a post-liver transplant patient compared to other patients who may present in shock. Being clear about goals of resuscitation and management of immunosuppression is essential. We have developed a hand-off algorithm from surgeon and anesthesiologist team to intensivist team that ensures a face-to-face discussion occurs in the transition of each patient, and goals of resuscitation are discussed. In open or closed ICU environments, joint development of post-liver transplant management protocols by surgeons, hepatologists, and critical care specialists is essential.

Key players in the management of a DCD liver transplant patient are the gastroenterologist specializing in advanced endoscopy and the interventional radiologist. DCD liver transplantation carries an 8–15% risk of ischemic cholangiopathy (IC), which is typified by non-anastomotic ischemic-type biliary strictures [3, 5, 8]. In any center with a considerable DCD liver transplant volume, the program will have to develop insight into managing IC. Programs must be aware of signs and symptoms of cholangiopathy. Several centers have employed routine surveillance for cholangiopathy through invasive or non-invasive cholangiography. Others have followed patients clinically and monitor liver function tests for signs of biliary injury, which trigger imaging studies. Importantly, IC is not a single disease but rather represents a spectrum of intrahepatic bile duct injury [6]. Management of these patients is rarely uniform. The utilization of endoscopically placed plastic and self-expanding metal stents (SEMS) is common in treating localized and diffuse strictures. Balloon cholangioplasty is used to open up strictures and to clear debris from the biliary tree. Strictures that cannot be treated endoscopically often need to be addressed through percutaneous access in the radiology suite, which can be difficult as the ducts are not typically dilated. IC introduces a significant clinical challenge to advanced endoscopists and interventional radiologists. We have found that with continuous engagement between transplant teams and these specialists, up to 50% of patients with IC can be managed without repeat transplantation and become stent-free.

Evaluation and Refinement of a DCD Liver Transplant Program

Performance Metrics

The SRTR reports on liver transplant program performance every 6 months. Public reports currently highlight waitlist mortality, transplant rate, and graft and patient survival. These metrics are subject to risk adjustment in order to ensure that programs are performing as they are expected to, based on the patients that they waitlist and transplant. It is important for programs to realize what areas affect SRTR reports of clinical outcomes, specifically with regard to risk adjustment. In a given DCD

liver transplant, there are hundreds if not thousands of data points that may affect clinical outcomes but simply remain uncollected or do not have significant effect size. Programs must be aware of what clinical measures the SRTR has identified as carrying a significant effect on graft and patient survival in liver transplantation, which are published and publicly available. Risk adjustment equations are subject to change depending on the dynamics of liver transplant activity over time, but programs should be aware of what donor and recipient factors carry significant weight. In turn, transplant program leaders should work with quality and compliance personnel at their center to ensure that risk factors are documented, easy to locate in the medical record, and submitted in a timely fashion to the Organ Procurement and Transplantation Network (OPTN). DCD liver transplant programs should aim to get optimal credit for each area of accountable risk taken in each transplant episode.

Even though every liver transplant program in the United States receives a program-specific report on its performance with regard to graft and patient survival from the SRTR every 6 months, DCD liver transplant programs should collect and evaluate their own data. These SRTR reports are lagging indicators of performance. Self-monitoring of clinical performance facilitates quality, and process improvement prior to falling below expected performance thresholds is key. This data collection and monitoring should identify leading indicators of adverse events and ideally should be viewed as one initiative in the quality monitoring of the broader liver transplant program. Metrics to evaluate performance should be identified a priori but should also be re-evaluated over time as the program matures. Metrics should include measures of waitlist morbidity and mortality, time to transplant and rate of transplant, MELD dynamics, as well as post-transplant performance. Post-transplant performance may include graft and patient survival, but it is becoming increasingly apparent that post-transplant performance monitoring should include more, such as the use of hospital services, readmission, freedom from invasive interventions, quality of life, return to normal functioning, or other metrics. DCD liver transplant programs should actively monitor rates of ischemic cholangiopathy, or proxies therein. Additionally, the SRTR also publishes CUSUM process control charts, which provide some indication of trends in performance deviation and the potential likelihood of being flagged for poor performance on a given report. Using extramural and intramural data tools to understand the status of the program is critical, as it helps reform program strategy, but also allows for educated engagement with transplant program and OPO stakeholders. It is particularly useful in discussions of post-transplant resource utilization, as DCD liver transplant complications can be significant, which can be a challenge to leaders and the program, as they can stress the system.

Monitoring DCD liver transplant program performance not only serves the purpose of monitoring for negative outcomes but also serves as a fulcrum to help expand the program. If program performance is strong, with low rates of death, graft loss, and ischemic cholangiopathy, programs can consider liberalizing criteria. This may include liberalizing recipient criteria as well as donor acceptance criteria. In our experience, stepwise reappraisals of performance and continually trying to innovate recipient and donor criteria have helped us develop into one of the most

aggressive DCD liver transplant programs in the United States, which has helped build liver transplant volume without a negative impact on transplant outcomes.

Concluding Remarks

Committing to develop a DCD liver transplant program in many ways requires a reinvention of the liver transplant program itself. It requires strong but collaborative leadership, identification of program demand for DCD livers, and broad stakeholder engagement inside the hospital with transplant and non-transplant personnel. Buy-in of clinical stakeholders is a must. Engagement with mentor DCD liver programs, OPOs, and others is a necessity. Additionally, protocols must be developed for recipient selection, donor acceptance criteria, and clinical management. A strong performance monitoring plan is necessary. Understanding the key principles discussed here may help DCD liver transplant programs provide wider access to liver transplantation to clinically vulnerable populations whose mortality risk is not well represented by their MELD score.

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Anesthesia for DCD Liver Transplantation

18

Ryan M. Chadha and Stephen Aniskevich

Brief Introduction to Liver Transplant Anesthesia

In 2011, the Organ Procurement and Transplantation Network/United Network for Organ Sharing (OPTN/UNOS) ratified a bylaw requiring all US centers to appoint a Director of Liver Transplant Anesthesia [1]. This was the first recognition by a central governing body of the existence of the field of liver transplant anesthesia. Leading up to this point, there had always been a discussion on whether these cases should be done by general anesthesiologists or subspecialized teams [2]. There is significant evidence in support of dedicated teams for liver transplant cases. It has been shown that a dedicated team correlates with reduction in overall transfusion, laboratory tests performed, time of postoperative mechanical ventilation, postoperative days in the ICU, and rate of postoperative complications [3, 4]. In addition, one study linked anesthesiologist experience with liver transplants to perioperative mortality [5]. Currently, the field continues to advance perioperative care with the creation of evidence-based coagulation management standards [6], the development of early extubation/fast track protocols for liver transplant recipients [7, 8], the development of liver transplant anesthesiology fellowship core competencies and milestones to standardize training for future liver transplant anesthesiologists [9, 10].

As mentioned earlier in this text, rates of DCD liver graft utilization are increasing internationally. Therefore, as the field of liver transplant anesthesiology continues to evolve, it is imperative that anesthesiologists understand how these grafts differ from standard brain death grafts, the literature on intraoperative outcomes for DCD grafts, and how to prepare intraoperatively for DCD liver transplant cases in order to have successful outcomes.

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Difference Between a DCD Graft and a DBD Graft: The Anesthesiologist's Perspective

DCD donors are classified based on the Maastricht classification [11]. Regardless of the classification, they all share the characteristic that they are exposed to a period of warm ischemia prior to the cooling and preservation of the organ. It is this warm ischemic interval that can contribute to a higher degree of ischemia-reperfusion injury and post-transplant graft dysfunction or failure. Specifically, it is the functional warm ischemia (discussed in Chap. 5) that is critical to minimize. [12] This hypoxic insult can be minimized by the surgical technique (rapid recovery of the graft), which has been discussed earlier in Chap. 3.

Why is this important? Ischemia time has been identified as one of the critical risk factors for post-reperfusion syndrome (PRS), one of the most feared complications for the anesthesiologist during the liver transplant procedure. Hilmi et al. defined mild PRS as a less than 30% decline of mean arterial pressure or heart rate lasting less than 5 minutes that is responsive to an intravenous bolus dose of calcium chloride (1 g) or epinephrine (100 μg) without the need to start a continuous infusion of vasopressors [13]. Significant PRS was defined as a greater than 30% drop in mean arterial pressure or heart rate, asystole, or hemodynamically significant arrhythmias or the need for continuous infusion of vasopressors during the intraoperative period following reperfusion. They also included in their definition of significant PRS prolonged (defined as lasting greater than 30 min) or recurrent (defined as reappearing within 30 min after resolution) fibrinolysis that requires treatment with antifibrinolytic agents [13].

The causes of PRS are not well understood but are believed to be multifactorial in nature. The most common contributors include acid-base and electrolyte disturbances (potassium, calcium), as well as hypothermia and air emboli [14]. In addition, it is believed that the profound hemodynamic disturbance of PRS occurs because of the release of vasoactive substances from both the donor graft and the recipient's immune system immediately after liver reperfusion [15, 16]. Ischemic reperfusion injury and intestinal bacterial products leading to endotoxemia are also considered to be contributors. [17, 18] Therefore, physiologically, it would make sense that DCD grafts are at an increased risk of developing this complication.

Does PRS impact overall graft outcomes? It has been found that PRS can predict 3-month mortality as well as primary graft non-function [19]. A 2009 study revealed that patients who experienced PRS were more likely to develop acute renal failure as well as decreased early (less than 15 days post-LT) survival [20]. Additionally, studies have confirmed the persistent and severe hypotension associated with PRS results in an increased incidence of acute renal failure, which is an independent risk factor for 30-day and 1-year mortality [21, 22].

DCD Liver Transplantation and Intraoperative Outcomes

Extended criteria grafts (older donor age, macrosteatosis, prolonged cold ischemia time) traditionally are associated with a higher risk of PRS, and DCD grafts have been included in this generalization [14, 23, 24]. While the pathophysiology of DCD

grafts would seem to predispose to PRS, the question arises if there is an increased association with these grafts and adverse intraoperative events. Unfortunately, there is minimal data looking at the association of DCD liver transplantation with PRS.

Blasi et al in a study looking at uncontrolled DCD grafts compared to DBD grafts found that the DCD group had a higher incidence of PRS [25]. In a study by Xia et al attempting to identify risk factors for hyperkalemia (commonly found in PRS) during liver transplantation, DCD grafts were found to be associated with hyperkalemia in the early post-reperfusion period on univariate analysis [26]. Furthermore, Xia et al published an additional propensity-matched study looking at perioperative complications with DCD grafts and found that when compared to DBD grafts, DCD grafts had a higher incidence of hyperkalemia and PRS [27]. However, a recent publication from our institution demonstrated that while DCD grafts require more vasopressor and transfusions intraoperatively, the incidences of hyperkalemia, PRS, and cardiac arrest/arrhythmia are similar between both groups [28]. While further research is needed in this area, the potential for intraoperative hemodynamic instability with DCD grafts is markedly higher.

Intraoperative Preparation for Liver Transplantation with DCD Grafts

Many aspects of preparation for an anesthetic for a DCD transplant are similar to a standard liver transplant. This includes a general anesthetic with endotracheal intubation, placement of invasive pressure monitoring, and large-bore central venous cannulation for rapid volume administration. A pulmonary artery catheter can be considered; however, it should be noted that there is no evidence supporting its routine usage in liver transplantation (regardless of the type of liver graft used) outside of patients with portopulmonary hypertension [29]. Laboratory testing with arterial blood gas and electrolyte monitoring, as well as viscoelastic testing (Thromboelastography (TEG) and Rotational Thromboelastometry (ROTEM)) for coagulation management, should be utilized as well [30]. However, with the potential for extreme hemodynamic lability and multiorgan dysfunction in DCD liver transplantation, there are several additional considerations for the anesthesiologist (Table 18.1).

The use of transesophageal echocardiography (TEE) is becoming more prominent in liver transplantation worldwide. A recent survey study demonstrated a high utilization rate in US centers with a large number of anesthesia team members being certified [31]. Several studies have demonstrated the minimal risk associated with TEE in terms of the complication of variceal bleeding [32, 33]. It is a valuable tool especially for the diagnosis of acute myocardial ischemia, right ventricular

Table 18.1 Additional considerations for the anesthesiologist with DCD liver transplantation given the higher rates of the following

Post-reperfusion syndrome
Vasoplegia
Hyperkalemia
Coagulopathy
Acute renal injury

dysfunction, left ventricular outflow tract obstruction, and intracardiac thrombus [34, 35]. There have been no specific studies looking at the benefit of TEE utilization in DCD liver transplantation.

Beyond standard vasopressor and inotropic support, methylene blue and hydroxocobalamin (Vitamin B12) can assist in the setting of vasoplegia. Methylene blue works through inhibition of nitric oxide with resulting overproduction of cyclic GMP, resulting in improved systemic vascular resistance, mean arterial pressure, and contractility [36]. There are small cohort studies (none including DCD patients) in liver transplantation showing the benefit of methylene blue for post-reperfusion hypotension [37, 38]. Contraindications for its usage include a history of MAO inhibitor or selective serotonin reuptake inhibitor use, due to the risk of developing serotonin syndrome, as well as glucose-6-phosphate dehydrogenase deficiency. Similar to methylene blue, hydroxocobalamin (Vitamin B12) causes alterations in NO metabolism, resulting in improvements in hemodynamics. Evidence for its usage in liver transplantation is limited to case reports at this point, with no specific evidence when DCD grafts are used [39, 40].

In the setting of cardiopulmonary collapse, intraoperative extracorporeal support can be considered as an option if there is institutional capability. While evidence of this therapy is mostly case report driven, this may be an effective means to reduce intraoperative events associated with these grafts [41].

Conclusion

With the advent of dedicated liver transplant anesthesia teams, it is critical to have an understanding of the intraoperative implications of DCD liver transplantation. The pathophysiology of DCD grafts with increased warm ischemia time puts them at higher risk of intraoperative events like post-reperfusion syndrome; however there is minimal research in this area. In addition to standard preparation for a liver transplant, the anesthesiologist can consider the utilization of TEE, advanced therapies for vasoplegia, and if available, extracorporeal support for cardiopulmonary arrest in these cases.

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DCD Liver Transplant: The OPO Perspective

19

Danielle Balbis and Heather Markuson

Introduction

The process of organ donation is multifaceted, and one of the many complexities is donation after circulatory death, or DCD. Organ donation following *brain death (also known as neurologic death)* is a more straightforward process, as organs are recovered for transplant from patients who have been declared brain dead. However, for DCD, organs are recovered for transplant from patients who have been declared dead by cardiopulmonary criteria following the removal of life-sustaining measures and a 2–5-minute waiting period. The majority of these patients have experienced a devastating neurologic insult, have not deteriorated to brain death, and have little to no chance for a meaningful recovery. Together with the physician(s), the family elects to withdraw life-sustaining therapies. The Organ Procurement Organization (OPO) offers organ, tissue, and eye donation options to the family if the patient had not already registered his/her donation wishes. After authorization and obtaining a past medical and social history, routine testing is completed and clinical information is gathered before organ offers to transplant programs can be made. The liver is among the more commonly recovered organ for transplant from DCD donors. This chapter will review the pertinent details surrounding DCD from an OPO standpoint. At LifeQuest, the OPO that serves northern Florida, we have been providing DCD donation options for families continuously since 1993 [1]. Table 19.1 below illustrates this 26-year DCD history from 1993 through 2019. LifeQuest has facilitated the recovery of 449 DCD donors, which resulted in 285 livers transplanted. Additionally, 592 kidneys, 30 lungs, 11 pancreases, and 1 heart were transplanted, totaling 919 organs from these 449 generous DCD donors.

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Table 19.1 LifeQuest organ recovery services DCD data

Year	DCD cases	Kidneys	Liver	Lungs	Pancreas	Heart
1993	1	2	0	0	0	0
1994	3	6	0	0	0	0
1995	2	4	0	0	0	0
1996	4	6	2	0	0	0
1997	4	4	2	0	0	0
1998	5	6	3	0	0	0
1999	6	9	3	0	0	0
2000	11	11	4	0	0	0
2001	11	14	6	0	0	0
2002	13	18	9	0	1	0
2003	12	17	9	0	1	0
2004	18	21	12	0	2	0
2005	25	24	23	0	1	0
2006	22	31	17	0	1	0
2007	43	57	29	0	1	0
2008	27	36	17	2	0	0
2009	17	20	10	0	1	0
2010	25	38	17	4	2	0
2011	21	33	14	2	0	0
2012	14	19	13	0	0	0
2013	26	26	17	0	0	0
2014	27	31	18	0	0	0
2015	28	39	16	10	0	0
2016	21	31	12	6	0	0
2017	19	25	9	4	0	0
2018	18	27	9	2	0	0
2019	26	37	14	0	1	1
Totals	**449**	**592**	**285**	**30**	**11**	**1**

Hospital Service

To assure timely notification of patients who may have life-sustaining therapies removed for the purpose of death, the OPO must provide all partner hospitals with routine education regarding the identification and referral of these patients. The OPO must assist the hospital with developing policies that require the timely referral of patients whose families may elect to terminate life-sustaining measures. Timeliness of the referral is of utmost importance for these cases. Often when a critical care physician speaks with the family about the poor prognosis and the option of removing life-prolonging treatments, families that elect to do so typically want it done quickly. Whenever possible, the referral to the OPO should be made prior to the physician's conversation with the family, so that the OPO can determine if the patient could potentially donate and be available to speak with them immediately following their decision to end life-sustaining measures on behalf of their loved one. If the referral is made after the family agrees to remove life support, the family is then put on hold until the OPO can arrive to perform a DCD assessment and speak with them about donation options. This not only delays the withdrawal process, but it also delays the organ donation process if the family authorizes it.

Early referral is the key to a successful DCD program for OPOs, as well as better service to families and transplant programs.

Even though it is required by the Centers for Medicare and Medicaid Services' (CMS) Conditions of Participation for hospitals [2] to refer every imminent and actual death, referral variances still occur. The OPO must serve the hospital by rounding on staff and maintaining frequent visibility, providing in-services, assisting with organ donation policies and protocols, and following up promptly with key contacts in the hospital whenever there is a variance. Examples of variances can include late referrals, missed referrals, pre-approaches (mentioning organ donation to the family too early in the process), and *extubation prior to calling the OPO*. All of these can cause the loss of an organ donor, but it is the latter that is the most frequent reason for losing a potential DCD donor for many OPOs. For example, some families will make a decision to withdraw life support on their own and proactively speak with the critical care team to have their loved one removed from life-sustaining measures. When this occurs and the physician agrees, sometimes the patient is removed from the ventilator hastily and only then is the referral made to the OPO. In this scenario, it is too late to offer organ donation options, and the donation opportunity is lost.

Organ procurement organizations must provide the appropriate resources to provide excellent hospital services and assure the referral of all potential DCDs in a timely manner in every hospital in the OPO's service area that has ventilated patients. Without the referral, there can be no organ donor, and consequentially, no liver or any other organ, for transplant.

Referral Response

When the referral of a potential DCD donor is made by the hospital to the OPO, a prompt response is crucial. OPO personnel must arrive on site to the hospital expeditiously in order to perform a DCD assessment before speaking with the family. The reasoning behind an assessment prior to speaking with the family is that the OPO can offer the legal next of kin/family an appropriate option for organ donation. Most patients who are referred to as potential DCD donors do not meet the requirements to become organ donors due to medical suitability and/or the time constraint associated with the period it takes the patient to expire following removal of life-sustaining therapies. Generally, for a DCD liver donor with no medical criteria rule out, the patient must die within 30 minutes after removal of life-sustaining measures in order to be a suitable liver donor. These 30 minutes are critical and provide the transplant programs valuable information about whether the liver will be suitable to transplant into their patient. At times during these 30-minute windows, the patient experiences a prolonged episode of hypotension or oxygen desaturation, which can lead to the liver not being viable for transplant. Other times, the patient dies very quickly, which is the optimal scenario for a transplant program to be able to provide a quality liver for their recipient. While it can be challenging to predict how long it will take a patient to die after life support is withdrawn, it is imperative for the OPO

to attempt to have a reasonable deduction based on clinical information gathered and, frankly, OPO experience. The University of Wisconsin and other OPOs have developed DCD assessment tools [3] that they find useful in improving accuracy when attempting to determine how long it will take a patient to expire once life-sustaining treatments are removed. Other OPOs do not take this consideration into account but rather pursue every potential DCD donor for whom authorization is obtained.

A thorough DCD assessment will include a review of the patient's current clinical status, past medical and social history, body mass index (BMI), hemodynamic status, Glascow coma score (GCS), and ventilator settings [4]. One component when reviewing the patient's past medical and surgical history is to identify any medical conditions or surgical procedures of the chest or abdomen that could have resulted in potential adhesions. This is of particular importance in the DCD liver assessment so that the OPO can provide the transplant programs with information that there may be challenges during an expeditious abdominal recovery. The size of the potential donor including height, weight, BMI, and abdominal girth are critical pieces of information for liver transplant programs, as they are attempting to match donor livers with the most appropriate recipient on their waiting list. Additionally, donors with higher BMIs, coupled with large abdominal girths, will often present recovery challenges for the abdominal team.

There is particular focus on the patient's hemodynamic status especially as it pertains to vasoactive medications. It is important to assess the potential donor's dependence on vasoactive medications to maintain hemodynamic stability, as this provides one important piece of information regarding how long the patient may sustain a state of hypotension and/or how long it may take the patient to die after removing such medications. Another area of specific focus is assessing the patient's respiratory drive. Some might argue this is the single largest determining factor. OPOs will assess the patient's native respiratory drive, if it exists, above the set mechanical rate. If possible, a negative inspiratory force (NIF) measurement is taken. A NIF > 30 indicates a patient has an adequate ability to ventilate themselves following extubation. When the NIF is <30, the patient is not generating enough strength in the diaphragm to create the negative pressure gradient necessary for adequate ventilation. Additionally, patients who require high ventilator support such as those with an FiO_2 > 70% or Peep >10 cmH_2O to maintain oxygenation provide valuable information on the determination of the respiratory status following extubation.

Not all patients who meet DCD criteria present with the traditional severe neurologic injury and ventilator dependence. There are other types of patients with injuries, both new and old, who may still meet the criteria for DCD donation. Patients with high spinal cord injuries who are dependent on a ventilator may meet DCD criteria even though they are considered neurologically intact. It is their life dependence on the ventilator for respiratory support that makes them a potential DCD candidate. If the ventilator is removed, there is a high likelihood the patient could not maintain their respiratory function and would expire in the time frame for DCD donation. Patients with end-stage Lou Gehrig's disease (ALS), for example, may be considered for potential DCD donation due to the progression of the disease and their dependence on the ventilator for respiratory support [5]. When evaluating for

potential DCD donation, the OPO coordinator must look at the patient's reliance on pharmacological (vasopressor) and/or mechanical (ventilator or other) support to determine the probability that if these measures are removed, would death occur in the timeframe to allow organ donation? Some examples of non-ventilator mechanical support could include extracorporeal membrane oxygenation (ECMO), intra-aortic balloon pump, left ventricular or assist device (LVAD), or diaphragmatic pacer wires.

Neurologically intact patients, like those with high spinal cord injuries, present a particular challenge with regard to authorization. In many of these cases, the patients are determined to be mentally capable of making medical decisions for themselves, including those related to end-of -life. In those instances and in the absence of a donor directive, the OPO will approach the patient for authorization for organ donation. It is not with great frequency that OPO staff speak with an awake patient about organ donation options, but it does happen and OPOs must be prepared for it. OPO's excellence in communication with the hospital staff, transplant centers, donor families, and the patient/potential donor is pertinent in ensuring a seamless and successful donation experience for everyone.

A thorough DCD assessment during the referral response phase is imperative so that the OPO can provide the family with the most accurate information possible to facilitate their making the best decision for them and their loved one. It is equally as important for the OPO to gather this information to determine whether patients would *not* be eligible DCD candidates so that information can be shared with the family as well. A timely referral made by the hospital and an expeditious referral response by the OPO is paramount to set up the donation conversation with the family the best way possible. The conversation about the option of termination of life-sustaining measures should take place independently from the conversation about organ donation options [6]. Bringing up both options within the same conversation may appear to the family that they are making a decision to withdraw life-sustaining measures for the purpose of organ donation, which should never be the case. Families should make the decision to end life-sustaining therapies because the patient has little to no chance of having a meaningful recovery. Only after the decision has been made, should the family be offered the option of organ donation following death, as these are two separate end-of-life decisions.

The Donation Conversation

There are two methods for organ donation authorization for a potential organ donor when the patient's legal next of kin is available by phone or in person. One way is by requesting organ donation with the legal next of kin if the patient had not already made their donation decision. The other is to honor the donation decision the donor already made during their lifetime when they joined the state/national registry. After a referral is made to the OPO, the OPO first responder will check the electronic donor registry to determine if the potential organ donor declared his/her donation decision by joining the registry. If the name of the patient who was referred by the hospital

appears on the registry, it is confirmed by driver's license number, date of birth, and/or other methods to ensure that this is the correct person. It is important for the OPO staff to check whether any details are provided on the registry. Some people want to donate everything, and others want to donate only particular organs or tissues. When someone has registered their decision to be an organ donor upon their death, it is often called first-person authorization or donor designation. Once this information is acquired, it is shared with the family/legal next of kin. With donation after *brain death*, first-person authorization is straightforward in that the patient is already deceased and the donor designation is activated. For DCD, the patient will not be deceased until after life-sustaining therapies are removed and the physician declares death by cardio-pulmonary measures. Therefore, the conversation the OPO has with the family regarding first-person authorization is worded very carefully so that the family understands that the donation decision has already been made and that no organs will be recovered for transplant before death is pronounced and a 2–5-minute waiting period is upheld [7]. Most OPOs favor honoring first-person authorization with DCD donors, but it can be challenging to work out the details of *the process* with the families. One example is when families choose to be present with their loved one when life-sustaining measures are removed, comfort measures are given, and death is declared by the physician or his/her designee. OPO staff must maintain excellent communication with all involved so that the donor's wishes can be honored, the family's requests can be respected, the ICU staff and the declaring physician can work through their desired order of events for their dying patient, the operating room is kept informed, and the transplant program personnel are continually updated.

What may be even more challenging is when the family of the registered donor opposes donation, despite the donor's recorded wishes. Each OPO must develop its own protocols for handling these types of cases. This can certainly be challenging in donation after brain death cases as well, but once again, that is a more straightforward situation because the donor is already deceased. It is more delicate with DCD, because the timing of the donation conversation between the family and the OPO occurs while the patient is still alive. The first-person authorization is activated upon the death of the individual, and when the family plans to surround their loved one's bedside during the declaration of death phase and beyond, the challenge can become insurmountable. The only consistent practice among OPOs for this scenario is that most OPOs handle these on a case-by-case basis, rather than attempt to draw up a standard protocol in an attempt to fit all scenarios of first-person authorization with family opposition.

It is beneficial for OPOs to proactively work closely with each hospital's legal services department, risk management, and ethics committee to develop a position statement in support of first-person authorization regardless of legal next of kin or family opposition. This eliminates any discord between the OPO and the hospital during these encounters and puts everybody on the path of honoring the donor's wishes with a strong attempt to respect the family's needs. Fortunately, most families support their loved one's end-of-life wishes and the authorization process goes smoothly. Whether it is the donor who made the decision during their lifetime to join the registry or it is the family who authorizes organ donation on behalf of their loved one, DCD requires many thorough conversations with the family regarding

the step-by-step process, especially when the family chooses to stay with their loved one during the declaration of death phase. These thorough conversations can set up a compassionate death experience for the donor and their family.

Medical Management of the DCD Liver Donor

Following authorization, the OPO will begin to coordinate with the medical care team to ensure the patient is properly medically managed so that the liver is offered to the transplant program(s) with the best organ function possible in order to lead to the best outcome possible for the recipient. Medical management of the *brain-dead* donor is directed by the OPO coordinator, but in the case of a DCD donor, medical management remains in control of the critical care medicine team in the unit. OPOs do not have authority to write orders for clinical management on a patient who is still alive. Proactive meetings with the critical care medical teams within the OPO's service area hospitals to discuss donor management goals is crucial prior to a DCD case so that expectations are met when a DCD donor case arises. Widely accepted donor management goals for adult donors include keeping the patient normothermic, the mean arterial pressure (MAP) between 60 and 110, the electrolytes within normal limits, the urine output at 1–3 cc/kg/hr., and ventilator settings that maximize oxygenation saturation and pulmonary function while keeping the pH normal [4]. The OPO and critical care medicine team must work seamlessly together, but ultimately, the critical care physician is in charge of the patient's end-of-life care, the comfort measures that are provided during the withdrawal of life-sustaining therapies phase, and the legal declaration of death.

Most OPOs avoid requesting any invasive procedures, such as bedside liver biopsies, but those that do obtain permission from the legal next of kin/family. Bedside, liver biopsies can provide important information about micro- and/or macrosteatosis to liver transplant physicians and surgeons, but it is not common practice for DCD donors. Non-invasive tests that are needed are ordered by the critical care physician. Some examples include laboratory tests (e.g., liver function test, prothrombin time, partial thromboplastin time), radiologic studies, and ultrasounds. Prophylactic antibiotic coverage is also standard on all DCD donors, as well as any medications needed to maintain perfusion of the organs during the evaluation and allocation process. In addition to the standard required deceased donor information, the United Network for Organ Sharing, or UNOS, has a minimum requirement for OPOs in order to present a donor liver offer [8] as outlined in the Table 19.2.

Table 19.2 UNOS policy 2.11.B required information for deceased liver donors

The host OPO must provide all the following additional information for all deceased donor liver offers: **1**. Human leukocyte antigen (HLA) typing if requested by the transplant hospital, including A, B, Bw4, Bw6, C, DR, DR51, DR52, DR53, DQA1, DQB1, and DPB1 antigens in the timeframe specified by the transplant program **2**. Other laboratory tests within 12 hours of the offer: **a**. Alanine aminotransferase/asparate aminotransferase (ALT/AST) **b**. Alkaline phosphatase **c**. Total and direct bilirubin **d**. International normalized ration (INR) or Prothrombin (PT) if INR is not available **e.** Partial thromboplastin time (PTT) **3**. Pre-procurement biopsy results, if performed **4**. Pre-procurement CT imaging results, if performed.

DCD Liver Allocation

At the time of writing this book chapter, liver allocation in the United States has never been more contentious. The outcome of this long-standing debate is that OPOs are required to allocate livers from adult deceased donors to the most urgent recipient candidates in need within a radius of 500 nautical miles from the donor hospital. After that, DCD donor livers are allocated to recipient candidates with a MELD or PELD of 15 or higher within a 150 nautical-mile radius of the donor hospital, then a 250 nautical-mile radius, then 500 nautical miles, and so forth with some differences when the donor is under the age of 18 in order to ensure pediatric candidates awaiting a liver transplant have increased priority when pediatric donor organs become available. The United Network for Organ Sharing (UNOS) is responsible for the management of the organ procurement and transplant network. A significant component of this responsibility is to ensure the programming is accurate according to the most recent liver allocation policy that is approved. The goal of liver allocation, and that of any organ allocation, is to attempt to ensure the most equitable means of allocating these precious gifts of life to those in need. If there were an abundance of livers for transplant, there would be few, if any, allocation issues, but because livers remain a scarce resource, it is unlikely that a consensus on policy related to their allocation would ever be reached. OPOs will continue to follow the order of the list and will need to answer to UNOS for any variances related to liver allocation policy.

When making a DCD liver offer to a transplant program, it is essential for OPOs to present the complete donor picture in order for the liver transplant program physician or surgeon to make an informed decision about the donor liver suitability for his/her recipient. It is especially important to share the radiological interpretation of any imaging studies completed on the DCD donor, but also to share the actual images for the transplant programs to view themselves. Specifically with older DCD donors, viewing the actual images can assist liver transplant program personnel to look for any vascular changes in the donor that may impede the recovery. This can include things such as atherosclerosis in the abdominal aorta or abdominal aortic aneurysms.

Part of the evaluation for all organ donors is serologic and nucleic acid testing for diseases such as hepatitis B (HBV), hepatitis C (HCV), human immunodeficiency virus (HIV), syphilis, cytomegalovirus, Epstein-Barr virus, emerging pathogens, and toxoplasmosis. Until recently, donors who tested positive for HCV were highly unlikely to become DCD liver donors. Even with the availability of treatment for HCV, many transplant programs will not accept DCD liver donors who test positive for HCV. OPOs must stay well informed regarding which transplant programs will accept DCD/HCV positive liver offers and determine what the age limits are on this potential donor pool. With an increase in the number of transplants from HCV positive donors to HCV negative recipients, the age limit for DCD transplants for donors who test positive may change and should be part of the routine communication between OPOs and transplant center partners. For donors who test positive for HIV, it was previously mandated by UNOS policy that only the liver and kidneys can be

allocated; however, in February 2020 that has been amended to include all organs [8]. The DCD donation age cutoff for HIV-positive donors is 50 years old, but like HCV, the OPOs must stay in frequent contact with regional and non-regional transplant programs to determine if that age limit has increased for some programs.

Communicating the donor's known behavioral risk factors is also crucial when offering a DCD liver to a transplant program. Some donors have known risk factors that could produce an increased risk of disease transmission at the time of transplant. When a potential liver donor is deemed to be an increased risk using the current Public Health Safety PHS guidelines [9], the transplant centers are notified and prior to transplant must get permission from the recipients to agree to the transplantation of a PHS increased risk donor liver.

In addition to providing the standard organ suitability information such as laboratory test results, imaging, and donor medical and behavioral history, the OPO must provide additional information about the patient's neurologic status for a DCD liver organ offer. In the brain-dead donor liver offer, there is no mention of neurologic status because there is no need. Providing the liver transplant programs the neurologic condition of the organ donor, as well as respiratory and hemodynamic status, will help the transplant programs determine if they have confidence that there is a suitable liver for their patient and that they will expend the resources needed (transportation, surgeon, transplant personnel, etc.) to recover that donor liver on behalf of their patient.

DCD Liver Recovery

Once DCD liver allocation is complete and there is a transplant program that has committed to traveling to the donor hospital to recover the liver, an operating room (OR) time is agreed upon by the OPO and the liver transplant program. The OPO must carefully coordinate the location of the removal of life-sustaining therapies with the attending physician and critical care staff and coordinate the logistics of getting to the OR in time to prepare the body for incision and rapid recovery of the liver following death declaration and the associated mandatory waiting period. Communication is among the most important components of the coordinator's job when it comes to DCD donors. If the family would like to be present during the withdrawal of life support measures and declaration of death, the goal is to locate an area in close proximity or in the OR. OPO staff do not engage in conversation with the declaring physician about details associated with the removal of life-sustaining therapies, comfort measures, or the declaration of death process. If asked, the OPO responds with "please do what you would normally do for any patient who is being removed from medical intervention and ventilator support for the purpose of death." The practice of withdrawing life-sustaining equipment and providing comfort measures should be no different whether the patient is an organ donor or not.

Prior to the termination of life-prolonging measures, the OPO will coordinate a huddle with the declaring physician, ICU staff, OR staff, and on-site transplant

program personnel, to go over the plan for after the patient expires and what everyone's role is in the DCD process. This is of particular importance for all cases but especially when the family is going to be present for the withdrawal and it is occurring outside of the operating room suite. Some of the topics discussed during this huddle are transportation of the donor to the OR suite, transfer of the organ donor to the OR table, the rapid skin preparation for the organ recovery, the plan if the patient does not die in the time it takes to become an organ donor, and a review of the individual hospital's policy on the DCD donor procedure, including the waiting period and the hospital-specific OR time out verification process. In hospitals where DCD donors are not commonplace, a walk-through of the transportation route from the withdrawal location to the OR suite should be considered prior to withdrawal to ensure that there are no obstacles that may slow down the transportation time to the OR once the donor sustains cardiac death.

It is our experience in our OPO service area that families, when present during the withdrawal process, are not always aware of when their loved one has been pronounced dead after the removal of life-sustaining measures. Often, the declaring physician is respectfully quiet when he/she is providing comfort measures and auscultating for heart sounds. Families are grieving the loss of their loved one, hoping there is no suffering, and often the critical care physician will declare death in a very quiet manner. It is for this reason that our OPO will communicate with the family about placing a hand upon their hand when death has been declared. The OPO coordinator will notify the family that within a few minutes from that point, the OPO will need to take the patient to the operating room. Communicating this to the family several times before the withdrawal process will help the process go smoother when the time comes. It is important that the OPO does not rush the family or appear hurried when transporting the donor to the operating room. Making the experience peaceful and respectful for the donor and family is essential. Good communication with the unit staff, the family, the OR staff, and the transplant programs is what makes for a successful, efficient DCD liver donor recovery. Transplant program personnel should never be in the room when the critical care attending physician is removing life-sustaining therapies, providing comfort measures, and declaring death. This eliminates the appearance of, or actual, conflicts of interest by keeping the end–of-life care and the death of the patient entirely separate from organ recovery.

After the physician declares circulatory death, the OPO will alert the family when it's time to take the patient to the operating room. There is a 2–5-minute waiting period that is maintained in order to assess the potential for auto resuscitation. Generally, 1 minute of that waiting period is spent with the family saying their goodbyes and the remaining minutes are used to transport the patient to the operating room. Once in the operating room, the donor is prepped and draped as promptly as possible. During this time, the declaring physician is monitoring the donor for auto-resuscitation. Once the waiting time is complete, the physician confirms there is no auto-resuscitation, and the transplant program personnel can enter the room and begin the organ recovery.

It is important to mention that every hospital has its own unique way of carrying out the DCD donor process. For instance some hospitals will have a 2-minute waiting period and others will have a 5-minute waiting period before the incision can take place. Some hospitals will allow families into the operating room so that the withdrawal of life-sustaining therapies, administration of comfort measures, and declaration of circulatory death can be provided without the need to transport the patient during the 2–5-minute waiting period. Other hospitals will not allow families in the operating room so the DCD process occurs similar to what is described above. It is not uncommon for families to say their goodbyes and leave the hospital after the authorization of organ donation. When this occurs, most OPOs will choose to carry out the entire DCD process in the operating room and call the family with an update after the procedure has taken place.

Following the waiting period and the preparation of the organ donor, the transplant program will begin the operation of rapidly recovering the liver for transplant with the goal of keeping the warm ischemic time to a minimum. The OPO staff must assist the transplant programs in the operating room to ensure an efficient DCD process. The transplant surgeon will provide a visual inspection of the liver, which offers an early report to the OPO on the likelihood the liver will be recovered and transplanted. If there is any question about the liver, a biopsy may be taken and sent to pathology for a frozen section. The results of the frozen section will be available to the transplant team before their departure from the operating room. When there is a question about whether or not the liver will be used by the transplant program recovering the liver, the OPO will often have a backup in place with another transplant program. This would be the time to alert that backup transplant program about what information has been gathered thus far. Once the liver is flushed and taken out of the body, it is brought to the back table for another inspection, as well as packaging and labeling. It is at this time that the primary transplant program will make a decision on whether or not they will be accepting the liver for transplant for their patient. If they choose to decline it, the liver is offered to the backup program. On occasion, a liver transplant program may request biopsy waivers. Some OPOs practice a firm stance on declining biopsy waivers due to financial reimbursement reasons related to expenses incurred pursuing the case. Others will liberally grant biopsy waivers, especially to transplant programs that have a proven track record of transplanting livers more than discarding them. Most OPOs will entertain biopsy waivers for donor livers on a case-by-case basis.

Donor Family Follow-Up

Donor family follow-up post organ recovery is an important part of the donation process not only to update the donor family on the recovery outcome, but also to ensure continued support through their grieving process. The follow-up begins during the authorization process when many OPOs provide the family a booklet on

what to expect in the following weeks after their loved one's death. This booklet contains information about the donation process, what to expect at the funeral home, obtaining death certificates, grief counseling, local community support groups, and other valuable information for navigating the upcoming weeks and months. During the many conversations with the family that follow authorization, the OPO coordinator also goes over the aftercare that the family can expect from the OPO. If during this conversation the family elects not to receive communication from the OPO regarding the donation process or potentially from future recipients, that is documented in the donor's record and it is honored. Once the recovery process is completed, the OPO coordinator will contact the family via phone to give them the outcome and what organs were able to be recovered for transplant. If the family elected not to be present for the withdrawal, the time of death is provided to the family during this conversation. A follow-up letter is sent from the clinical coordinator or family advocate within the first 2–4 weeks of the donation providing the family with information about the recipients. To protect privacy this is typically limited to non-identifying information provided by the transplant center.

OPO Finances

OPOs must never let finances affect decision-making regarding the pursuit of DCD donors or liver-only donors. Even if an OPO will not receive cost reimbursement that meets the expense of a single donor, that donor must still be pursued. Every donation opportunity must be pursued until there are no more patients on the nation's organ transplant waiting list. Some organ donors yield more organs than others and therefore more organ acquisition charges from OPOs to transplant centers, but it is not a single donor that drives an OPO's financial health, rather the accumulation of all expenses, revenues, and cost reimbursement. This is thought through every year during the budgeting cycle. Some years OPOs might need to make adjustments if the number of single organ donors or DCD donors is on the rise. It is better to make these adjustments in the organ acquisition charge than to attempt to make individual donor decisions based on finances. That said, there are a significant number of patients being withdrawn from life-sustaining measures in hospitals throughout the country. Most of those patients do not meet criteria for DCD donation. Pursuing donation options with every patient for whom life-sustaining therapies are being removed, may be an irresponsible use of staffing resources, family time, hospital personnel time, and yes, expenses. For example, many of these patients are over the age of 80, some have cancer, or other medical rule out criteria. OPOs experienced in DCD donation will get very proficient at determining suitability of DCD donors. Having ample staff to be able to respond to the appropriate DCD referrals and perform thorough DCD assessments to determine medical suitability is crucial for a successful DCD program. Keeping abreast of transplant programs that accept DCD livers from older donors, donors with multiple co-morbidities, hepatitis C, etc., is fundamental. When OPOs engage in the pursuit of every potential organ donor regardless of yield, the finances will work themselves out.

After Action Review

Recovering organs from DCD donors can be challenging for both the OPO and the transplant program, and problem prevention can be learned through experience and through after-action review. OPOs should take the responsibility of coordinating communication with their local transplant programs to discuss every organ donor case, especially DCDs. LifeQuest and the Mayo Clinic Florida have been partners since 1998. In 2005, LifeQuest created the after-action review committee which meets once per week by conference call to discuss every donor that occurred in the LifeQuest service area. The e-mail invitation for this conference call is sent to hundreds of people within the three local transplant centers and LifeQuest. In the beginning, many people joined the call to discuss what went well and what could be improved during each of the donor cases. Over the years we have experienced a decrease in the number of participants on the after-action review call and attribute this to problem prevention due to frequent communication for 14 years. As liver allocation algorithms change in the next couple of years and livers are shared on a broader geographic scale, OPOs will be challenged to maintain this type of frequent communication. The donation service area (DSA) will be redefined or eliminated altogether. OPOs will need a further reach in order to maintain relationships with multiple liver transplant programs so that DCD donations can continue as seamlessly as when OPOs were working with only a small number of regular transplant program personnel. New technology such as liver perfusion machines could also change DCD practices. Perhaps more transplant programs will be inclined to accept DCD livers or marginal livers. Nevertheless, after-action review will be just as important, but the method may need to change.

Summary

Donation after circulatory death is on the rise (see Table 19.3). OPOs must continue to keep hospitals informed of this rising trend and continue to educate hospital personnel on the identification and early referral of potential DCD donors. Likewise, OPOs will need to continue to build upon their already-existing palliative and critical care physician relationships to make certain DCD organ donors are medically managed in a way that optimizes organ function while maintaining excellent end-of-life care. OPOs will need to analyze their trends to be sure staffing models keep up with the increase in referrals and actual donors to ensure that no donation opportunity is lost. Public education to encourage citizens to join the organ donor registry will continue to be a priority. OPOs should add DCD education to their community education repertoire, as there still remains a need for education for this type of organ donation. Finally, OPOs will need to carefully monitor the liver allocation changes, technology, and innovation related to DCD liver donation and transplantation. While DCD is increasing, it still remains the greatest opportunity to increase the liver donor pool in the United States.

Table 19.3 DCD donors in the US 1993–May 2019

Year	DCD donors
Total to date	19,214
Jan–May 31, 2019	1039
2018	2132
2017	1883
2016	1684
2015	1494
2014	1292
2013	1207
2012	1107
2011	1057
2010	943
2009	920
2008	849
2007	791
2006	642
2005	564
2004	393
2003	270
2002	190
2001	167
2000	118
1999	87
1998	75
1997	78
1996	70
1995	64
1994	57
1993	41

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Index

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