Extending Donor Pool with Donation after Cardiac Death in Kidney and Liver Transplantation: What is the Price to Pay?

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JURY

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Science needs a heart…

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ABBREVIATIONS

A&E	accident and emergency room
CIT	cold ischemia time
CPB	cardio-pulmonary bypass
CPR	cardio-pulmonary resuscitation
DD	deceased donors
DCD	donation after cardiac death, donation after circulatory death
cDCD	controlled donation after cardiac death
uDCD	uncontrolled donation after cardiac death
DBD	donation after brain death
ECD	extended criteria donors
ECMO	extracorporeal membrane oxygenation
HBD	heart beating donation
HMP	hypothermic machine perfusion
ICU	intensive care unit
IRI	ischemia reperfusion injury
ISP	in-situ perfusion
KT	kidney transplantation
LT	liver transplantation
MP	machine perfusion
NHBD	non-heart beating donation
NMP	normothermic machine perfusion
OR	operating room
ORPD	number of organ retrieved per donor
OTPD	number of organ transplanted per donor
SCD	standard criteria donors
SCS	static cold storage
UNOS	United Network for Organ Sharing
UW	University of Wisconsin
WIT	warm ischemia time
WLST	withdrawal of life-sustaining therapy/treatment

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Introduction and Aims

1.1 DCD donors - The forgotten donors

Historical aspects

In the infancy of clinical transplantation, organs were recovered from donors declared dead by cardio-pulmonary criteria, known as non-heart-beating donation (NHBD). In 1968, given the availability of the Harvard's brain-dead criteria,[1] and given the better results of organ transplantation and the potential for multi-organ procurement from donation after brain death (DBD),[2] heart-beating donation (HBD) has almost replaced NHBD. NHBD is now termed 'donation after cardiac death' or, more recently, 'donation after circulatory death' (DCD), or donation after circulatory determination of death" (DCDD).[3]

The renewed interest in DCD started since the 1990s following the growing gap between the demand for transplantation and the supply of optimal DBD donors (i.e. standard criteria donors, SCD), and following the limited success of the transplant community to expand the donor pool through the liberalization of the donor acceptance criteria, the use of suboptimal or marginal donors (extended criteria donors - ECD), the application of split technique (transaction of an entire deceased-donor (DD) organ into two transplantable portions), and the promotion of living donors (kidney, liver, pancreas, small bowel, and lung). Even with these persistent and innovative efforts, the disparity between organ supply and demand never comes to an end. The inability to address the transplantation need and donation shortage represents the root causes for many patients dying or having a poor quality of life and for unacceptable practices, such as organ trafficking and transplant tourism.[4] Continuing organ deficiency increases the number of patients on the waiting list with longer waiting time, higher pre-transplant mortality and worse post-transplant outcomes. More patients are now believed to die while waiting for a DD transplant than actually receive one.[5] The use of this alternative donor source is hence hopefully thought to solve this large discrepancy.

DCD classification

In the United States (US), DCD is considered *uncontrolled* (uDCD) when the cessation of cardio-pulmonary activity occurs suddenly and unexpectedly without any prior plans to procure organs, and *controlled* (cDCD) when the cardio-pulmonary arrest is expected shortly after a planned withdrawal of life-sustaining treatment (WLST) and is coordinated with a subsequent organ procurement.[6] In Europe, DCD is differentiated into 4 categories by the Maastricht classification, relying upon the mode and place of death (**Table 1.1.1**).[7]

Categories 1 and 2 are perceived as uncontrolled, category 3 as controlled, and category 4 as either uncontrolled or controlled depending on the individual circumstances. This classification is helpful in discussing some of the legal and ethical issues surrounding DCD. It also highlights differences in the potential for organ viability between categories.[8] New types of DCD have been recently suggested in Spain[9,10], Italy[11], and Belgium.[12]

Table 1.1.1. DCD Maastricht classification

Category	Circumstance of death	Location of death	Organ viability
1	Dead upon arrival	Outside the hospital	Viability testing
2	Unsuccessful resuscitation	A&E (Accident and Emergency Unit) ICU (Intensive Care Unit)	Viability testing
3	Awaiting cardiac arrest	ICU	Transplantation
4	Cardiac arrest while brain dead	ICU	Transplantation

In DCD, the heart must cease beating before organ recovery can begin. DCD organs are therefore subjected to variable degrees of warm ischemia (WI) prior to organ retrieval. Warm ischemia time (WIT) is usually unpredictable and longest in categories 1 and 2, but shorter and possibly predictable in categories 3 and 4. As a result, organs from cDCD suffer less damage and have better chance of recovery compared with those from uDCD. By contrast, in DBD, the heart remains beating. DBD organs are perfused by the donor's heart throughout the recovery process, and do not thus experience WI. Anoxia, acidosis, loss of intracellular homeostasis, and activation of inflammatory pathways may occur during WIT, and hence characterizing the fundamental difference between DCD and DBD. In this regard, WIT is the most important factor for damage to DCD organs.

Elements of protocols for recovering organs after cardiac death

Generally, cDCD donors are individuals who have an unrecoverable catastrophic neurologic injury resulting in ventilator dependency but not fulfilling brain-dead criteria, or who suffer from a terminal illness, like high spinal cord injury, end-stage neuro-muscular disease, and end-stage cardio-pulmonary disease. The clinical decision to discontinue medical treatment is based on the futility of further treatments, and on the request of the donor or the next of kin. The DCD candidate is then evaluated for the medical suitability and the request

for organ donation is discussed with the family. Attempt should be made to determine whether a patient will expire in a time frame consistent with donation. Subsequently, life-sustaining measures are withdrawn in the ICU or the operating room (OR) with or without the presence of the family. Once there are circulatory arrest and lack of respiration, a period of observation (also namely, no-touch period, hands-off period, or stand-off time) is mandated before organ retrieval can begin. After the observation period and death declaration, the recovery team may begin flushing preservation solutions and start the surgical procedure if withdrawal takes place in the OR. If withdrawal undergoes in the ICU, transport to the OR may start during or after the observation period in accordance with the family's wishes and the procedure is initiated only after the waiting period and death pronouncement.[13] In cDCD, the retrieval team is in place, and the donor is usually in stable condition prior to cardiac arrest, therefore limiting WI.

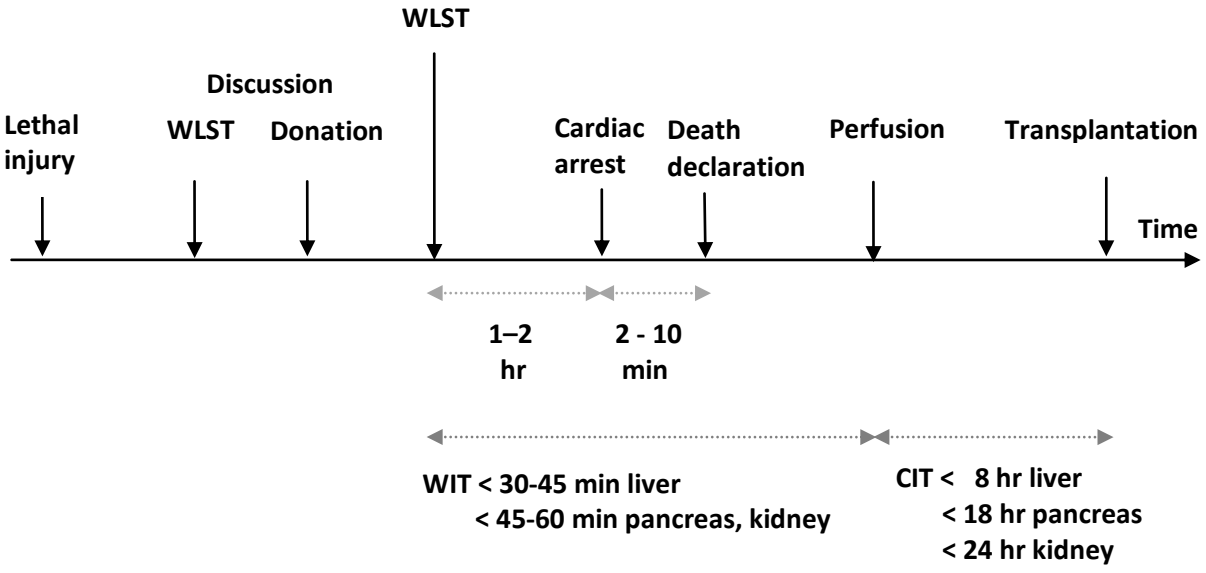

Figure 1.1.1. Timeline of events associated with cDCD.[14-16] Withdrawal of life-supporting therapy (WLST) is a critical event in the process of cDCD, which affects the time to donor death and thus needs to be meticulously delineated.

uDCD donors have an unexpected and irreversible cardiac arrest outside or inside the hospital, leading to an extensive WI of the organs. The recovery and use of these organs requires a permanent availability and a fast answer from the transplant team, as well as a strict WI protocol and careful donor management.[17] After a failed CPR, the potential donor is taken to the hospital in a mobile ICU under mechanical ventilation, external cardiac massage, and fluid perfusion to maintain adequate hemodynamic conditions. Upon arrival, the physician in

charge of the A&E room diagnoses the death and signs the death certificate. There is no additional 'no-touch' period. The DD is then checked for the conventional prerequisites for donation and transferred to the OR where an in-situ cold perfusion (using double-balloon triple-lumen (DBTL) catheters) or a cardio-pulmonary bypass (CPB) with external oxygenation and hypo- or normo-thermia, known as ECMO (extracorporeal membrane oxygenation), is performed to preserve the organs inside the body until retrieval while all legal requirements (judicial permission and family consent) are obtained. Afterward, organ extraction can start.

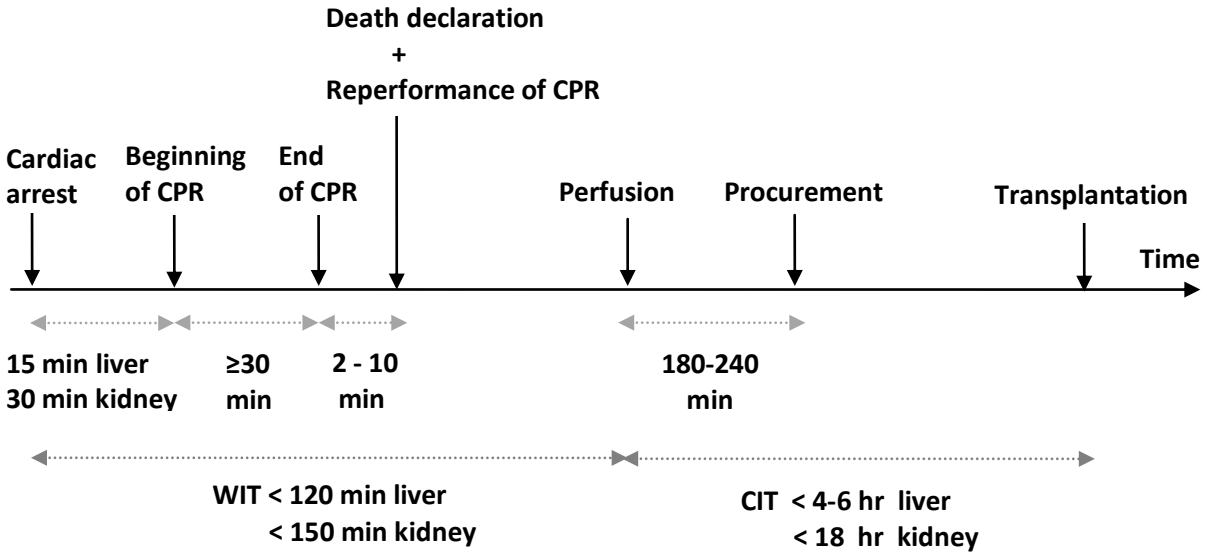

Figure 1.1.2. Timeline of events associated with uDCD.[10,17,18] CRP: cardio-pulmonary resuscitation. Cardiac arrest is only considered irreversible if lesions provoking the cardiac arrest are incompatible with life, and if effective heartbeats cannot be recovered after a stipulated period of at least 30 min.

Although the aforementioned principles for the recovery of DCD organs are widely recognized, considerable variations exist between transplant centers in the US, Europe and other countries regarding the ethical and procedural aspects of DCD (**Table 1.1.2**).[19-21] The lack of consistency in DCD practice may cause disparate organ recovery results that may impact organ function, contribute to public confusion, misunderstanding, and hesitation in acceptance of this mode of donation, and place health care providers at risk of civil or criminal liability.[22,23] Organ donation efforts can go terribly wrong if appropriate procedures are not followed.[24] Increased consistency of procedures, along with complete transparency, serves directly to increase public trust in DCD as an ethical means of organ retrieval, and appears increasingly important as the practice of cDCD continues to expand.[25]

Table 1.1.2. Some controversies and debates over the policies of DCD (predominantly cDCD)

Topics	Problems	Current consensus	References
Donor selection	Various donor acceptance criteria	?	[26-28]
Donor management (end-of-life care)	Premortem medications	-Heparin: standard of care -Other drugs?	[14,29]
	Premortem femoral cannulation	Under presumed consent or family's informed consent	[15]
WLST	Location and mode of WLST	In the OR, extubation and cessation of all inotropes	[15,16]
Death prediction	Various predictive tools for imminent death after WLST	Donation procedure should be initiated in every potential donor?	[30-34]
Death determination	Various confirmatory tests	Arterial line or Doppler study (mechanical asytole)	[14,35]
Warm ischemia time	Various definitions and recommended thresholds of WI	WIT: time interval from WLST to initiation of cold perfusion	[8,14-16,34,36-39]
Withdrawal (or agonal) period	Various time frames after which organs could no longer be recovered (1 – 5 hours)	Time frame consistent with organ donation is 1-2 hours	[13,40-42]
No-touch period	Various lengths of waiting time (2-20 min)	At least 2 min and not more than 5 min	[14,25,43,44]
Perfusion techniques	Various perfusion techniques	In-situ perfusion: technique of choice in uDCD	[10,45]
		Super-rapid laparotomy with direct aortic cannulation: technique of choice in cDCD	[46-49]
Organ preservation methods	Machine perfusion (MP) Static cold storage (SCS)	MP for all DCD categories? (kidney, liver, lung)	[50-55]
Surgical technique of organ retrieval	En-bloc removal or separate removal technique	?	[15,56]
Recipient selection (organ allocation)	High or low risk recipients Local/national sharing	Low risk recipients Local sharing	[14,57-61]

Logistic requirements for recovering organs after cardiac death

Implementation of a DCD program implies a very important logistical effort, both inside and outside the hospital, with an increased resource utilization in view of a lower yield of organs per retrieval episode and, to some extent, uncertain long-term outcomes.[26] With regard to WI, DCD is *an emergency* and *a race against the clock* because of the need to preserve organs as quickly as possible after cardiac arrest. To achieve an acceptable WIT, it is

necessary to have good planning, management, and organization, as well as a well-trained rapid-respond team.[62] uDCD requires more complex organization than cDCD. With regard to medical efficiency, DCD is *a challenge* for the transplant team because advanced medical technologies must be used to assure organ viability and acceptable post-transplant results and thus are associated with high medical costs. Estimates of 30-50% increase in hospital charges for patients receiving DCD kidneys and livers have been reported.[63,64]

Apart from legal and ethical barriers, logistics appears to be the most difficult part of the policy on DCD, mainly because it depends on the collaboration of many individuals. Locating these people and motivating them are the keys.[65] Efforts focused toward improving resource utilization such as better scoring systems and identifying donor risk variables would contribute to making DCD programs more economically productive.[66]

Ethical and legal issues

The renewed interest in DCD has resulted in renewed examination of the concept and meaning of death, the nature of consent, the propriety of interventions for the benefit of the recipient and not the donor, potential conflicts of interest, and the definition of futility.[67,68] Sensible ethical recommendations for the establishment of DCD programs have been published elsewhere. The Institute of Medicine in the US states that "recovery of organs from DCD is an important, medically effective, and ethically acceptable approach" in meeting the need for donated organs.[69]

Legal problems depend on the legislation of each country (opting out - presumed consent or opting in – informed and explicit consent), and in some instances, specific changes on the legislation must be done. Legal and ethical problems are specific for each type of DCD, controlled or uncontrolled, and can be solved by reaching agreements with the government, society, and medical community.[68,70,71]

The ethical, legal, organizational, and technical issues make evident the inherent difficulties in starting and consolidating a program of this nature and explain why DCD activity is just confined in some experienced transplant centers and some countries. Five European countries with highest DCD activity are UK, Netherlands, Spain, Belgium and France. While the organization of DCD procurement and transplant is at national level in UK, Netherlands, and Belgium, it is confined to center level in Spain and France.[19] Particularly, three countries in the world that have published national recommendations on the use of cDCD are Canada, the US, and the UK.[15,72,73]

Potential and efficiency of DCD programs: are DCD donors a true additional donor source?

Though the transplant outcome from DCD may not be as good as that from DBD, its potential donor pool is much larger for both the adult and pediatric populations. uDCD even has a greater potential than cDCD despite the fact that it now just makes a smaller contribution to the total DD pool.[74] Nonetheless, WIT is a limiting factor for this potential. The current stand-down rate is about 20-40%, essentially due to a prolonged time to death following WLST that results in severe ischemic injury to the organ or makes organ recovery logistically impracticable.[16,75] DCD donors usually contribute 10-30% of the national DD pool (exceptionally 2% in France, 5% in Spain, 30-50% in the United Kingdom (UK) and Netherlands, and exclusively the main donor source (>80%) in some Asian countries, like Japan).[76-78] Due to the great potential of DCD to resolve the problem of organ shortage, no hospital with an established program in organ donation should lose a potential category-4 donor. Hospitals with extensive experience in organ donation and transplantation should have a policy on uDCD, seeking for these donors in the A&E room or ICU, and hospitals with the most experience in DBD and in-hospital uDCD should begin an out-of-hospital DCD policy with donors coming from the streets, since this is the biggest source for DCD.[65] In the US, all organ-procurement organizations (OPO) and transplant centers are required to develop protocols to facilitate DCD organ recovery, according to the Organ Procurement and Transplantation Network and the United Network for Organ Sharing (OPTN/UNOS).[69]

Some experts in the field question whether DCD really adds to DD pool available. While uDCD is really a clear additional donor source for transplantation in France and Spain, cDCD might negatively impact DBD activity in Belgium, Netherlands and United Kingdom.[19] The shift from potential DBD to DCD without enlargement of the donor pool, some kind of donor-type substitution or redistribution, has been observed in some studies.[75,79-81]

The efficiency of a DCD program is evaluated not only by the number of donors per million population (pmp), but also by the number of organs recovered and transplanted per donor (ORPD and OTPD), and the discard rate. The ORPD and OTPD are always substantially lower for DCD than for DBD while the discard rate is consistently higher. uDCD is related to a higher discard rate of organs. Inspection of UNOS data reveals that an average of 3.6 and 3.1 organs were recovered and transplanted from DBD donors compared to 2.5 and 1.9 organs from DCD, respectively. On average per 100 donors, DCD donates 20 less kidneys (170 versus 190), 40 less livers (40 versus 80), 5 less pancreases (2 versus 7) when compare

to DBD.[82] Therefore, if a negative impact of cDCD on DBD is a reality, it certainly influences the transplantation practices, especially for organs such as hearts because of lower yield of organs per retrieval episode.[19] Furthermore, the lower degree of utilization of DCD organs makes the initial optimistic impression that DCD could compensate for the dwindling supply of DBD donors may not be the case.[83]

Organs especially suitable for transplantation from DCD are kidney, liver, pancreas, and lung. DCD kidney transplantation (KT) has progressively evolved into the routine clinical practice and currently makes up 10-50% of all DD-KT at the national level.[77] However, DCD remains underused and its contribution to the DD kidney pool is expected to increase further in the coming years. The full use of DCD kidneys could expand the DD kidney pool 2-4.5 times, reduce or even resolve the shortfall of kidney supply and thus eliminate the waiting list.[84]

The use of DCD livers is more limited in experienced transplant centers due to a high rate of biliary complications that leads to a reduced graft survival and an increased need for re-transplantation, as well as a lack of a reliable viability testing prior to liver transplantation (LT). The rate of DCD- over DD-LT in the world varies between 5% and 20%. Using a mathematical model to analyze the potential impact of a DCD policy on LT programs, Chaib reported if 1%, 5% and 10% of deceased individuals became DCD donors, there would be 8%, 27%, and 37% relative reductions in the size of waiting list, respectively.[85]

Pancreas transplantation (PT) from DCD has not yet gained widespread acceptance due to concerns about the primary graft dysfunction, graft thrombosis and no validated means of testing viability before implantation. The total number of DCD-PT is still very limited and has grown at a slow pace. It is still unknown exactly how much the DCD donor pool could contribute to expand PT. Present data endorse the use of DCD pancreas in select circumstances to expand the donor pool.[86]

Lung transplantation from DCD is just a slowly emerging field, but represents a significant and increasing source of DD lungs. The lack of awareness of DCD lung suitability for transplantation is the main reason for their non-availability.[87]

General results of thoracic and abdominal organ transplantation from DCD

Almost DCD programs in the world started with KT and expanded later with extra-renal organ transplantation. The success of extra-renal allografts from DCD has encouraged the investigation into the possibility of even DCD heart transplant.[88] Long-term follow-up

data confirm the value of DCD in alleviating the organ shortage crisis and promote the idea that DCD donors are on par with DBD transplants in keeping patients off the waiting lists with functioning grafts.[89] In the following section, we will examine the general results regarding each organ.

Kidneys

All studies agree that DCD- compared to DBD-KT results in a higher rate and longer duration of early graft dysfunction, including primary non-function (PNF) and delayed graft function (DGF). Consequently, the hazard of graft loss is greater for DCD than for DBD kidneys in the early post-transplant period. Viable DCD kidneys that have overcome the early post-operative period function as well and as long as DBD counterparts with the same risk of graft failure, a comparable rate of graft survival and a similar rate of glomerular filtration rate (GFR) decline over time. Survival of transplant recipients from DCD and DBD donors is equivalent. Long-term follow-up data are now available up to 15 years post-transplant.[89-91]

The benefit of accepting a DCD kidney was clearly demonstrated in a recent study, in which dialysis patients who are on the waiting list will enjoy longer life-expectancy after DCD-KT compared to continuation of dialysis treatment with the option of later receiving a conventional DBD kidney.[92] Nonetheless, DCD-KT may induce unnecessary risks of surgery, immune-suppression, and allo-immunization for transplant candidates with PNF;[90] extended hospital stays, increased health-care costs, and patient dissatisfaction in case of DGF.[93]

Livers

LT from DCD has poorer outcomes than from DBD. Higher risk of early graft dysfunction (PNF and IPF - initial poor function), more frequent vascular and ischemia-type biliary lesions, higher rates of re-listing, and re-transplantation, and lower graft and patient survivals are all definite disadvantages in DCD liver grafts. However, the dangers of DCD liver grafts need to be viewed from the perspective of the consequences of not receiving a liver transplant in time.[89] Although DCD liver grafts are not as good as DBD counterparts, it is still better than dying because of turning down a DCD offer and continuing to wait for a DBD liver on these days as the patient's choice is frequently not between marginal livers (including DCD) and standard livers but between marginal livers and no livers.[94] The benefit of earlier access to LT provided by a DCD graft could outweigh the risks of prolonged waiting for a standard graft.[95]

Pancreases

Equal graft and patient survivals between cDCD and DBD groups up to five-year follow-up have been reported in large series of simultaneous pancreas and kidney transplants from DCD despite higher risks of pancreas thrombosis, kidney DGF and longer hospital stay. DCD pancreases function as well as DBD organs with respect to glycemic control as measured by fasting serum glucose, HbA1c levels, and assisted glycemic control.[86,96] Isolated DCD pancreas transplants are less reported and results seem inferior to DBD counterparts, thus DCD pancreases are better utilized if implanted simultaneously with a kidney [66]. Pancreases from DCD might be also useful for islet transplantation.[97,98]

Lungs

Graft and patient survivals of cDCD lung grafts appear to compare well with those of DBD grafts up to 5-year follow-up, in combination with no difference in the incidence of primary graft dysfunction and bronchiolitis obliterans syndrome (BOS), as well as lung graft function, despite few long-term follow-up data available.[99,100] The high rate of recovery, utility, and excellent clinical results make DCD lung transplantation be considered at all DCD opportunities.[101]

Hearts

Transplantation of DCD heart grafts remains essentially in the pre-clinical phase so far. Myocardial vulnerability to ischemic injury would make donor management in the DCD setting challenging.[102] Although the potential donor pool expansion could be interesting, no centres have transplanted DCD hearts on a relevant scale.[103]

Table 1.1.3. Clinical evidences in organ transplantation from DCD

Organs	Graft and patient survivals	Challenges
Kidney	DCD kidney < = DBD kidney	PNF, DGF
Pancreas	DCD pancreas < = DBD pancreas	PNF, DGF Graft thrombosis Reperfusion pancreatitis
Liver	DCD liver < DBD liver	IPF, PNF Ischemic cholangiopathy
Lung	DCD lung > = DBD lung	IPF, PNF Bronchiolitis obliterans syndrome

PNF: primary non-function, DGF: delayed graft function, IPF: initial poor graft function.

Allocation policy

DCD organs are more likely to be transplanted locally, firstly because of the transplant center's preference to inspect and procure the organs personally, secondly due to allocation policies (center - driven allocation), and thirdly in order to minimize the ischemic time. Nonetheless, parallel (back-up) offers should also be made to expedite organ placement.[14] Only Eurotransplant countries (except Germany and Croatia) distribute organs from DCD nationally, by applying general allocation criteria.

Low immunologic risk or unsensitized recipients are prone to be chosen to receive DCD transplants to reduce the ischemic time lost due to a potentially positive crossmatch.[66,104] Transplantation with organs that provides prolongation of life (liver or lung) merits consideration. In these patients, DCD organs should only be offered if a DBD graft cannot be quickly obtained and patients can be dead due to rapid deterioration of the medical conditions, or rapid progression of the underlying disease, such as cirrhotic patients with high MELD (model of end-stage liver disease) score, hepato-cellular carcinoma outside the Milan criteria…Otherwise, transplanting a marginal organ into a critically ill patient is associated with worse results for both the recipient and the graft. Perhaps the optimal environment for a DCD graft is a low-risk recipient.[61] However, high-risk recipients should be meticulously considered as their risk of death on the waiting list outweighs that of receiving a DCD graft.[105] Donor - recipient matching remains a controversial problem.

Ischemia - reperfusion injury and its consequences

Organs procured from DCD donors sustain the insult of ischemia reperfusion injury (IRI) at 4 distinct phases: (i) a variable and inevitable period of WI at body temperature between cardiac arrest and initiation of cold perfusion, (ii) a rather long period of cold ischemia (CI) when organs are stored on ice at 0 - 4°C, (iii) a relatively shorter period of WI during the vascular anastomosis - this is when organs are taken out of ice and slowly warm up, and finally, (iv) a reperfusion period when organs are suddenly re-instituted with the recipient's oxygenated normothermic blood. Each phase plays a role in organ damage, and each can influence the likelihood of transplantation success and interplay in the ultimate outcome. Prolongation of any of the ischemia phases (warm, cold, and re-warm) is expected to result in poor graft outcomes.[106]

Warm ischemia

Ischemia renders tissues and cells devoid of blood, oxygen and nutrients, and eliminates the means for disposal of metabolic waste products. At the cellular level, main biochemical changes are *anaerobic glycolysis, accumulation of metabolic end-products* (such as lactates, protons, hypoxanthine…), *depletion of cellular energy stores* (high-energy phosphates and energy substrates), *reduced intracellular pH* (due to build-up of acidic products), *increased intracellular calcium* (due to redistribution of calcium from endoplasmic reticulum stores and influx of extracellular calcium), *activation of lysosomal enzymes* (proteases like calpains and caspases, phospholipases, and nuclease), *production of free radicals* (superoxide O_2-, hydrogen peroxide H_2O_2, hydroxyl radicals OH-…), *inhibition of cytoprotective mechanisms* (heme oxygenase-1 (HO-1) and heat shock protein-70), and *cell swelling* (due to intracellular hyper-osmolarity and Na^+/K^+ pump insufficiency).[107] These alterations induce an accelerated structural and functional cellular deterioration, leading to cell death by cell membrane rupture (or necrosis). Because the injury rate is greater at higher temperature, a relatively short period of WI is more detrimental to cells than a much longer period of CI. Each minute of WI has been considered equivalent to an hour of CI. This WI considerably reduces the cold storage period and can make organs unusable.[108]

Kidneys can tolerate WI at 37°C for 30 min and recover from acute tubular necrosis in a predictable manner. 30 to 60 min of WI results in severe injury with unpredictable recovery and 25% mortality. Lengthening WI up to 90 min causes permanent loss of function and 80% mortality in experimental studies.[109,110] Renal tubular cells (especially proximal convoluted tubules and proximal ascending limb of the loop of Henle) are the primary target of injury by WI.[111,112] For other organs, the WI tolerance is far more limited.

The lung is unique when compared with other solid organs as lung parenchymal cells do not rely solely on perfusion for cellular respiration and can maintain tissue ATP levels as long as oxygen is supplied.[113] Lungs remain viable for at least 60 to 90 min (and potentially up to 4 hours) post-circulatory arrest. Ventilation adds to the lung viability during the WI period by providing alveolar expansion and oxygenation.[114] However, a lack of perfusion with oxygenated blood to the airway may contribute to ischemic damage of the airway post-transplant.

There is no strict maximum WIT. In practice, allowable maximum WIT varies in a qualitative manner, depending on donor age and donor co-morbidities, such as diabetes mellitus, hypertension, and peripheral vascular disease (**Table 1.1.4**).[16,115] Moreover, the lack of a universal agreement in the description and calculation of WIT has made

recommendations on the desirable duration of WIT complex and the comparison between various studies difficult (**Figure 1.1.3**).

Recently, extraction time, defined as the time between aortic cross-clamp and perfusion/cooling and removal of kidneys from the body and placement on ice on the back table, has been proposed as an additional insult of WI.[116] During this time, after the usual interval for aortic and sometimes portal perfusion, the ice packed in the abdomen is removed, and the kidneys are left to begin re-warming while other organs are removed.

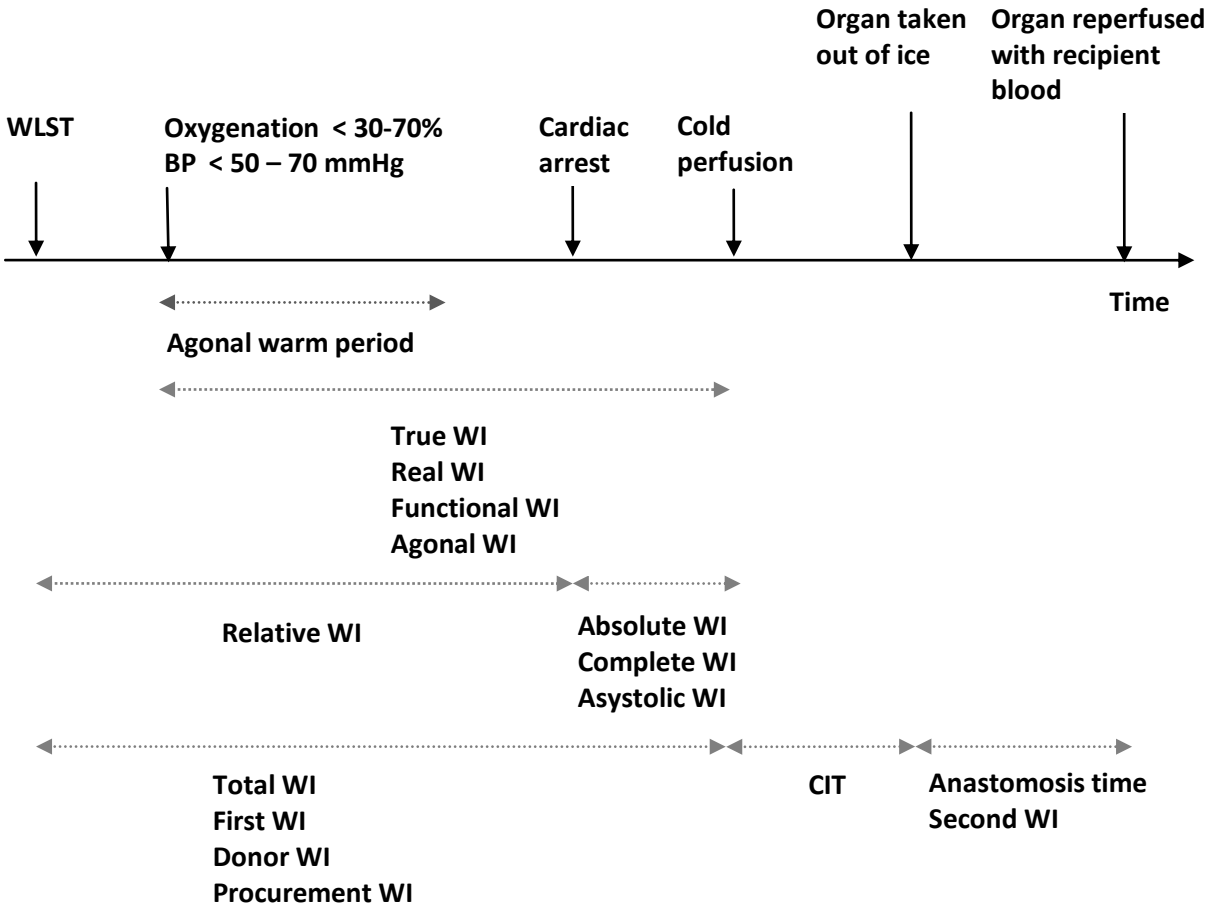

Figure 1.1.3. Heterologous definitions of warm ischemia in cDCD.[8,15,16,34,36-38] BP : blood pressure. Given the importance of events (hypotension, hypoxia) in the agonal phase (from WLST to cardiac arrest), the ***agonal warm period*** needs to be accurately and clearly described to enable informed decisions on the safety of transplantation of organs from DCD donors. This time period could arbitrarily start once the systolic blood pressure, MAP or oxygenation falls below a given value.

Cold ischemia

Cold itself is detrimental to tissues. It can cause changes similar to those observed in WI even with continued blood flow.[107,117] The major difference between warm and cold

ischemia is the rate at which injury develops. At 0 – 4°C, accumulation of injury will continue at a rate of approximately 10% from normal.[118] Organs exposed to cold ischemic (CI) damage may or may not recover function depending on the length of cold storage.[119] Otherwise, hypothermia is known to provide considerable protection against ischemic damage by suppressing over 95% of the organ metabolism at 0 – 4°C, or the metabolic rate is reduced 12-13 fold.[120]

Organs can tolerate prolonged CI or some WI without significant deterioration of function, but when both factors act in the same tissue, their additive or synergistic effect easily produces profound injury with marked cell death. Limiting the cold storage period is thus of paramount importance when transplanting warm ischemically-sustained organs.[115,121] The combined effect of cold and warm ischemia may be explained by the differing sensitivities of vascular endothelial cells and parenchymal cells to warm and cold ischemia leading to different patterns of cell killing. In kidneys, CI damages glomerular podocytes, peri-tubular endothelial cells and proximal tubules, whilst WI triggers injury primarily to proximal tubular cells.[122] WI alone causes minimal damage to the renal vasculature, but when combined with cold storage causes severe renal vascular injury with a loss of endothelial cell function.[123] Cell death induced by CI is primarily necrotic in nature,[124] although apoptotic mechanism is also observed. In livers, WI renders prominent injury to hepatocytes and Kupffer cells. CI followed by reperfusion causes marked changes in sinusoidal endothelial cells and little influence on hepatocytes, whereas Kuffer cells shows activation with increasing CI.[125-128]

In practice, the length of CIT is correlated with the occurrence of both DGF and PNF. Shortening the CIT less than 16 hr allowed a significant reduction in the percentage of DGF and better graft survival for DCD kidneys.[129,130] When CIT was limited to less than 12 hr, the rate of DGF in DCD kidneys approached that of SCD kidneys (25.2% versus 19.5%, p = ns), and was reduced by 15% compared to CIT greater than 12 hr.[131] In DCD-LT, the incidence of PNF was 2.5 times less in patients with CIT ≤ 8 hr versus those with CIT > 8 hr (5% versus 13%).[60] The incidence of graft failure within 60 days of transplantation was 10.8% if CIT < 8 hr and substantially increased to 30.4% and 58.3% if CIT >8 hr and >12 hr, respectively.[58] The recommended CIT is less than 4-6 hr for uDCD, and less than 8 hr for cDCD liver grafts. For DBD liver grafts without additional risk factors, the maximal CIT may be up to 16 hr, but is desired less than 10 hr in case of associated risk factors.[132]

Table 1.1.4. Potential clinical viability of human organs for transplantation after static cold storage (SCS) at 4°C[14,16,108,133,134]

	DBD	Controlled DCD		
	CIT (hr)	Total WI (min)	True WI (min)	CIT (hr)
Heart	6	-	-	-
Lung	8	-	60*	6
Small intestine	12	-	-	-
Liver	18-20	30-45	20-30**	8
Pancreas	18-20	45-60	30	18
Kidney	36-48	45-60	30-45	24

*Time to re-inflation of the lungs rather than cold perfusion. Despite the comments on the protective effect of ventilation cited earlier, it is the long-term function of the small and moderate sized airways and their vasculature that determine graft and patient survival in lung transplantation.[39]
**May be limited to 20 min in sub-optimal donors

Re-warm ischemia

At the time of implantation, organs are removed out of cold preservation solutions and re-warm from 4°C toward body temperature. The injury process that has begun during WI and hypothermia is furthered during the re-warming period. The length of this period depends mainly on the surgical technique, besides recipient BMI, donor and recipient's vascular anatomy, and biliary and urinary tract status…

Human kidneys warm up at a rate of approximately 0.5°C/min according to a logarithmic curve, and at the end of vascular anastomosis, the average kidney temperature is about 16-20°C (range: 7-30°C). Larger kidneys warm up more slowly than do smaller ones. Keeping the kidney temperature during the time of vascular anastomosis below 16 or 17°C is strongly suggested. Increased second WI over 30-45 min is associated with an increased risk of DGF.[135,136] Therefore, the prognostic factor for DGF is not only the time itself, but also the actual kidney temperature prior to reperfusion.[137,138] In DBD-LT, prolonged CIT only (>12 hr) or re-warming time only (>45 min) was not associated with early graft dysfunction and graft loss, but simultaneously prolonged CIT and re-warming time significantly caused hepatic allograft failure, suggesting some cumulative effects on post-operative liver graft function.[139]

Reperfusion injury

Reperfusion injury is characterized by the repair and regeneration processes occurring in parallel with the cellular apoptosis, autophagy, and necrosis. The fate of an organ thus

depends on whether cell death or regeneration prevails. Reperfusion produces re-warming, re-oxygenation, a return to aerobic metabolism (including oxidative phosphorylation), and production of ATP (adenosine triphosphate). However, the paradox of reperfusion is that ischemic injuries are continued and further exacerbated. The postulated mechanisms consist of *a rapid burst of reactive oxygen species (ROS)* shortly following reperfusion which exceeds the protective ability of their scavengers, the *action of pro-inflammatory mediators*, the *infiltration of leukocytes* (neutrophils, monocytes/macrophages, natural killer cells, and T cells) into the graft tissues, and the *"no-reflow"* phenomenon (due to intra-vascular obstruction by necrotic cells, thrombosis, accumulation of neutrophils and platelets within blood vessels, and interstitial edema extrinsically compressing blood vessels, which all attenuate flow and prolong focal ischemia). ROS are toxic molecules that alter cellular proteins, lipids and ribonucleic acids, leading to cell dysfunction or death. They probably trigger endothelial injury, since only after reperfusion, endothelial cells, which seem fairly well preserved after the ischemic phase, become edematous and leaky to proteins and small particles. Neutrophils may cause direct cytotoxicity via the production of ROS and release of cytokines. They control peri-vascular tissue edema, damage endothelial cells directly, and promote platelet aggregation. The characteristic feature of severe reperfusion injury is vascular endothelial cell death leading to graft thrombosis.[107,140]

Ischemia-reperfusion and immune injury

Apart from the risk of initial graft dysfunction, IRI may increase the graft allogenicity and mediate the links between tissue damage, innate and adaptive immune responses through Toll-like receptors (TLR) and antigen presenting cells (Matzinger's injury theory).[141] According to this theory, the less the initial insult, the smaller the agitation of adaptive immunity and the lower the chances for early and late responses to the allograft. "Danger signals", "alarmins" or damage-associated molecule patterns (DAMP) are released during ischemia and reperfusion, and include ROS, graft-derived DNA and RNA, oxidized proteins and lipids, HMGB1, uric acid, and calcium pyrophosphate crystals... TLR, expressed on the surface of various cells (macrophages/monocytes, dendritic cells, and natural killer cells), recognize DAMP and trigger a significant cytokine release. These cytokines recruit and activate neutrophils and macrophages as part of the innate immune system, which in turn, activate the adaptive immune response, promoting rejection, and inhibiting tolerance induction. [142,143]

In short, IRI represents a continuum of events that are triggered when the organ is deprived of oxygen and then re-oxygenated, culminating in parenchymal and endothelial cell injury. The resultant functional derangement has varying degrees, the severest is primary non-function (PNF) which is irreversible, and less severe forms are DGF (for kidney and pancreas), or IPF (for liver and lung), which is reversible. In the long-term, non-anastomotic biliary strictures and increased incidence of acute and chronic rejection have been attributed to the consequences of IRI in case of liver transplantation, and bronchiolitis obliterans syndrome in case of lung transplantation.[27,112]

Strategies to improve results of organ transplantation from DCD

Various strategies intervening in both donors and recipients at different phases of the transplantation process have been proposed at the aim of alleviating the marginality of this type of donation.

Donor management

Donor selection criteria are not generally different between DCD and DBD. The criteria for medical suitability depend on the DCD donor types (controlled or uncontrolled) and transplant teams. Potential donors are usually assessed individually for acceptance.[10,18,45,144] More restrictive selection criteria will improve the results of DCD organ transplantation, but will unavoidably be associated with the discard of viable organs.[48]

Techniques for in-vivo organ preservation have been developed and encompass the in-situ cold perfusion (using DBTL catheters), the mechanical chest compression and mechanical ventilation (using automated cardio-pulmonary resuscitation devices) with or without manual abdominal compression, and the CPB with ECMO. They effectively maintain organ viability inside the body for a short period of time (5 – 6 hr), which is enough for the logistic preparations for procurement, family consent and legal formalities, therefore making kidney and liver transplantation from uDCD feasible.[10,45,145,146] For cDCD, rapid laparotomy and direct aortic cannulation (or supra-rapid recovery technique) is superior over in-situ cold perfusion, and rests the preferred method.[46,47] CPB with ECMO (pre-mortem cannulation and post-mortem ECMO) has also been used to support category-3 DCD with excellent results and offers logistical advantages over a supra-rapid recovery technique.[147]

Anti-coagulatory (heparin) and thrombolytic agents (streptokinase) have been administered to a potential donor before WLST to prevent blood clotting after cardiac arrest

and subsequent poor organ wash-out.[148] Administration of other agents (like cyto-protective substances…) would also be useful approaches. However, serious ethical considerations preclude most forms of donor pre-treatment.

Donor management plays a critical role in the determination of organ quality and thus in the expansion of donor pool.

Organ preservation and assessment (viability testing)

Preservation solutions and preservation modes aim at reducing the effects of IRI. Although being the current gold standard for static cold storage (SCS) of kidney, liver, pancreas, and intestine, University of Wisconsin (UW) solution has some drawbacks (high cost, high potassium, high viscosity, red-blood-cell aggregation, crystallization at 2–8°C, and glutathion oxidation).[133,149-151] Newer preservation solutions with beneficial additives and enriched compositions, like Institut George Lopez (IGL-1), Solution de Conservation des Organes et Tissus (SCOT), and Polysol, have proved advantages over UW solution.[152] SCS, despite being an efficient technique for organ preservation in the past and even now, has three fundamental limitations: (i) tissue damage caused by the cold itself, (ii) difficulty in assessing function and predicting viability during cold storage, and (iii) inevitable IRI.[134] These barriers have impeded its application in preserving marginal organs which have an increased vulnerability to IRI and compromised repair mechanisms. SCS is believed to have reached its limitations in maintaining the viability of less than optimal organ. Future progress in the resuscitation and preservation of DD organs, especially less than ideal organs, may lie not in further refining the cold storage or the basic composition of preservation solutions, but instead in supplementing cold storage, or even replacing it in large part, by a more dynamic preservation method that better fulfils the metabolic demands of ischemically-damaged organs.[153-155]

Hypothermic machine perfusion (HMP) has been experimentally and clinically demonstrated to improve organ quality, transplant outcome and utilization rates in KT from all DD types (SCD, ECD, DCD),[50-52,156] and in LT.[53,157,158] The proposed beneficial mechanisms may include a continuous elimination of toxic break-down products, a continuous supply of nutrients with or without oxygen, a decrease in vasospasm, a protection of endothelial cells via sustained expression of flow-dependent genes (particularly Kruppel - like factor 2), a possibility of viability testing, and potential therapeutic interventions (addition of pharmacological agents or gene therapy).[159]

Normothermic machine perfusion (NMP) offer a greater chance to recondition ischemically-injured organs thank to the maintenance of cellular metabolism in a physiological environment, thereby overcoming the 3 major weaknesses inherent in the traditional SCS. It is particularly relevant in organs with extensive WI injuries coming from DCD. This technique would allow an organ to be transplanted on the basis of its quality rather than the current system of donor characteristics and ischemic intervals to judge its suitability.[160,161] First clinical applications of NMP have been reported in kidneys[162] and lungs.[163] The use of MP for preservation of other extra-renal organs, like pancreas and heart, is still in the pre-clinical step, and needs to take account of the organ-specific aspects.[159]

Pressure-flow characteristics, reno-vascular resistance, and perfusate enzyme levels during HMP have once been used to select and discard the kidneys because MP is believed to predict organ viability and allow one to transplant the kidneys with confidence.[112] It has been advocated that DCD programs should only be established if MP is available.[164] Subsequent studies, however, demonstrated although these parameters were independently associated with the risk of PNF or DGF, their predictive value was relatively low. The decision to either accept or reject a kidney should remain multi-factorial.[165-167]

Recipient management

Choosing a right recipient for a particular DCD organ is essential. Transplantation of a marginal graft in a low risk recipient is commonly accepted. The center-driven allocation policy that is now applied in DCD to shorten the CIT facilitates the donor – recipient matching.

In KT, several strategies help to improve the early graft function. Optimization of the renal transplant perfusion in the peri- and post-operative phases by maintaining adequate MAP (>70 mmHg) or systolic blood pressure (>110 mmHg), and central venous pressure (>6 cmH_2O) is crucial to minimize the incidence of DGF and PNF.[168,169] Immunosuppressive protocols using a delayed calcineurin-inhibitor (CNI) therapy after induction with interleukin-2 receptor antagonists, polyclonal anti-thymocyte globulin, or alemtuzumab are efficient in avoiding acute rejection and early CNI-associated nephrotoxicity.[170,171]

1.2 Implementation of DCD programs in Liège and Belgium

The first cadaveric KT in Belgium was performed from a DBD donor on June 3rd, 1963 at the Catholic University of Louvain. It was also the first ever in the world. Since that time, almost all cadaveric organs were procured from DBD donors, including the first lung transplant in 1968, the first LT in 1969, the first heart transplant in 1973, and the first pancreas transplant in 1982. The Belgian Law on organ donation and transplantation was published on February 1987, relying on the presumed consent principle (or opting-out system). On the basis of this Law, the National Council of Physicians has specified rules and definitions for DBD and DCD organ retrieval on September 1987 and on June 1994, respectively. Following the first International Workshop on NHBD in Maastricht in 1995, several DCD protocols have been approved by the Hospital Ethics Committees during the period of 1995 to 2000, based on the 12 Maastricht recommendations and statements. However, it took 3-4 more years to convince the Belgian medical community for the need of a national DCD program with the establishment of a central lab for organ machine perfusion. Currently, all 7 Belgian transplant centers have active DCD programs, exploring essentially the Maastricht category-3 DCD donors for kidney, liver and lung transplantation; and Belgium is a member of the Eurotransplant organization, along with Austria, Croatia, Germany, Luxemburg, The Netherlands, and Slovenia.[172,173]

At the University Hospital of Liège, clinical transplantation has begun very early since 1965. The first KT from a related living donor was on July 1st, 1965, followed by the first heart transplant on February 9th, 1983; the first simultaneous kidney and pancreas transplant on October 18th, 1984; and the first LT on June 20th, 1986.[174] Up to the year 2011, more than 1000 kidneys, 500 livers and 400 hearts have been successfully implanted here. Like other transplant centers in Belgium and in the world, transplantation has become the victim of its success when the number of patients on the wait list always exceeds the number of organs available for transplantation. In an attempt to increase the donor pool, DCD was utilized in Liège since 2003 firstly for liver and thereafter for KT since 2005.[175,176]

The program was approved by the Hospital Ethics Committee in 2004, and after several meetings convoking the ICU and OR representatives, anesthesiologist, and the transplant team from the University Hospital of Liège and its collaborating donation hospitals (particularly the CHR Citadelle and CHC Saint-Joseph), a common DCD protocol has been issued in November 2009, specifying the information mandatory in the medical records, the

end of life care procedure, the determination of death, and the issue of pre-mortem organ preservation measures (**Table 1.2.1**).[177] The first Conference of Hospital Collaboration on Organ Donation was held in January, 2012 by the University Hospital of Liège, discussing a wide range of ethical, moral, legal and technical aspects of DBD and DCD.[178]

Table 1.2.1 Detailed controlled DCD protocol at the Liège University Hospital (Belgium)

Protocol elements	Consensus
Potential cDCD donors	Maastricht category 3 in the ICU Donor age <65 years for kidneys, no age limit for livers
Decision of WLST	At least 3 physicians (intensive care physicians, specialists, and the treating physician)
Family consent for donation	Intensive care physicians and transplant coordinators
Pre-mortem medications	-Heparin just prior to WLST -Analgo-sedative medications are switched to volatile anesthetics (sevoflurane or desflurane)
Location of WLST	-In the operating room -During the daytime -Under responsibility of 3 senior anesthesiologists of the Abdominal Surgery and Transplantation Department (or anesthesiologist intensivists at the 2 main collaborating hospitals)
Mode of WLST	-Ventilator switch-off or extubation -Cessation of all inotropes
Determination of cardiac arrest	Femoral arterial line: lack of arterial pulsation and arterial blood pressure <30 mmHg
No-touch period	5 min
Maximum agonal time (from WLST to cardiac arrest)	≤ 60 min
Total warm ischemia time (from WLST to aortic cold perfusion)	≤ 30 - 45 min for livers ≤ 45 - 60 min for kidneys
Death declaration	Senior anesthesiologists of the Abdominal Surgery and Transplantation Department or anesthesiologist intensivists at the 2 main collaborating hospitals, who are independent of retrieval/transplant teams
Organ preservation technique	-Super-rapid laparotomy and direct aorta cannulation -Static cold storage
Cornea and tissue donation	Under family's explicit consent

1.3 Aims

In a series of clinical studies, this thesis aims to answer the following questions:

1. Does the DCD source really contribute to the deceased donor pool in Liège and Belgium?

2. Is the use of DCD in Liège and Belgium worth the effort in terms of kidney and liver transplant outcomes in comparison with those from DBD in the literature?

3. Could the current Maastricht DCD classification be ameliorated?

2

Contribution of DCD Source to Organ Procurement and Transplantation Activity in Liège and Belgium

2.1 DCD activity in Liège

Published as

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Contribution of Donors after Cardiac Death to the Deceased Donor Pool: 2002 to 2009 University of Liege Experience

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ABSTRACT

Objectives: The organ procurement and transplantation activity from donation after cardiac death (DCD) at our institution over an eight-year period was evaluated to determine whether this program had any impact on donation after brain death (DBD) activity.

Methods: We prospectively collected our procurement and transplantation statistics in a database for a retrospective review.

Results: *We observed an increasing trend in the potential and actual DCD numbers.* The mean conversion rate turning potential into effective donors was 58.1%. DCD accounted for 16.6% of the deceased donor (DD) pool over 8 years. The mean age for effective DCD donors was 53.9 years (range, 3–79). Among the effective donors, 63.3% (n=31) came from the transplant center and 36.7% (n=18) were referred from collaborative hospitals. All donors were Maastricht III category. *The number of DCD kidney and liver transplants tended to increase*. DCD kidney transplants represented 10.8% of the DD kidney pool and DCD liver transplants made up 13.9% of the DD liver pool over 8 years. The DBD program activity increased in the same time period. In 2009, 17 DCD and 33 DBD procurements were performed in a region with a little more than 1 million inhabitants.

Conclusion: The establishment of a DCD program in our institution enlarged the donor pool and did not compromise the development of the DBD program. In our experience, DCD is a valuable source for abdominal organ transplantation.

Introduction

Confronted with the organ shortage for transplantation, many countries around the world have been re-addressing the donation after cardiac death (DCD) as an alternative donation source for expanding the donor pool. Estimates suggested that potential DCD number may be as high as twice the donation after brain death (DBD) number[179] and that DCD kidneys might contribute to 20-40% of the deceased donor (DD) kidney pool.[180,181] Liver, pancreas, lung and even heart from DCD could also be used with success despite a greater risk of primary graft dysfunction, re-transplantation and other organ-specific complications.[88,182-186] The University Hospital of Liège in Belgium has a long tradition in transplant surgery.[174,187] The Liège region has one transplant center and 16 collaborative donor hospitals. A Maastricht category III DCD program was initiated in 2002[173,175] following the success of DCD programs in pioneering countries like the Netherlands and Spain,[188] and after the 12 Statements and Recommendations of the first International Conference on DCD in Maastricht in 1995[189] which were later approved by the Council of Europe in 1998.[190] In this report, we retrospectively reviewed our experience in organ procurement and transplantation from DCD source from 2002 to 2009, in order to assess if this DCD activity significantly impacted the transplantation activity of the center, and to exclude any decrease of DBD donation as a consequence of the DCD program.

Methods

The authors prospectively collected all data related to donation and transplantation activities at the Department of Abdominal Surgery and Transplantation of the CHU Liège. These informations were retrieved from the department database and completed with the annual reports of the Eurotransplant organization (accessible via the member site of www.eurotransplant.be) and the Belgian Section of Transplant Coordinators.[191-194] Retrieved data related to donation activity included potential and effective donor numbers, percentage of donation refusals, reason for denial of donation, and organ yield. Donor profile included donor Maastricht type, origin, age, cause of death, time from ventilator switch-off to cardiac arrest, and primary warm ischemia time. The local transplantation activity was compared to the Belgian experience within the same period. Conversion rate was defined as the percentage of actual donors giving at least 1 clinically transplanted organ, amongst potential organ donor referrals.

Data are presented as mean ± standard deviation (SD) or percentage. All statistical analyses were performed using SPSS 16.0. Statistical significance was determined with $p<0.05$. Tests used for the analyses included Fisher's exact or Chi-square and Student's *t* tests.

Results

Donor statistics

The DCD number varied from year to year, with a progressive increase in DCD procedures (**Figure 2.1.1**). All donors were Maastricht III category (**Table 2.1.1**). The proportion of DCD within the deceased donor pool increased from 3.7% in the first year of the DCD program, up to 34% in 2009. In addition, in the same time period, the absolute number of DBD increased. On average, DCD contributed to 16.6% of the DD pool over 8 years. From 2006 to 2009, 43 donor procedures were performed among 74 potential donors (conversion rate: 58.1%). Among potential donors, reasons of no donation were medical contra-indication (53.1%) and family refusal (46.9%).

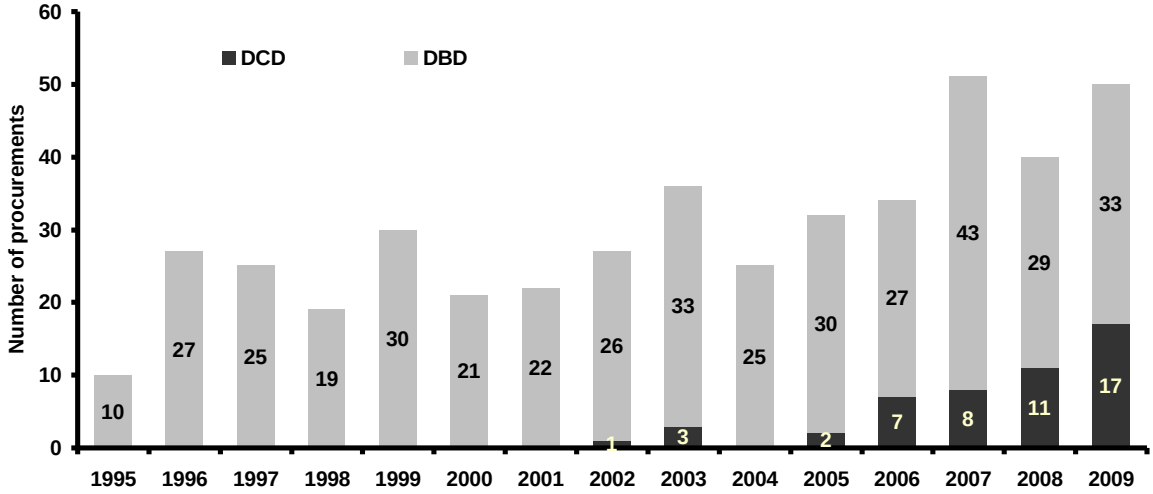

Figure 2.1.1. Annual number of DBD and DCD procurements in Liège region (Belgium) leading to at least one transplant from 1995 to 2009.

The mean organ yield per DCD donor was 2.3 organs, which was lower than that of DBD. Mean organ yield per donor according to age category was 2.5 organs in the age group <60 years and 1.9 organs in the age group ≥60 years (**Table 2.1.2**). The mean age for the effective DCD donor was 53.9 years (ranges: 3-79 years). Donors ≥60 year-old made up

40.4% of the DCD pool. The rate of retrieved livers and kidneys in this age group was 85% and 52.5% respectively. Causes of death were differentiated between DCD and DBD. From 2006 to 2009, comparing DCD and DBD groups, 26.5% vs. 37.9% died of a cerebro-vascular accident, 18.4% vs. 47.7% died of a cranial trauma, 40.8% vs. 6.8% died of brain anoxia, and 14.3% vs. 7.6% died of other reasons (suicide, intoxication, tumor…). Among the effective donors, 63.3% (31 donors) came from the transplant center and 36.7% (18 donors) were referred from affiliated non-university hospitals. The mean time from life-support withdrawal to cardiac arrest was 11.7 ± 6.4 min (ranges: 1-30 min) and the mean time from life-support withdrawal to aortic cold perfusion was 20 ± 9.5 min (ranges 5-60 min). Waiting period or no-touch period varied between 3 and 5 minutes.

Table 2.1.1. DCD profile in Liège from 2002 to 2009 (n=49)

Donor characteristics	Data
Age (mean ± SD) (y)	53.9 ± 15.1
Age range (y)	3–79
Age category (%), y	
<40	14.3
40-59	44.9
>60	40.8
Gender (male/female) (%)	69.4/30.6
Cause of death (%)	
Cerebral vascular accident	26.5
Cranial trauma	18.4
Anoxia	40.8
Suicide	14.3
Donor type	100% Maastricht III
Donor origin (%)	
Transplant center	63.3
Collaborative donor hospital	36.7
Time from switch-off to cardiac arrest (mean ± SD), min	11.7 ± 6.4
Range of time from switch off to cardiac arrest (min)	1 - 30
Time from switch off to aortic cold perfusion (mean ± SD), min	20 ± 9.5
Range of time from switch-off to aortic cold perfusion (min)	5 - 60
Number of retrieved organs	
Kidney	70
Liver	37
Pancreas	0
Heart	0
Lung	4

Transplant statistics

From 49 effective DCD donors, 110 organs were harvested and transplanted into 106 recipients, which included 70 kidneys, 36 livers and 4 lungs. All these organs were allocated by the Eurotransplant organization. Twenty-four kidneys and 31 livers were locally transplanted, and the other organs were sent to other transplant centers. In addition, one liver and one pancreas were retrieved for hepatocyte and islet preparation, respectively. Twenty-nine hearts were also procured and sent to a tissue bank for homograft valve preparation and cryopreservation.

Table 2.1.2. Donor activity and kidney and liver transplantation in Liège

	2002	2003	2004	2005	2006	2007	2008	2009
Effective DCD/potential DCD	-	-	-	-	7/9	8/15	11/25	17/26
(%)					**77.8**	**53.3**	**44**	**65.4**
DCD/DD	1/27	3/36	0/25	2/32	7/34	8/51	11/41	17/50
(%)	**3.7**	**8.3**	**0**	**6.3**	**20.6**	**15.7**	**26.8**	**34**
NTOD in DCD	2	2.7	0	2	2.4	2.6	1.7	2.1
DCD/DD kidney transplant	0/23	0/49	0/25	2/34	2/38	11/56	7/42	12/49
(%)	**0**	**0**	**0**	**5.9**	**5.3**	**19.6**	**16.7**	**24.5**
DCD/DD liver transplant	0/25	2/33	0/29	0/22	5/26	6/29	8/28	13/31
(%)	**0**	**6.1**	**0**	**0**	**19.2**	**20.7**	**28.6**	**41.9**

Single kidney transplants (including kidney en bloc)/combined kidney transplants. NTOD: number of transplanted organs per donor.

The number of DCD kidney and liver transplants also had a tendency to increase each year (**Figure 2.1.2 and 2.1.3**). From 2007 to 2009, the rate of kidney transplants and liver transplants using DCD varied between 16.7% and 24.5% of the DD kidney pool and between 20.7% and 41.9% of the DD liver pool. On average, DCD kidney grafts represented 10.8% of the DD kidney pool and DCD liver grafts made up 13.9% of the DD liver pool over 8 years.

Discussion

The long transplantation waiting lists have triggered interest in expanding the organ pool by using DCD again in mid-1990s despite medical and ethical concerns. The potential contribution of this type of donors to the entire donor pool is unclear and may approach 25%.[195] The potential increase in the supply of kidney transplants by exploration of DCD kidneys is estimated about 2-4.5 times.[196] Promising calculations in the Netherlands and the US proposed that the potential supply of DCD kidneys is large enough to satisfy the demand

for renal transplantation and therefore the shortage of kidneys would be a thing of the past.[84,196] However, in practice, single-center reports usually described a proportion of DCD kidney transplants of about 20-40% of the DD kidney pool.[180,181,197-200] Exceptionally, a few transplant centers obtained a percentage of 50-70%, as in Maastricht[77] or Madrid.[45,201]

In the field of liver transplantation, the use of DCD liver could increase the supply of liver transplants by 53%.[202] Using a mathematical model to analyze the potential impact of using a DCD policy on liver transplant program, Chaib found that if 1%, 5% and 10% of the deceased became DCD, it could result in a relative reduction of 8%, 27% and 37% in the size of the waiting list respectively.[85] Centers with active DCD liver transplantation program reported a rate of 4-10% of liver transplants came from DCD source.[203] At our institution, between 19.2% and 41.9% of DD liver transplants were carried out using organs from DCD in recent years (**Table 1**).[175]

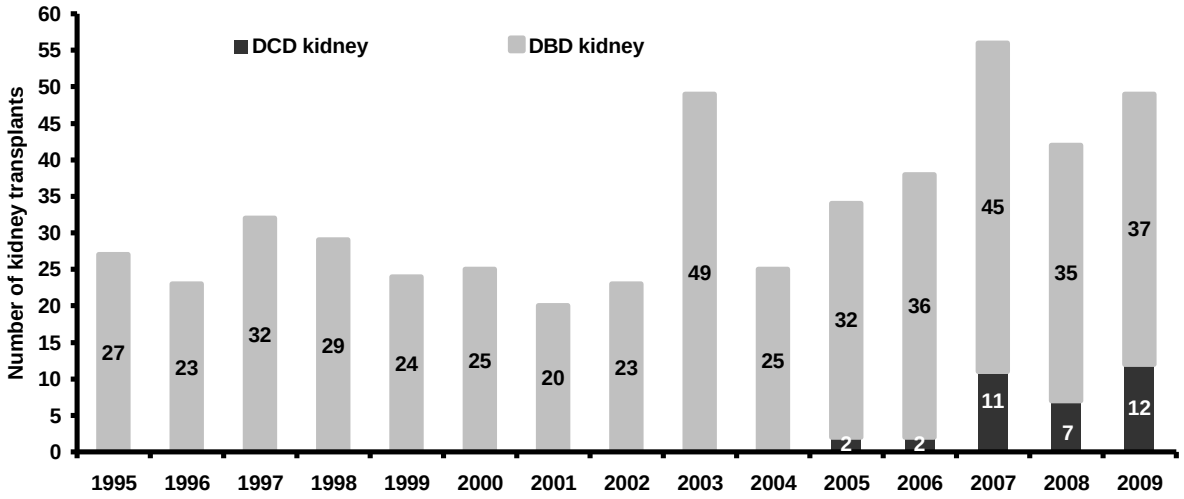

Figure 2.1.2. Annual number of kidney transplants from DBD and DCD in Liège region (Belgium) from 1995 to 2009.

However, the introduction of a DCD protocol might have a negative effect on DBD program. Some transplant centers observed a remarkable increase in the number of DCD with a concomitant decrease in the DBD number, resulting in no significant change in the donor pool.[79,80] As a consequence, DCD may lead to a redistribution of donor types within the donor pool. Explanation for this phenomenon may reside in changes of neurosurgical practices in patients with cerebral injury, in family choice between a controlled DCD and a DBD procedure, or in the eagerness of the medical staff to initiate donation procedures due to high

pressure on intensive-care-unit beds.[167] This was not the case in our experience, as the absolute number of DBD increased in parallel to the DCD program development.

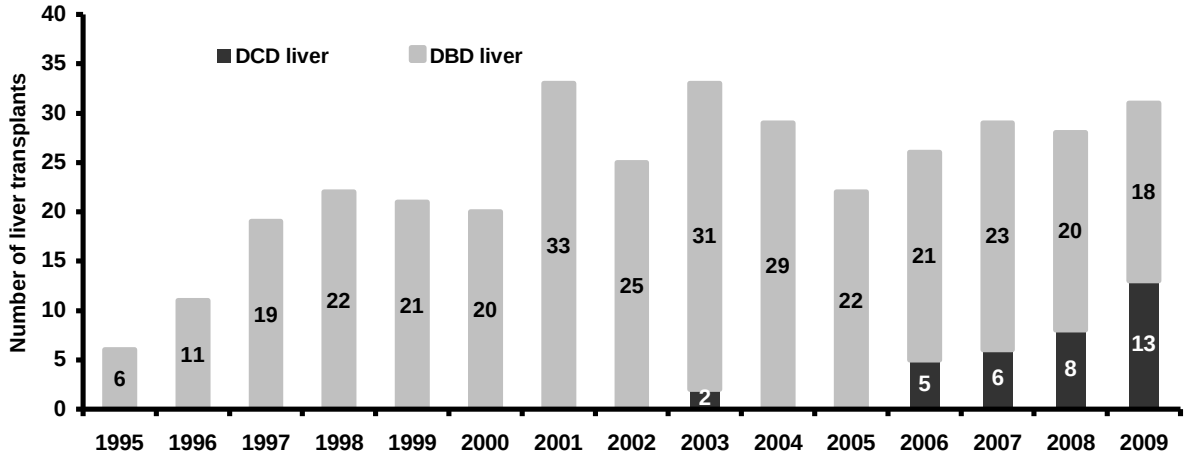

Figure 2.1.3. The annual number of liver transplants from DBD and DCD in Liège region (Belgium) from 1995 to 2009.

Additionally the efficiency of DCD programs is also lower than DBD programs in terms of number of transplanted organ per donor. In the Liège experience, from 2006 to 2009, this number between DCD and DBD was 1.7 - 2.6 organs versus 3 - 3.8 organs.

Conclusion

This report describing the establishment of a DCD program at the University of Liège, showed that DCD may enlarge the total DD pool without compromising the development of an existing DBD program. DCD may be a valuable donor source for transplantation.

2.2 DCD activity in Belgium

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Kidney Donation after Circulatory Death in a Country with a High Number of Brain Dead Donors: Ten-Year Experience in Belgium

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ABSTRACT

Objectives: Worldwide shortage of standard brain dead donors (DBD) has revived the use of kidneys donated after circulatory death (DCD).

Methods: We reviewed the Belgian DCD kidney transplant (KT) experience since its reintroduction in 2000. Risk factors for delayed graft function (DGF) were identified using multivariate analysis. Five-year patient and graft survival was assessed using Kaplan–Meier curves. The evolution of the kidney donor type and the impact of DCDs on the total KT activity in Belgium were compared with the Netherlands.

Results: Between 2000 and 2009, 287 DCD KT were performed. Primary non-function occurred in 1% and DGF in 31%. Five-year patient and death-censored graft survivals were 93% and 95%, respectively. In multivariate analysis, cold storage (versus machine perfusion), cold ischemic time, and HTK (histidine-tryptophan-ketoglutarate) solution were independent risk factors for the development of DGF. Despite an increased number of DCD donations and transplantations, the total number of deceased donor KT did not increase significantly. This could suggest a shift from DBDs to DCDs.

Conclusion: In order to increase KT activity, Belgium should further expand controlled DCD programs while simultaneously improve the identification of all potential DBDs and avoid their referral for donation as DCDs before brain death occurs. Furthermore, living donation remains underused.

Introduction

Organ shortage has urged transplant physicians to expand the acceptance criteria of deceased donors (DD). The use of expanded criteria donor (ECD) kidneys and kidneys donated after circulatory death (DCD) has increased significantly. About one-third of DD kidney transplant (KT) activity in the United States is performed with kidneys from ECDs and DCDs.[204] Although DCD was common practice in the early era of transplantation, the introduction of brain death criteria and the superior results achieved with organs donated after brain death (DBD) pushed DCD to the background.[205] DCDs were reported to have considerably higher incidences of delayed graft function (DGF) and primary non-function (PNF) as compared with DBD kidneys (28–88% and 1–18% vs. 13–35% and 1–10%, respectively)[206,207] and inferior graft outcome. However, with the successful course of clinical transplantation activities, the DBD pool rapidly became insufficient to sustain the increasing demand for kidney grafts. Consequently, DCD kidney programs were established as the full potential of the DCD pool was estimated larger than that of the DBD pool and could double or even quadruple the number of DD KT.[208] In addition, some landmark publications at the turn of the century showed that excellent long-term graft survival, equivalent to DBD kidneys, could be achieved with DCD kidneys.[188,209] These early reports were subsequently confirmed in larger series.[206,210,211] The excellent results of DCD KT combined with the growing organ shortage has led to a steady increase of DCD KT activity in countries with the required legal framework and now reaches up to 30–40% of DD KT in the United Kingdom (UK) and the Netherlands.[210,212]

Despite a legal framework allowing maximal efforts to stimulate organ donation and transplantation (opting-out, legality of DBD, DCD, and living donation[213]) and one of the highest deceased donor rates per capita world-wide, Belgium is still confronted with a renal graft shortage. Less than 50% of wait-listed patients are transplanted yearly.[212] Therefore, in an attempt to increase the number of KT, DCD KT programs were reintroduced in Belgium at the turn of the century. In this report, we review the 10-year Belgian DCD KT experience with particular emphasis on (i) results, (ii) risk factors for DGF, (iii) the evolution of the different types of kidney donation, and (iv) the evolution of the overall KT activity.

Patients and Methods

Study population

Donor and recipient data from all DCD KT performed in Belgium between January 1st, 2000 and December 31st, 2009 were retrieved from the registry of the international organ-exchange organization Eurotransplant[212] and the seven Belgian kidney transplant centers, represented by the Kidney-Pancreas Committee. Recipients younger than 18 years of age at the time of transplantation were excluded, as were combined transplantations.

Delayed graft function was defined as the need for dialysis in the first week after transplantation, preceding return of graft function. PNF was defined as a graft that never regained function. Warm ischemic time (WIT) was defined as the time from withdrawal of life support to start of cold perfusion, acirculatory time as the time from cardio-circulatory arrest until start of cold perfusion, cold ischemic time (CIT) as the time from start of cold perfusion to start of the vascular anastomoses, and anastomotic time as the time from start of the vascular anastomoses until reperfusion of the graft. HLA mismatching between donor and recipient was categorized according to differences at the HLA-A, HLA-B, and HLA-DR loci; with 0–1 of six possible mismatches categorized as 'level 1', 2–4 mismatches as 'level 2', and 5–6 as 'level 3'. Graft survival was defined as the time from transplantation to return to dialysis, graft nephrectomy or to patient death with a functioning graft, whichever came first. Early acute rejection was defined as the treatment of biopsy-proven rejection within the first 3 months after transplantation.

The evolution of kidney donation and transplantation rates in Belgium and the Netherlands, both Eurotransplant countries, was studied by comparing activity in three chronological eras (1995–1999, 2000–2005, and 2006–2010). Kidney donation and kidney-only transplantation rates were obtained from the Eurotransplant registry. Rates were adjusted for the number of inhabitants using Eurostat population data.[31]

Statistical analysis

Continuous variables are expressed as median (inter-quartile range), categorical variables as number (and percentage). Comparisons of continuous variables between groups were performed using Mann–Whitney U-test or Kruskall–Wallis test. Comparisons of categorical variables were performed using Chi-squared or Fisher's exact test. Univariate and multivariate logistic regression models were constructed to find independent risk factors of DGF. The multivariate model was constructed by backward stepwise regression using covariates with a univariate p-value <0.15. As only three cases of PNF occurred, no further analyses on PNF were performed. Kaplan–Meier curves were used to assess patient and graft

survival. The effect of DCD type (controlled versus uncontrolled DCD) on five-year patient and graft survival was assessed using log-rank tests. Because of a limited number of deaths and graft losses (n = 25 and n = 18, respectively), no Cox regressions were performed. P-values <0.05 were considered as statistically significant. All data analyses were performed in SPSS-16.

Results

Study population

A total of 287 DCD KT were performed in Belgium during the 10-year study period (i.e., 7.4% of all DD KT). In the same period, 175 DCD procedures were performed (i.e., 7.8% of all DD procedures). Donor and recipient characteristics are shown in **Table 2.2.1**. During the study period, pediatric donors were not considered for DCD and generally the upper age limit for DCD was considered to be 60 years. DCD kidneys were allocated following standard Eurotransplant allocation rules and were transplanted for all common transplant indications (**Table 2.2.2**). Ninety-one percent of DCD kidneys were procured in Belgium, whereas 9% were imported. Ninety-three percent of kidneys were recovered from controlled Maastricht Category III donors leading to relatively short warm ischemic and acirculatory times, 7% were recovered from uncontrolled Maastricht Category II donors (**Table 2.2.1**).[7] Prior to 1998, duration of the 'no-touch' period varied from 2 to 10 min, depending on center practice. However, since the US recommendation of the Institute of Medicine, a 5-min period became standard in most centers.[214]

Histidine-tryptophan-ketoglutarate (HTK) solution was used as flush solution in 83% of donors, and University of Wisconsin solution (UW) in 16%. Kidneys were preserved either by cold storage (47%) or by machine perfusion (53%), depending on the preference of the recipient center. Of machine-perfused kidneys, 82% were placed on the machine directly after procurement in the donor center (immediate perfusion). In 18%, machine perfusion was started after an initial period of cold storage (delayed perfusion). All kidneys preserved on the machine were perfused with Belzer's machine perfusion solution, available as KPS-1 (Organ Recovery Systems, Itasca, IL, USA).[215] Between 2000 and 2003, the RM3 machine (Waters Medical Systems, Rochester, MN, USA) was used. Thereafter, kidneys were perfused on LifePort Kidney Transporter machines (Organ Recovery Systems). Eighty-nine percent of machine-preserved kidneys were perfused on LifePort machines.

Recipient immune-suppression varied according to center-specific practice (**Table 2.2.1**): 72.6% of recipients received induction therapy, the introduction of calcineurin inhibitors was delayed in only 12.3% of cases. Maintenance immune-suppression consisted of calcineurin inhibitors (100%), mycophenolate mofetil (93%), and corticosteroids (100%).

Recipients were followed for a median of 34 months (18–46), during which time PNF developed in 1% and DGF in 31% of cases. Machine-perfused kidneys experienced a numerically 9% lower DGF rate compared with cold stored kidneys (27% and 36%, respectively, p = 0.07). The DGF incidence of kidneys with delayed versus immediate machine perfusion was similar (33% and 26%, respectively, p = 0.48). DGF rate in uncontrolled DCD was higher compared with controlled DCD (65.0% vs. 28.5% respectively; p = 0.001); however, PNF rates were similar (0% vs. 1%, respectively; p = 0.63). DCD KT resulted in excellent 5-year patient and death-censored graft survival (93% and 95%, respectively) (**Table 2.2.1, Fig. 2.2.1**). Patient and death-censored graft survival of uncontrolled DCD was similar to controlled DCD (85% vs. 93%; p = 0.22 and 94% vs. 95%; p = 0.98, respectively).

Risk factors for the development of DGF

Results from univariate and multivariate regression analyses are shown in **Table 2.2.3**. After correction for donor and recipient variables, cold storage (versus machine perfusion), CIT, and flush with HTK were independent risk factors for DGF. The type of DCD donor (uncontrolled or controlled) was not an independent risk factor in multivariate analysis, nor was WIT or acirculatory time.

Evolution of kidney donation and transplantation rates in Belgium since 1995

Between 1995 and 2010, the majority of effective Belgian kidney donors were DD [20.6 per million population (pmp) (19.0–22.4)], mainly DBD [19.4 pmp (18.3–20.9)] with a small portion of DCD [0.4 pmp (0.2–2.8)]. Living donation [2.2 pmp (1.5–3.8)] increased the total number of effective kidney donors in Belgium to 23.0 pmp (21.1–26.0) (**Fig. 2.2.2a**). KT rates showed a similar distribution: a majority of DD [37.9pmp (31.9–38.8)], mainly DBD [33.5pmp (30.3–37.1)] and a few DCD [0.7 pmp (0.3–4.8)]. Living donation [2.5 pmp (1.5–4.0)] increased the total number of KT to 39.2 pmp (34.7–42.8) (**Fig. 2.2.2b**).

Although Belgium reintroduced DCD KT in 2000, the number of DCD KT was low until 2003, after which a steady increase occurred with DCD comprising up to 16% of DD

Table 2.2.1. Characteristics of DCD donors and DCD KT recipients in Belgium between 2000 and 2009

Donor characteristics (n=179)		Recipient characteristics (n=287)	
Age (years)*	44 (31–55)	**Age (years)***	54 (45–61)
Gender, n (%)		**Gender, n (%)**	
Male	116 (65)	Male	173 (60)
Female	63 (35)	Female	114 (40)
Terminal SCr (mg/dl)*	0.70 (0.56–0.91)	**Dialysis duration (months)***	29 (17–48)
History of arterial hypertension, n (%)†	27 (17)	**Previous transplants, n (%)**	
		First transplant	261 (91)
		Retransplant	26 (9)
Donor type, n (%)‡		**Panel reactive antibodies, n (%)**	
Uncontrolled (category I + II)	11 (6)	n = 0–5%	257 (89.5)
Controlled (category III + IV)	168 (94)	n = 6–84%	29 (10.1)
		n ≥ 85%	1 (0.3)
Warm ischemic time (min)*	20 (15–29)	**HLA mismatches, n (%)**	
		Level 1	32 (11)
		Level 2	252 (88)
		Level 3	3 (1)
Acirculatory time (min)*	10 (8–14)	**Donor type, n (%)**	
		Uncontrolled (category I + II)	20 (7)
		Controlled (category III + IV)	267 (93)
Flush solution, n (%)		**Immunosuppression, n (%)†**	
HTK	149 (83%)	**Induction therapy**	207 (72.6)
UW	28 (16%)	Anti-thymocyte globulin	37 (32.4)
Other solutions	2 (1%)	IL-2 receptor antagonist	139 (67.1)
		Calcineurin inhibitor	285 (100)
		Delayed	35 (12.3)
		Mycophenolate mofetil	265 (93)
		Corticosteroids	285 (100)
Surgical process	287	**Primary non-function, n (%)**	3 (1)
Preservation method, n (%)		**Delayed graft function, n (%)**	89 (31)
MP	152 (53)		
SCS	135 (47)		
Cold ischemic time (h)*	16 (12–19)	**Immediate function, n (%)**	195 (68)
Anastomotic time (min)*	31 (11–71)	**Acute rejection, n (%)†**	50 (17.5)
		Graft loss 5 years after transplantation	
		All causes	34 (12%)
		Censored for patient death	14 (5%)
		Recipient death 5 years after transplantation	21 (7%)

*Median (inter-quartile range).
†Data are missing from some recipients who were excluded from percentage calculations.
‡Donor type was stratified according to the Maastricht Categories.[7]

Table 2.2.2. Indication for transplantation in 287 recipients of kidneys donated after circulatory death in Belgium between 2000 and 2009

Indication for transplantation	n (%)
Glomerular diseases	77 (27)
Polycystic kidneys	58 (20)
Uncertain etiology	35 (12)
Tubular and interstitial diseases	30 (11)
Retransplant/Graft failure	26 (9)
Diabetes	22 (8)
Hypertensive nephroangiosclerosis	15 (5)
Congenital, rare familial, metabolic disorders	11 (4)
Renovascular and other renal vascular diseases	9 (3)
Neoplasms	3 (1)
Others (familial nephropathy)	1 (<1)

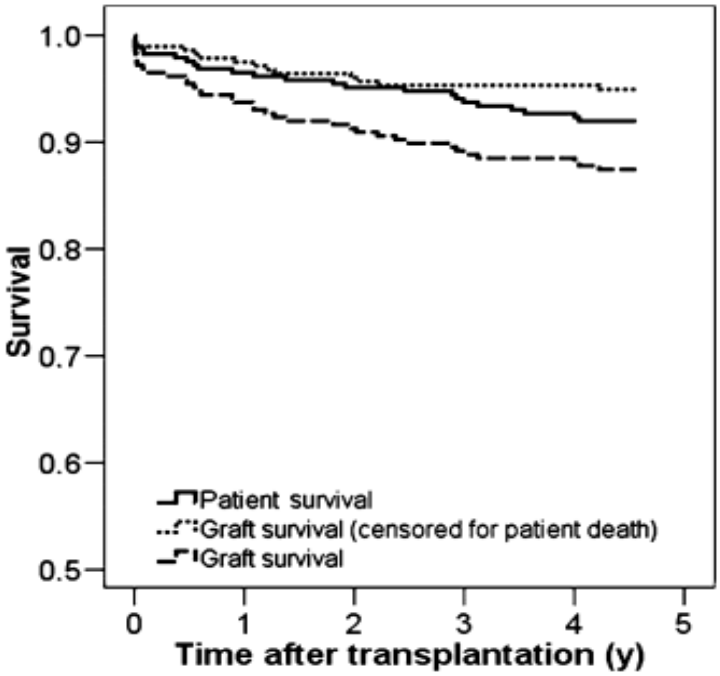

Figure 2.2.1. Patient and graft Kaplan–Meier survival curves until 5 years post-transplant of all kidneys donated after circulatory death in Belgium between 2000 and 2009

kidneys in 2010. Between 2000 and 2005, only 1.5% (0.75–4.25) of all transplanted deceased donor kidneys originated from DCD donors. Between 2006 and 2010, this number increased to 16% (12–16.5; p = 0.04). **Table 2.2.4** shows the evolution of kidney donation and

transplantation rates. Despite an increase in DCD donation, total deceased kidney donor rates did not increase. Living donors only slightly increased the total kidney donation rates. Increased kidney transplants from DCDs and living donors did not result in a significant increase of total kidney transplant activity.

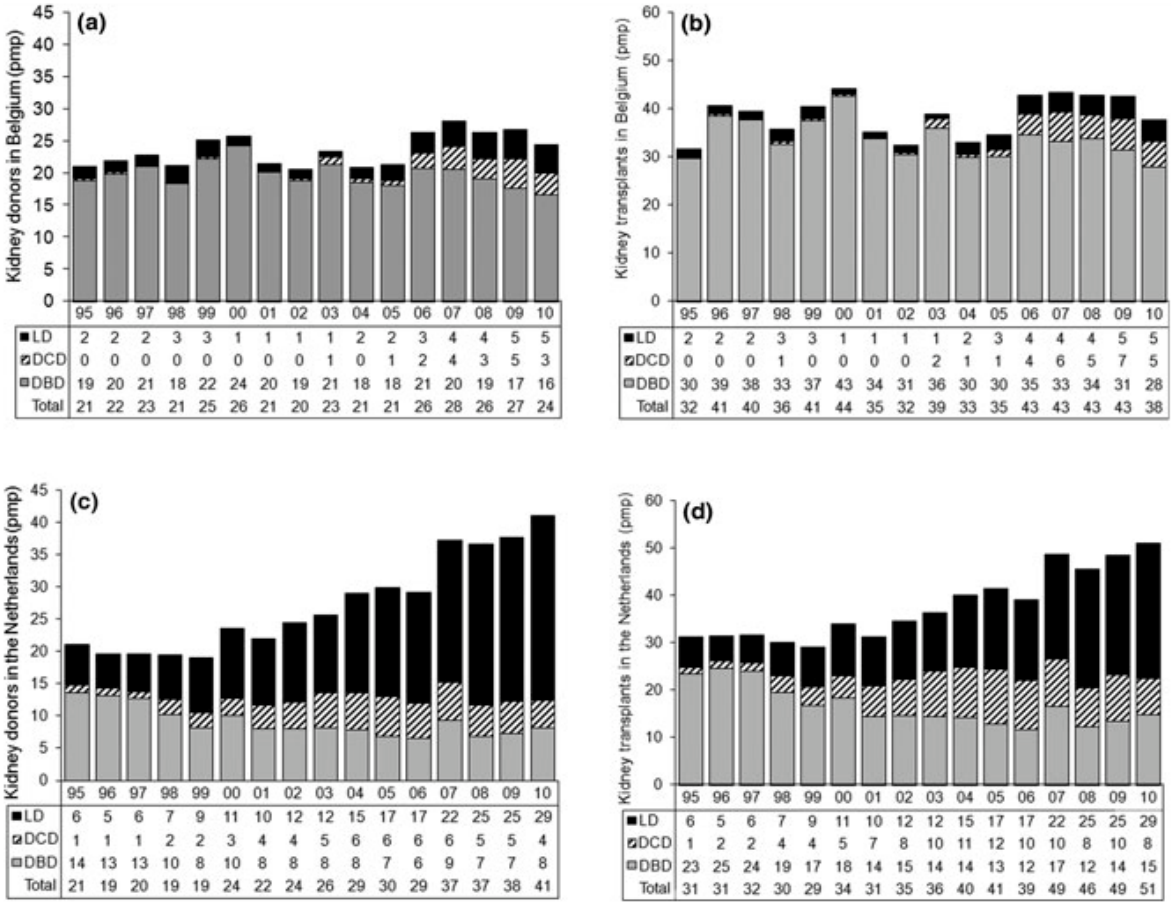

Figure 2.2.2. Total number of effective kidney donors and transplantations per milion population in Belgium (panel a–b) and the Netherlands (panel c–d) between 1995 and 2010. Data adapted from Eurotransplant[31,212]

Evolution of kidney donation and transplantation rates in the Netherlands since 1995

In the Netherlands, effective kidney donation rates reached 25.0 pmp (19.9–34.9) between 1995 and 2010. Kidney donors were equally distributed between living donors [12.2 pmp (7.3–20.8)] and DD [12.5 pmp (12.0–13.6)], with DBD [8.1pmp (7.4–10.2)] as well as DCD [4.1 pmp (2.2–5.5)] (**Fig. 2.2.2c**). Kidneys were mainly transplanted from DD [23.2 pmp (22.1–24.9)], both from DBD [14.7 pmp (13.7–19.1)] and DCD [7.6 pmp (3.7–10.0)]. Living donor transplants [12.4 pmp (7.3 - 20.8)] increased the total number to 35.4 pmp (31.3–44.6) (**Fig. 2.2.2d**). **Table 2.2.4** shows the evolution of kidney donation and transplantation rates. Living donation resulted in increased kidney donation rates. Deceased

donation activity remained stable, but DBD activity decreased significantly, whereas an exponential increase in DCD was observed (**Table 2.2.4, Fig. 2.2.3**). KT rates also increased, mainly because of increased living donations (in 2010, 57% of transplantations were with living donor kidneys). DD KT rates remained stable, with increasing use of DCD kidneys and decreasing transplants from DBD (**Table 2.2.4, Fig. 2.2.3**).

Table 2.2.3. Uni- and multivariate logistic regression for the development of delayed graft function*

Variable	Univariate (n = 287)†		Multivariate (n = 203)‡	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Donor and surgical characteristics				
Age (years)	1.00 (0.97–1.02)	0.73		
Gender – female versus male	0.78 (0.46–1.34)	0.37		
Terminal SCr (mg/dl)	1.93 (0.90–4.12)	0.09		
History of arterial hypertension	0.91 (0.44–1.90)	0.80		
Uncontrolled versus controlled DCD	4.59 (1.77–11.96)	0.002	3.13 (0.99–9.91)	0.05
UW versus HTK solution	0.14 (0.04–0.47)	0.001	0.19 (0.57–0.67)	0.01
Machine perfusion versus cold storage	0.66 (0.40–1.09)	0.11	0.35 (0.16–0.74)	0.01
Delayed versus immediate machine perfusion	1.44 (0.59–3.52)	0.43		
Warm ischemia time (min)	1.01 (1.0–1.03)	0.10		
Acirculatory time (min)	1.05 (1.01–1.10)	0.03		
Cold ischemic time (h)	1.06 (1.01–1.12)	0.03	1.11 (1.32–1.19)	0.01
Anastomotic time (min)	1.00 (0.97–1.02)	0.73		
Recipient characteristics				
Age (years)	1.02 (1.00–1.04)	0.07		
Gender - female versus male	0.65 (0.39–1.10)	0.11	0.52 (0.26–1.04)	0.06
Pre-transplant dialysis duration (mo)	1.01 (1.00–1.02)	0.09	1.02 (1.00–1.03)	0.06
Retransplant versus first transplant	1.18 (0.50–2.76)	0.71		
Panel reactive antibodies (%)	1.01 (0.99–1.02)	0.58		
HLA mismatches				
Level 2 versus Level 1	0.73 (0.34–1.57)			
Level 3 versus Level 1	0.83 (0.07–10.2)			

*Multivariate model was constructed using backward stepwise regression of covariates with a univariate $p < 0.15$.

†Data are missing for some recipients; these were excluded case wise from multivariate analysis.

‡Hosmer-Lemeshow test of final model: χ^2 5.8 on 8 d.f., $p = 0.67$.

Table 2.2.4. Evolution of kidney donors and transplants in Belgium and the Netherlands between 1995 and 2010

	1995–1999	2000-2005	2006–2010	p value
Belgium				
Kidney donors (pmp)				
Total	22 (21–24)	21 (21–24)	26 (25–27)	0.01
Living donors	2 (2–3)	1 (1–2)	4 (4–5)	<0.01
Deceased donors	20 (19–22)	20 (19–23)	22 (21–24)	0.30
DBD	20 (19–22)	19 (18–22)	19 (17–21)	0.62
DCD	0 (0–0)	0 (0–1)	3 (3–4)	0.01
Kidney transplants (pmp)				
Total	40 (34–41)	35 (33–40)	43 (40–43)	0.01
Living donors	2 (2–3)	1 (0–3)	4 (4–5)	0.01
Deceased donors	38 (31–38)	33 (31–39)	39 (36–39)	0.21
DBD	37 (31–38)	32 (30–38)	33 (30–34)	0.57
DCD	0 (0–1)	1 (0–2)	5 (5–6)	0.01
Netherlands				
Kidney donors (pmp)				
Total	19 (19–20)	25 (23–29)	37 (33–39)	<0.01
Living donors	6 (6–8)	12 (11–16)	25 (20–27)	<0.01
Deceased donors	14 (11–15)	13 (12–13)	12 (12–14)	0.59
DBD	13 (9–13)	8 (8–9)	7 (7–9)	0.01
DCD	1 (1–2)	5 (3–6)	5 (5–6)	0.01
Kidney transplants (pmp)				
Total	31 (30–32)	35 (33–40)	49 (42–50)	<0.01
Living donors	6 (6–8)	12 (11–16)	25 (20–27)	<0.01
Deceased donors	25 (22–26)	24 (22–25)	23 (21–25)	0.57
DBD	23 (18–24)	14 (14–16)	14 (12–16)	0.01
DCD	2 (2–4)	9 (6–11)	10 (8–10)	0.01

pmp, per million population. Values are presented as median (inter-quartile range).

Discussion

This Belgian survey shows that DCD KT programs resulted in good immediate function and excellent medium-term outcome. Indeed, a 31% DGF incidence in DCD kidneys is lower than commonly reported and is in fact comparable to DGF rates observed in DBD kidneys (13–35%).[206,207] This low DGF rate likely results from short CIT and the use of machine perfusion. Our multivariate analysis, although limited by its retrospective nature, showed that CIT and cold storage are independent risk factors of DGF. This is consistent with a recent Eurotransplant randomized controlled trial showing that machine perfusion significantly reduces the risk of DGF in DCD kidneys.[51,52] Of note, 16% of the kidneys in the

current analysis were part of the Eurotransplant trial. Following the report of a UK randomized controlled trial that did not show the benefit of machine perfusion,[216] it has been suggested that kidneys should be machine-perfused immediately following procurement until transplantation.[217] In this analysis, no difference was observed in DGF between immediate versus delayed perfusion. However, an effect could have remained undetected because only a minority of kidneys underwent delayed machine perfusion.

We observed only three PNF cases (1%), contrary to generally higher PNF rates reported in DCD kidneys.[206,207] Although no formal analysis on the risk factors of PNF could be performed, the low PNF rate is likely explained by the majority of controlled Maastricht Category III donors, the relatively short warm ischemic and acirculatory times, anastomotic time and CIT, and possibly the use of machine perfusion.[218] In addition, donors were young with excellent kidney function and only rarely suffered from hypertension.

Unfortunately, the introduction of DCD KT did not lead to a major increase in the Belgian KT activity. There are several possible contributing factors.

Firstly, despite the high number of DBD in Belgium there is room for improvement. Only 67% of potential DBDs are identified and of these 10% are never reported.[219] One strategy to improve donor identification and referral is the Spanish model of the 'donor facilitator': professionals responsible for donor identification and evaluation, supporting intensive care personnel charged with donor maintenance, and interviewing donor families.[220] In Belgium, donor facilitators have recently been appointed through a national initiative, the GIFT-project. In addition, training of health-care professionals involved in donation and transplantation and national campaigns to increase public awareness should be pursued.[221]

Secondly, the full potential of controlled DCDs is not used. As many as 26% of all ICU deaths are potential controlled DCD donors, but less than 4% of DCD are identified, indicating a real possibility to increase the donor pool (survey Ministry of Health, L. De Pauw, personal communication). A possible explanation could be the extreme caution and skepticism by which DCD were originally approached in Belgium. The initial mixed results of international DCD programs reporting high DGF and PNF rates[188,222-226] held the Belgian DCD programs back for another 2–3 years.[173] At the time, it was advocated that 'the development of a non-heart beating program is no longer acceptable if machine perfusion and viability testing are not available'.[164] The publication by Weber et al., showing equal long-term results for DBD and DCD kidneys, even without machine perfusion,[209] increased confidence in DCD and lead to a marked increase in DCD KT after 2003. Meanwhile, it has

also been shown that viability testing - based on renal vascular resistances and biomarkers in the perfusate - is not as straightforward as has always been assumed.[166,167,227]

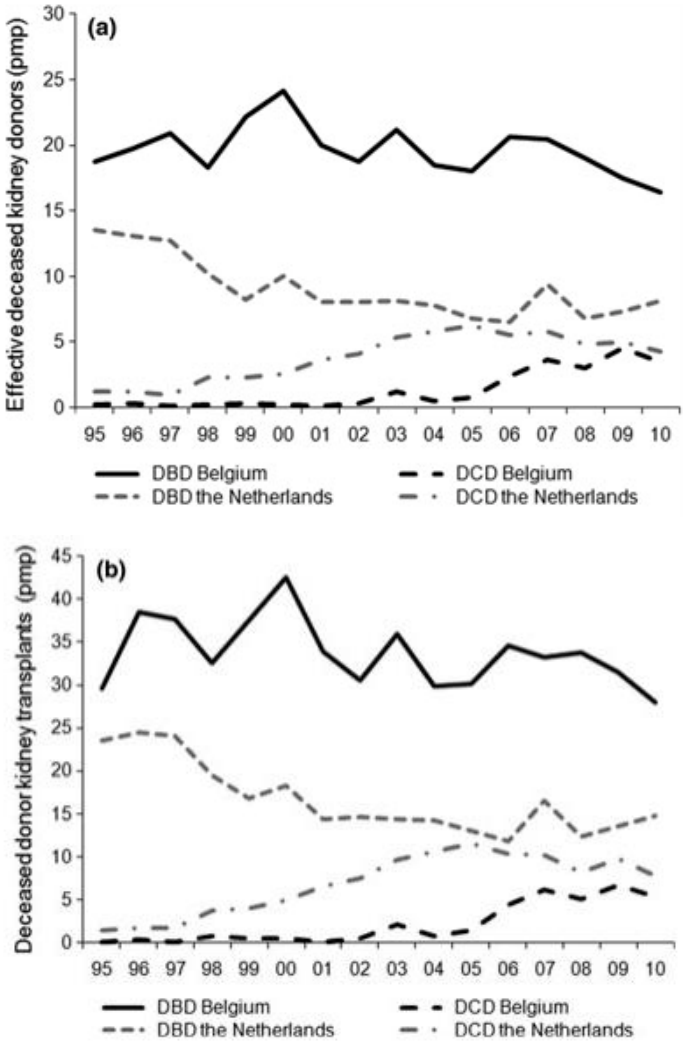

Figure 2.2.3. Evolution of effective deceased kidney donors (panel a) and transplants (panel b) per million population in Belgium and the Netherlands between 1995 and 2010. Data adapted from Eurotransplant[212]

Although it might be too early to distinguish the effect of DCD programs on the overall transplant activity, there is an increasing concern that DBD are being recovered as DCD, i.e. potential donors with major, irreversible neurological injury are prematurely referred as DCD, before brain death occurs. Especially in the UK[228] and the Netherlands (**Figs 2.2.2 and 2.2.3, Table 2.2.4**) the increase in DCD has been accompanied by an alarming decrease in DBD. The shortage of ICU resources and perhaps the erroneous perception that DCD and DBD have equivalent results may encourage physicians to refer potential donors earlier as DCD, even if they may progress to brain death at a later stage. In addition, the

possibility to offer withdrawal of life support earlier could avoid unnecessary prolonged suffering for patients and families in case of unrecoverable neurological damage.[75] Furthermore, improved and more aggressive neurosurgical decompressive treatments delay or even prevent development of brain death after neurological disasters.[75] Although an alleged substitution of DBD for DCD is very difficult to prove, the possibility of it occurring is extremely worrisome because, as a result, total DD transplant activity is not increasing. Furthermore, DCD liver transplantation results in higher rates of biliary complications and decreased graft survival, DCD critically diminish the donor population for heart transplantation, and there are fewer organs retrieved from DCD with a lower utilization rate. The observation that DBD activity has continued to increase – albeit slightly – in most European countries, except those with established DCD programs like the Netherlands and UK, supports a substitution phenomenon. A survey of the Belgian Ministry of Health has shown that the potential of DBD has decreased from 8% to 6% of ICU deaths between 2007 and 2010 (L. De Pauw, personal communication).

To effectively increase the DD pool without compromising the excellent results of transplantation, DCD should ideally only concern donors that would otherwise not progress to brain death. In this regard, uncontrolled DCD (Maastricht Category I and II) represent a scarcely explored source of kidney grafts that does not compete with DBD. Uncontrolled DCD is predominant utilized only in Spain and France, where controlled DCD is not allowed.[19] Although graft survival of uncontrolled DCD kidneys seems to be similar to controlled DCD in experienced centers, data on long-term results in large patient cohorts are scarce.[9,19,218,229] Our limited experience with uncontrolled donation has resulted in a higher DGF rate, but equally good 5-year outcome compared with controlled DCD. Unfortunately, procurement and organ utilization rates in these uncontrolled DCD are lower than in controlled DCD with considerably increased use of resources and potentially demotivating donor hospitals and procurement teams.[19]

Another potential source of DCD organs are organs donated after euthanasia. Since 2002, euthanasia is legal in Belgium under strict conditions.[230] At the explicit wish of the patient requesting euthanasia and after Ethical Committee approval, organ donation can be considered. A limited number of cases have been performed with excellent results.[12,231] The potential of donation after euthanasia is substantial; 335 cases of euthanasia with a noncancerous diagnosis were performed in Belgium between 2002 and 2007, with increasing numbers every year.[232]

Because of the high rate of deceased donation in Belgium, it has long been thought that the need for living donation was less urgent than in countries with low deceased donation. However, this review shows that overall DD activity has not increased significantly over the last 15 years, whereas waiting times for a deceased kidney have increased (median of 787 days in 2000 and 864 days in 2010). Extensive worldwide experience with living kidney donation, the safety of unilateral nephrectomy in selected healthy living donors,[233-235] the development of minimally invasive surgery, and the superior results of living versus DD KT,[236] support the further development of living donation in Belgium. Matching the living donor activity to that in the Netherlands or in the United States would double the total transplant activity in Belgium.

Conclusion

DCD KT in Belgium results in good immediate function and excellent medium-term outcome. However, until now DCD programs have not resulted in an increase of total DD KT activity, possibly related to a substitution of DBD to DCD donors. To increase its KT activity, Belgium should (i) improve the identification and reporting of all DBD donors with support of appointed donor facilitators; (ii) pursue the development of controlled DCD while avoiding premature referral of potential donors who may progress to brain death; (iii) explore uncontrolled DCD, and (iv) increase living donation.

3

Results of Kidney Transplantation from DCD

3.1 DCD kidney transplantation in Liège and Belgium

Published as

H Le Dinh, L Weekers, C Bonvoisin, JM Krzesinski, J Monard, A de Roover, JP Squifflet, M Meurisse, and O Detry

Results of Kidney Transplantation from Controlled Donors after Cardio-Circulatory Death: a Single Center Experience

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ABSTRACT

Objectives: The study aimed at determining results of kidney transplantation (KT) from controlled donation after cardio-circulatory death (DCD). Primary end-points were graft and patient survival, and post-transplant complications. The influence of delayed graft function (DGF) on graft survival and DGF risk factors were analysed as secondary end-points.

Patients-Methods: This is a retrospective mono-center review of a consecutive series of 59 DCD-KT performed between 2005 and 2010.

Results: Overall graft survival was 96.6%, 94.6% and 90.7% at 3 months, 1 and 3 years, respectively. Main cause of graft loss was patient's death with a functioning graft. No primary non-function grafts. Renal graft function was suboptimal at hospital discharge, but nearly normalized at 3 months. DGF was observed in 45.6% of all DCD-KT. DGF significantly increased post-operative length of hospitalisation but had no deleterious impact on graft function or survival. Donor body mass index ≥30 was the only donor factor that was found to significantly increase the risk of DGF ($p<0.05$).

Conclusions: Despite a higher rate of DGF, controlled DCD-KT offers a valuable contribution to the pool of deceased donor kidney grafts, with comparable mid-term results to those procured after brain death.

Introduction

Confronted with the universal critical organ shortage, many transplant centers have started the use of donation after cardio-circulatory death (DCD) as an alternative donor source. Results of kidney transplantation (KT) from DCD over the past 30 years showed comparable results with those from donation after brain death (DBD).[90,131,199,212,237-239] These results of DCD-KT have led Belgian transplant centers to revisit this option and urged the Belgian National Council of Physicians on organ procurement from DCD.[173] The first DCD-KT was performed in Belgium in 2000, and up to now all seven Belgian transplant centers have active DCD-KT programs.[193,194] In 2009 there were 60 DCD procurements (21.7% of the deceased donor (DD) pool) and 74 DCD-KT (17.3% of the DD kidney pool) in comparison to 9 DCD procurements (3.8%) and 14 DCD-KT (3.9%) in 2005. A preliminary report over 44 DCD-KT in Belgium during the 2003–2005 period showed a delayed graft function (DGF) rate of 20.5% and a primary non-function (PNF) rate of 9.1%. DCD kidneys preserved by machine perfusion had a significant lower rate of DGF than cold-stored kidneys (25% versus 42%) and the risk of graft loss of 3%.[173]

The University Hospital of Liège initiated a program of controlled DCD-KT in 2005.[240] This study aimed at evaluating results of DCD-KT at our institute with regard to short- and mid-term graft function, graft and patient survival, rejection and surgical complications. The influence of DGF on graft function and survival as well as the potential DGF risk factors were also analyzed as secondary end-points.

Patients and Methods.

This study is a retrospective review of the experience of the Department of Abdominal Surgery and Transplantation at the University Hospital of Liège with controlled DCD-KT from 2005 to 2010. Kidneys procured from DCD donors were distributed within the Eurotransplant organization according to the same allocation rules as DBD kidneys (except Germany and Croatia where organ procurement and transplantation activity from DCD are prohibited by Law). The rate of local, national and international sharing was 47.5%, 44.1% and 8.5%, respectively, in this series. The acceptance criteria for DCD kidneys were as follows: donor age less than 65 years; no history of renal disease, uncontrolled hypertension, complicated diabetes mellitus, systemic sepsis or malignancy; warm ischemia time (WIT) less than 45 minutes (from cardio-circulatory arrest to aortic cold perfusion) or less than 60

minutes (from withdrawal of life-support to aortic cold perfusion)[14] and terminal serum creatinine < 20 mg/L. Donor characteristics are presented in **Table 3.1.1**.

Withdrawal of life-support occurred in the operating room. Heparin was injected intravenously prior to withdrawal of both ventilator and cardiac support in most DCD donors. Vital signs (blood pressure, heart rate, respiratory rate and trans-cutaneous oxygen saturation) were monitored after discontinuation of treatment until cardio-circulatory arrest took place. Cardio-circulatory arrest was defined by femoral mean arterial pressure less than 30 mmHg without arterial pulse. A 5-minute no-touch period was respected after cardio-circulatory arrest, then cardio-circulatory death was declared. Rapid laparotomy with direct aortic cannulation technique was utilized to in-situ perfuse organs. HTK was the most common used preservation solution (84.7%) and kidneys were cold-stored in most cases (83.1%). Ten kidney allografts were preserved by the hypothermic machine perfusion (HMP) technique in the context of an Eurotransplant randomized controlled trial about the efficacy of HMP over static cold storage (SCS).[51] Mean total WIT was 20.1 ± 7.2 min (range: 8-39). This time period comprised the withdrawal phase (from treatment discontinuation to cardio-circulatory arrest, mean: 9.4 ± 5.5 min, range: 2-30) and the acirculatory phase (from cardio-circulatory arrest to initiation of aortic cold perfusion, mean: 10.6 ± 4.8 min, range: 5-27). Mean cold ischemia time (CIT), defined as the time interval from aortic cold perfusion until removal of the kidney graft out of the cold preservation solution for implantation, was 731.3 ± 267.5 min (range: 207-1255). Mean vascular anastomosis suture time was 35.1 ± 9.7 min (range: 18-60).

Recipient variables are summarized in **Table 3.1.2**. Mean recipient age was 54.9 ± 13.5 years (range: 21 – 76). Recipient older than 65 years received kidneys from older donors in the context of Eurotransplant Senior Program.[241] Mean PRA (panel reactive antibodies) at transplant was 5.2% ± 15.2% (range: 0-75). Mean number of HLA (human leukocyte antigens) mismatches was 2.8 ± 1.0 (range: 0-4). The frequency of 0, 1, 2, 3 and 4 HLA mismatches was 1.7%, 8.5%, 28.8%, 32.2% and 28.8%, respectively. Ureteral double J catheter was utilized in half of the patients (49.2%), largely depending on the surgeon's preference and experience. All recipients received induction therapy with anti-CD25 monoclonal antibody (basiliximab) and a standard triple therapy with tacrolimus or cyclosporin, mycophenolate mofetil or mycophenolic acid and steroids. Anti-infective prophylaxis comprised sulfamethoxazole/trimethoprim for pneumocystis and urinary tract infection for at least 6-12 months, valganciclovir for cytomegalovirus (CMV) depending on donor and recipient CMV serologic status (if D+/R-: valganciclovir for 3 months, other cases:

Table 3.1.1 and Table 3.1.2. Donor and Recipient characteristics

Donor characteristics	Mean ± SD or n (%)	Recipient characteristics	Mean ± SD or n (%)
Age (years)	45 ± 12.9 (3-68)	**Age (years)**	54.9 ± 13.5 (21–76)
Gender		**Gender**	
Male	35 (59.3)	Male	37 (62.7)
Female	24 (40.7)	Female	22 (37.3)
BMI (kg/m^2)	25.4 ± 3.2 (20–31.4)	**BMI (kg/m^2)**	26.8 ± 5.3 (15.9–38.2)
Hypertension		**ESRD etiology**	
Yes	9 (15.3)	Primary GN	8 (13.6)
No	38 (64.4)	Hypertension	7 (11.9)
Unknown	12 (20.3)	Diabetes	7 (11.9)
Diabetes		Lupus	2 (3.4)
Yes	2 (3.4)	Tubulo-interstitial nephropathy	4 (6.8)
No	43 (72.9)	HIV nephropathy	1 (1.7)
Unknown	14 (23.7)	Hemolytic uremic syndrome	1 (1.7)
Donor cause of death		Hepato-renal polycystosis	12 (20.3)
Head trauma	16 (27.1)	Uropathy	5 (8.5)
CVA	22 (37.3)	Unknown causes	12 (20.3)
Anoxia	19 (32.2)		
Euthanasia	2 (3.4)		
Length of ICU stay (days)	7.1 ± 6.5 (0–24)*	**Time on waiting list (days)**	535.7 ± 498.5 (3–2160)
Terminal SCr (mg/l)	7.5 ± 3.1 (2.3–17.2)	**Pre-transplant dialysis duration (days)**	933.2 ± 617.1 (0–2425)**
24 h diuresis (ml)	2841.6 ± 1312.2 (1270–5940)	**Residual diuresis (ml)**	650.4 ± 748.9 (0–2520)
Last hour diuresis prior to procurement (ml)	144.2 ± 125.3 (10–600)	**Previous transplants**	
		First transplant	55 (93.2)
		Retransplant	4 (6.8)
		Peak PRA (%)	11.5 ± 18.7 (0-70)
		PRA at transplant (%)	5.2 ± 15.2 (0–75)
		Number of HLA mismatches	2.8 ± 1.0 (0-4)

*Euthanasia donors did not stay in the ICU.

**One pre-emptive kidney transplant in the context of combined liver-kidney transplantation.

BMI, body mass index; ICU, intensive care unit; ESRD, end-stage renal disease; PRA, panel reactive antibody; HLA, human leukocyte antigens; HIV, human immune-deficiency virus.

acyclovir for herpes virus for 3 months). Diagnosis of renal allograft rejection was suggested by an unexplained rise in serum creatinine level of > 0.3 mg/dL or a 25% increase from baseline level and confirmed by ultrasound-guided per-cutaneous biopsy. Renal biopsy was also routinely done for all grafts at 3 months post-transplant for the purpose of deciding to withdraw steroids or not. Given the importance of subclinical rejection as a risk factor for interstitial fibrosis and tubular atrophy as well as worse glomerular filtration rate (GFR) and graft survival, they were all treated with bolus of steroids. Donor specific HLA antibody was checked periodically at the hospital discharge, 3 months and every year post-transplant, simultaneously at the time of graft biopsy and after a sensitizing event. Doppler ultrasound was systemically done at hospital discharge, 3 months and every year post-transplant or at any change of renal allograft function without clear explanation.

The renal transplant was primary transplant in most cases (93.2%) with one combined liver-kidney transplantation. There were four re-transplant recipients (6.8%), of which, one was immunized with peak PRA of 61% while the remaining three had no panel reactive antibodies. No patients developed donor specific antibodies which were routinely screened by single antigen Luminex technique. The average number of HLA mismatches was 2.2 ± 1.5 (range: 1-4). Cross-match tests were performed at the procurement center with the recipient's historic sera and repeated again at the transplant center with a recent serum and these tests must be negative prior to graft implantation. For primary transplant recipients who were at low immunological risk, kidney transplantation was allowed before the result of cross-match test to shorten the CIT.

Primary endpoints of the study were PNF, DGF, graft function at the hospital discharge, 3 months, 1 and 3 years post-transplant, graft and patient survival at 3 months, 1 and 3 years post-transplant. *PNF* was defined as inadequate renal function after transplantation that necessitates continuation of dialysis, excluding operative technical problems. *DGF* was defined as the requirement for hemo-dialysis during the first week post-transplant, with subsequent recovery of renal function, except dialysis treatments to correct hyper-kalemia or volume overload.[242] *Graft function* was estimated via serum creatinine and GFR according to the abbreviated Modification of Diet in Renal Disease (MDRD) equation.[243,244] Secondary endpoints of the study were the potential risk factors for DGF, the effect of DGF on graft and patient survival, duration of post-transplant hemo-dialysis, length of patient's hospital stay, acute rejection rate within the first 3 months post-transplant and the

occurrence of vascular or urological complications. *Acute rejection* was diagnosed on the base of the initiation of anti-rejection treatment or renal biopsy result.

Statistical analysis was as follows: continuous variables were presented as mean ± standard deviation (SD) and categorical variables as percentage. Differences between groups were evaluated by non-parametric Mann Whitney U/Wilcoxon Ranked Sum tests for continuous variables and Fisher's exact test or Chi square test for categorical variables. Survival rates were estimated by the Kaplan–Meier method and compared by the log rank test with graft failure and patient death as events. Multivariate logistic regression analysis was used to identify potential risk factors for DGF. All tests were two-tailed and p-values < 0.05 were considered as significant. All analyses were performed using the SPSS statistical software, version 11.0 for PC Windows.

Results

During the 6-year period, there were 59 and 215 renal transplants from controlled DCD and DBD donors, respectively. In other words, DCD kidneys made up 21.5% of the DD kidney pool and helped to increase the activity of kidney transplantation up to 27.4% without impairing the DBD kidney source. The organ procurement and transplantation activity of the KT program at the University Hospital of Liège from 2005 to 2010 is presented in **Figure 3.1.1**.

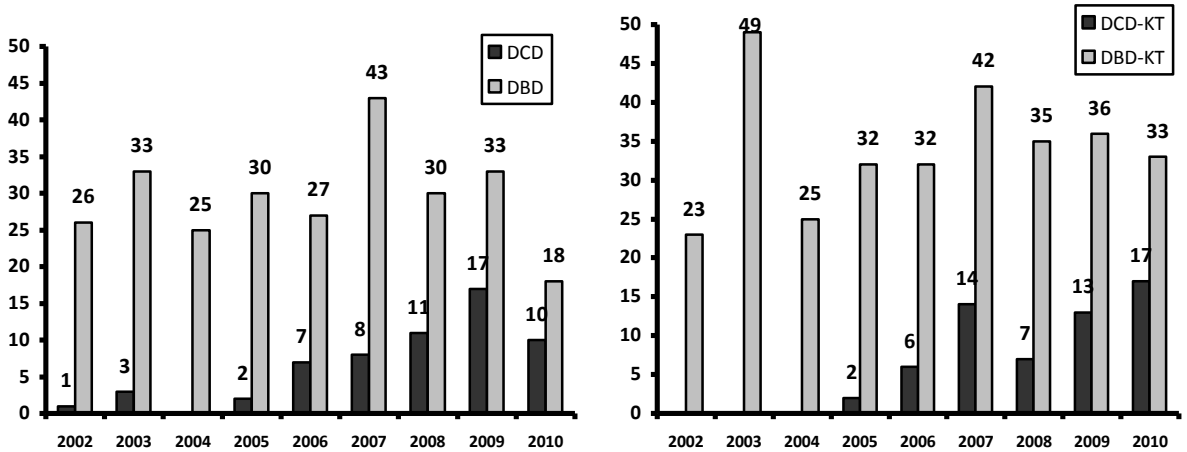

Figure 3.1.1. Organ donation and kidney transplantation activity in Liège over time. The number of DCD-KT increased without impairing the number of DBD-KT.

Functional and survival data

Analysis of Kaplan-Meier survival curves showed overall and death-censored graft survival rates were 96.6% and 96.6% at 3 months, 94.6% and 96.6% at 1 year, 90.7% and 92.6% at 3 years, and 84.6% and 92.6% at 4 years, respectively (**Figure 3.1.2**). Five renal grafts were lost during the post-transplant follow-up, one due to renal vein thrombosis, one secondary to the relapse of HIV infection in the allograft and three others because of patient deaths. Mean follow-up of patients was 26.5 months (range: 0.5-62 months). Patient survival rates at 3 months, 1, 3 and 4 years were 98.3%, 96.3%, 96.3% and 90.3%, respectively (**Figure 3.1.3**). Three patients (5.1%) died during follow-up, one due to acute myocardial infarction 24h post-operatively and other two due to broncho-pneumonitis caused by CMV and Aspergillus infection at 5 and 41 months.

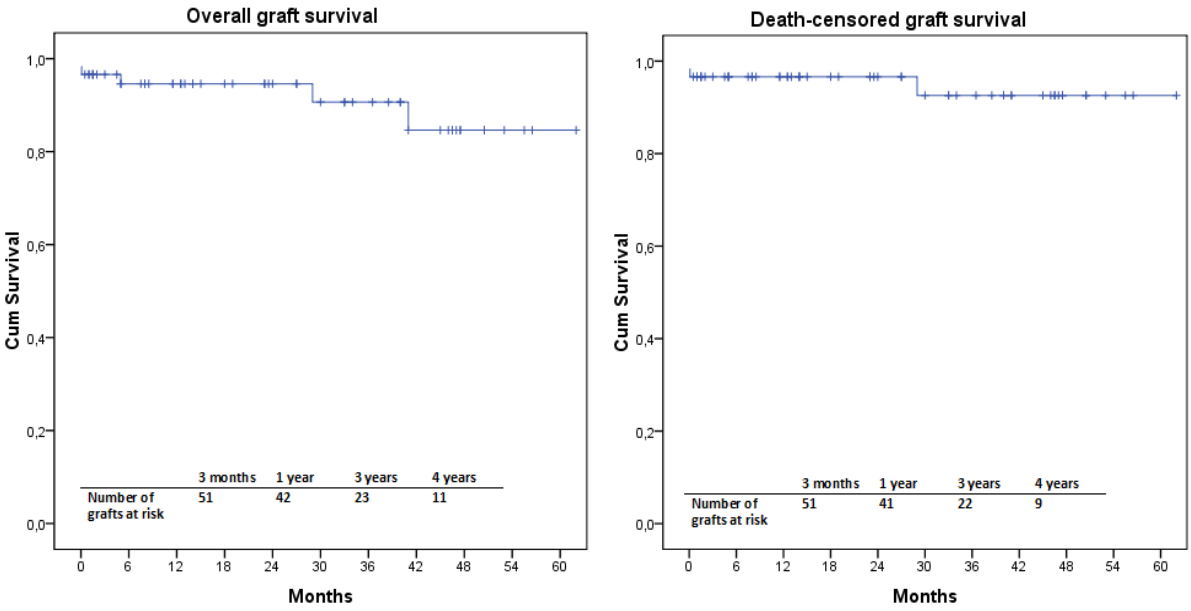

Figure 3.1.2. Overall and death-censored graft survival after DCD-KT (n = 59). Overall and actuarial graft survival rates were 96.6% and 96.6% at 3 months, 94.6% and 96.6% at 1 year, 90.7% and 92.6% at 3 years, and 84.6% and 92.6% at 4 years, respectively.

No PNF grafts were observed in this series. Two recipients were excluded from the analysis of DGF rates because one died 24h post-transplant and it was not known whether the graft was functioning at the time of patient death, the other lost the kidney graft due to renal vein thrombosis. Twenty-six of 57 patients (45.6%) experienced DGF. The occurrence of DGF did not adversely influence graft survival, as overall graft survival rates were 100%, 95%, 95% and 83.1% for patients with DGF compared with 100%, 100%, 91.7 and 91.7% for patients without DGF at 3 months, 1, 3 and 4 years, respectively (p=0.52, **Figure 3.1.4**). In addition, DGF did not increase the risk of acute rejection or surgical complications: among 26

recipients with DGF, 8 (30.7%) developed acute rejection compared with 8 (25.8%) recipients without DGF (p=0.67). The rate of all surgical complications was 34.6% and 25.8% in recipients with and without DGF, respectively (p=0.46).

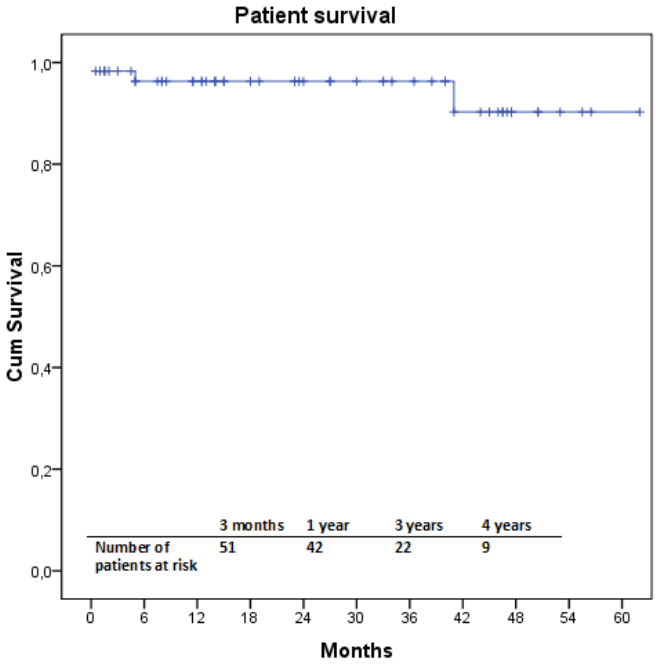

Figure 3.1.3. Overall patient survival after DCD-KT. Patient survival rates at 3 months, 1, 3, and 4 years were 98.3%, 96.3%, 96.3%, and 90.3%, respectively.

The use of HMP (n=10) was associated with a non statistically significant lower rate of DGF in comparison to that of SCS (30% versus 48.5%, respectively, p=0.31). Likewise, donor age (≥60 years), donor terminal serum creatinine (≥15 mg/L), recipient age (≥60 years), recipient BMI (BMI ≥30), kidney allocation policy (national or international sharing), WIT (≥45 min), suture time (≥45 min) as well as CIT (≥18 h) had no apparent effect on the risk for DGF (p=NS, both in univariate and multivariate logistic regression analysis, **Table 3.1.3**). Donor body mass index (BMI), in contrast, had an impact on DGF in multivariate model (not in univariate analysis). Kidneys from donors with BMI ≥30 compared to ones with BMI< 30 was 17 times more likely to have DGF (p=0.03).

One patient was transplanted due to HIV nephropathy and lost quite rapidly her renal allograft (29 months post-transplant) secondary to the relapse of HIV infection in the allograft. This was a rare indication of transplantation and this patient was excluded in the assessment of renal allograft function. Mean serum creatinine level at hospital discharge was 22.1 ± 11.7 mg/L (range: 6.8-56.6). The percentage of patients with serum creatinine level at

hospital discharge < 20, 20 – 40 and > 40 mg/L was 61.1%, 25.9% and 13%, respectively. Renal graft function continued to improve up to 3 months post-transplant and nearly stabilized over the following 4 years (**Figure 3.1.5**). The mean GFR at hospital discharge, 3 months, 1 and 3 years was 37.1 ± 16.6, 50.7 ± 11.7, 50.9 ± 11.3 and 49.2 ± 11.2 ml/min respectively. Among 4 recipients who underwent re-transplantation, two developed DGF. However the four kidney grafts functioned well during the study period.

Table 3.1.3. Multivariate logistic regression analysis between the risk of DGF and different factors linked to the donor, recipient or transplantation procedure

Factors	Odds ratio	95% CI	p value
Donor age ≥50 years	0.902	0.235 – 3.465	0.881
Donor BMI ≥30	17.415	1.258 – 241.179	0.033
Donor serum creatinine ≥15 mg/L	0.000	0.000	1.000
Recipient age ≥60 years	3.249	0.776 - 13.610	0.107
Recipient BMI ≥30	3.505	0.872 – 14.088	0.077
Kidney allocation policy (national or international sharing)	0.801	0.221 – 2.907	0.736
WIT ≥30 min	1.982	0.239 – 16.457	0.527
Suture time ≥45 min	2.276	0.380 – 23.650	0.368
CIT ≥12 h	2.886	0.572 – 14.556	0.199
CIT ≥18 h	3.252	0.210 – 50.358	0.399
Preservation method (HMP)	0.462	0.058 – 3.647	0.463

Postoperative evolution and complications

The average number of hemo-dialysis post-transplant in case of DGF was 4.96 ± 6.01 sessions (range: 1-32). Mean duration of hemo-dialysis was 10.6 ± 17.1 days (median: 7, range: 1-90). Mean hospital stay was 17.8 ± 5.7 days (range: 2-32). There was a significant difference in length of hospitalization between DGF and IGF (immediate graft function) groups (19.3 ± 5.3 versus 13.4 ± 3.9 days, $p < 0.001$).

Sixteen of 59 patients (27.1%) experienced graft rejection during the first 3 months post-transplant, making up 17 rejection episodes. Rejection might be either clinically suspected without graft biopsy (10.1%) or biopsy-proven at the time of rejection suspicion (8.5%) or diagnosed only at 3-month protocol biopsy (8.5%).

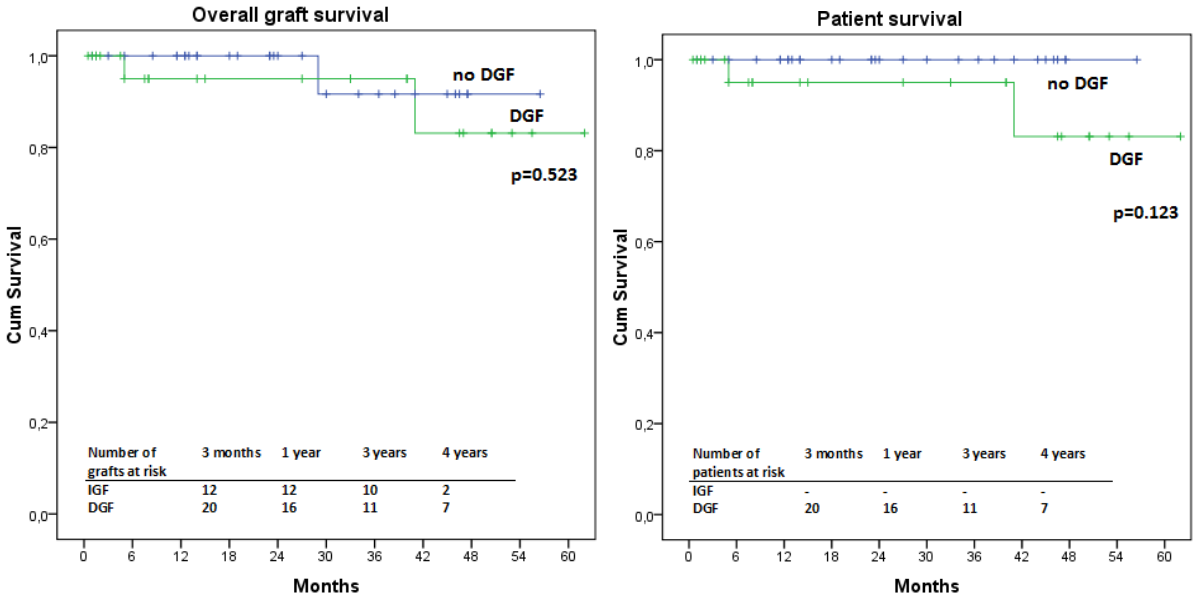

Figure 3.1.4. Graft and patient survival between DGF and no DGF groups. The presence of DGF did not adversely influence graft and patient survival (p=NS).

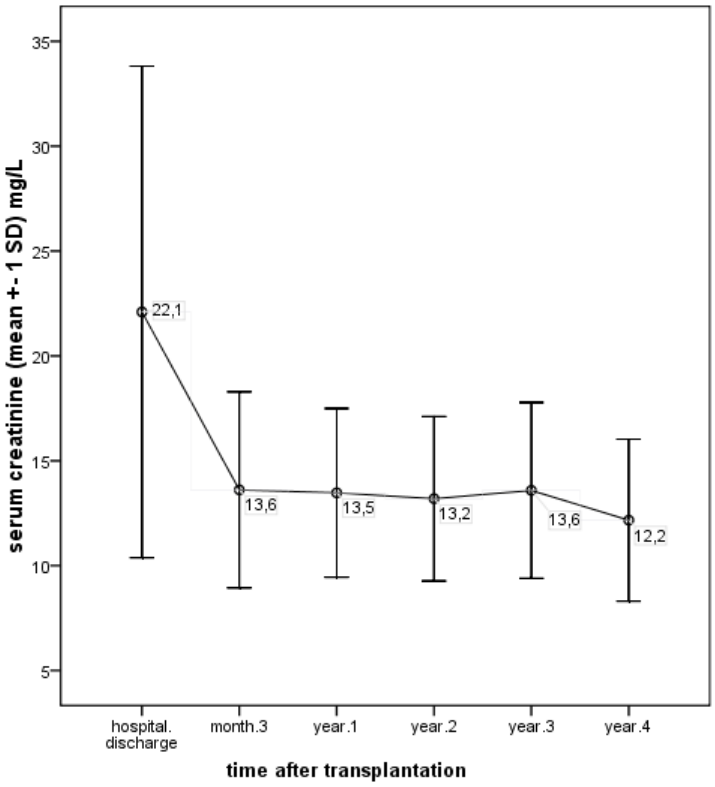

Figure 3.1.5. Sequential serum creatinine levels over time.

Early post-operative complications are presented in **Table 3.1.4**. After hospital discharge, renal artery stenosis was detected in two patients (3.4%) and stenting was necessary in one of them. Peripheral artery disease developed in two patients and all of them

were stented at the level of iliac arteries. Infectious complications included pulmonary tuberculosis (one patient) and urinary tract infection (11 patients). Urologic exploration was performed in one patient due to repeated urinary infection but no urinary anomaly was found. Peri-renal lymphocele occurred in one patient and was treated by puncture aspiration technique. One patient became pregnant 20 months post-transplant and gave birth of a healthy boy at 33rd amenorrheal week due to pre-eclampsia. No urinary leakage or ureteral obstruction was observed during the study period.

Table 3.1.4. Early post-operative complications

Complications	n	Treatment
Renal vein thrombosis	1	transplantectomy
Peri-graft hematoma	5	conservative treatment (4 patients), surgical re-intervention (1 patient)
Hematuria	5	bladder irrigation
Hydronephrosis	2	resolving spontaneously without urologic intervention
Abdominal wall bleeding	1	surgical re-intervention
Rupture of drainage catheter	1	surgical re-intervention
Urethral stenosis and benign prostatic hypertrophy	3	urethrotomy (1 patient) and transurethral resection of prostate (2 patients)
Acute myocardial infarction	2	coronary artery stenting (1 patient death)
Cardiac rhythmic disorders	2	cardio-pulmonary resuscitation (1 patient) and cardiac pace-maker placement (1 patient)
Anemia	11	blood transfusion

Discussion

This study showed excellent results of controlled DCD-KT which were comparable to those from DBD in the literature although the use of DCD kidneys led to an elevated rate of DGF due to the unavoidable WIT between the withdrawal of life-support and the initiation of cold preservation. DGF increased significantly the length of hospitalization, nonetheless had no deleterious impact on post-transplant DCD kidney outcomes as demonstrated in several other studies.[245,246] A recent meta-analysis in studies with controlled DCD donors showed no difference in PNF rate between 2 groups of DBD and DCD kidneys. The only significant difference was the DGF rate.[206] In our series, we did not experience any PNF and found a DGF rate of 45.6%. However, this high rate of DGF was not associated with an increased graft loss. When evaluating risk factors for DGF, only donor BMI ≥30 was significantly associated with an increased rate of DGF in multivariate logistic regression model. The significance of this finding is not clear.

DCD kidneys recovered their function slowly and in majority of cases failed to optimize their function at the time of hospital discharge. However their function continued to improve and nearly normalized at 3 months post-transplant. Afterwards renal allograft function stabilized over the following 4 years. By examining outcomes of DCD kidney transplants which functioned for at least 1 year and had a follow-up of 2–5 years, Chapman found that the rate of graft loss at 5 years was similar between DCD and DBD grafts (approximately 3%) and both groups showed similar declines in GFR after 1 year (-1.3 mL/min for the DCD group versus -1.4 mL/min for the DBD group). This means that DCD kidneys might have a reduced functioning glomerular mass because of the initial ischemic damage, but once transplanted there was no evidence of accelerate deterioration.[247]

Graft survival rates in this study were favorably comparable to other reported series.[198,199,237,248] The major cause of graft loss was patient death with a functioning graft. Although DCD kidneys experienced worse early transplant outcomes than those coming from DBD donors, they did provide real survival benefit to patients.[249] Patients who were willing to accept a standard-criteria DCD kidney had a 56% reduction in mortality risk compared with those remaining on dialysis or awaiting a standard-criteria DBD kidney. This reduction in mortality translates into 2.4-month additional expected lifetime during the first 4 years after transplantation for recipients of DCD kidneys in comparison to patients who wait for a DBD kidney.[92]

The rate of clinical and subclinical rejection in our study was similar to that reported in many studies, either single center reports,[211,237,250] national databases[212,251] or a recent meta-analysis.[206] DCD kidneys, despite experiencing greater DGF rates, do not display a greater incidence of acute allograft rejection episodes (10%-19%) compared with DBD kidneys (9%-18%). Similarly, in a recent publication, Saeb-Parsy did not find any difference in the rate of major urological complications (urinary leak and ureteral stenosis) between DCD and DBD kidney grafts (3.5% versus 1.7%, p=0.28).[252] Inversely, Droupy found that the risk of ureteral stenosis and fistula was significantly higher for DCD than DBD kidneys (15% versus 7%, p=0.04).[253] In 76 controlled DCD-KT performed at Leiden University Medical Centre, Khairoun reported one urinary leakage because of ureteral necrosis and two ureteral obstructions (one after removal of the double J stent and the other due to blood clot).[254] The rate of renal artery stenosis in this study was 3.4%. Although the incidence of transplant renal artery stenosis is expected to be higher in DCD kidneys because of the exposure to an

excessive ischemic injury, many published series, as ours, also did not find any significant difference between DCD and DBD kidneys.[255,256]

Estimates suggested that the potential increase in the number of DCD kidneys might be 2–4.5 times that of DBD kidneys.[196] However, in practice, single-center reports usually described a 20%–40% proportion of DCD kidney transplants among the DD kidney pool.[197-200] Exceptionally, a few transplant centers have obtained 50–70%, such as in Maastricht[77] or Madrid.[45,201] Recently several transplant centers in the Netherlands,[80] the United Kingdom (UK)[79] and the United States (US)[75] have observed a remarkable increase in the number of DCD donors with a concomitant decrease in DBD donors, resulting in no significant change in the DD pool, some kind of redistribution of donor types within the pool. We have not yet observed such a trend in our experience.

No significant difference in the rate of DGF between ice-stored and machine-perfused DCD kidneys was noted in this study, although the DGF rate was lower among machine-perfused grafts. A recent multi-centric randomized controlled trial, in which 164 DCD kidney pairs were split and one allocated to each preservation modality, convincingly demonstrated that HMP produced less frequent and less severe DGF as compared with SCS group (54% versus 70%).[51] In a study design similar to Moers's study, Watson in the United Kingdom found no benefit of HMP over SCS for DCD kidneys. Nevertheless the author emphasized on the ischemia time as an important factor for the differences between the two trials.[257] A meta-analysis undertaken by Wright[50] and studies in the US using the national database[131,258] all confirmed the advantage of HMP over SCS in DCD kidneys.

Conclusion

The use of controlled DCD kidneys might be an effective way to increase the number of kidneys available for transplantation because of good transplant outcomes and acceptable post-operative complications. Despite a higher rate of DGF with longer hospitalization, DGF had no harmful effect on the graft future in this series. By using this donor source, transplant centers could help optimize the quality of life and minimize the mortality of end-stage kidney disease patients on the waiting list.

3.2 DCD kidney transplantation in the world

Published as

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Clinical Results of Kidney Transplantation from Donors after Cardiac Death

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ABSTRACT

Objectives: Confronting the critical organ shortage, many transplant centers are now increasingly using donation after cardiac death (DCD) since 1990s as an alternative donor source to the insufficient donation after brain death (DBD). This review aimed at examining the clinical experience in DCD-KT in the world during the 1990s and 2000s, in order to help KT programs to develop DCD-KT and to better allocate DCD kidney grafts.

Methods: We conducted a systemic review of all mono- and multi-centric DCD-KT studies in the world over the past 20 years, and evaluated the short- and long-term results of DCD-KT in terms of initial graft function (delayed graft function-DGF and primary non-function-PNF), graft and patient survival, rejection, post-operative surgical and urological complications.

Results: Follow-up studies comparing DCD- and DBD-KT have shown comparable long-term graft function and survival up to 10 - 15 years post-transplant, despite higher rates of DGF and PNF in the early post-transplant period. Better transplant outcomes are obtained in controlled rather than uncontrolled DCD.

Conclusion: *DCD programs* should be continued and expanded. *DCD donors* constitute a potential donor source that may partially solve the imbalance between the number of end-stage kidney disease patients on the waiting list and the number of available kidney grafts. *DCD kidneys* do not mean sub-optimal grafts and merit to be allocated the same as DBD grafts.

Introduction

In the early days of transplantation, all cadaveric transplant organs were retrieved from donors after cardiac death (DCD). After the establishment of the concept of brain death in 1968 [1], DCD have been largely abandoned in the mid 1970s and replaced by donors after brain death (DBD). The interest for DCD was renewed in the early 1990s as a potential solution for the critical universal shortage of kidney grafts.

The practice of DCD differs greatly around the world as a consequence of different cultures, religions, and legislations. To date DCD donation has been concentrated in Europe, the United Kingdom, the United States and Japan (**Table 3.2.1**). Most countries use mainly Maastricht type 3 DCD, except France and Spain, where type 2 DCD are more widely used. While type 1 DCD are not used in many countries because of concerns about logistic difficulties, ethics and procured organ quality, it turns out to be the main DCD type in Spain. In Japan, donation after cardiac death has relied almost exclusively on type 4 DCD. Some countries are now starting to use type 2 DCD.

The contribution of DCD source to deceased donor pool also varies considerably between countries (**Table 3.2.1**). In 2007, the proportion of DCD kidney transplantation (KT) was 10.7% of the total cadaveric kidney pool in the United States[259] and 22.1% in the United Kingdom.[260] In Netherlands almost 50% of deceased donor kidneys are provided by DCD.[77] Estimates suggest that DCD programs may contribute 20-40% of cadaveric kidneys for transplantation[180,181] and there might be two times more potential DCD than DBD.[179] Therefore the use of DCD might have considerable impact on the kidney graft pool, markedly shortens waiting times and improves the survival and quality of life of the patients on the waiting lists.

It is therefore likely that DCD kidneys will be a large part of the transplantable kidney graft pool in a next future. The aim of this review is to examine the clinical experience in KT using the different types of DCD during the 1990s and 2000s, in order to help KT programs to develop DCD-KT and to better allocate DCD kidney grafts.

Differences between DCD and DBD pertinent to transplant outcomes

DCD differs from DBD in many aspects. The essential differences involve circumstances of death, warm ischemia and brain-dead process, as well as allocation of kidney grafts.

Table 3.2.1. DCD programs in some countries around the world in 2007

Country	DCD type used for transplant	Kidney allocation	Number of DCD-KT	% DCD-KT / DD-KT	% DCD / DD pool	DCD / pmp
Belgium [261]	2,3,4	ETKAS	65	14.7	13.1	3.7
Netherlands [261,262]	2,3,4	ETKAS	166	36.1	41.1	7
Spain [76,261]	1,2,4	Locally	104	5.1	5.7	2
France [261,263]	1,2,4	Locally	42	1.6	2.4	0.6
United Kingdom [261,264]	2,3,4	Locally	313	22.1	23.3	3.1
United States [265,266]	2,3,4	Locally	1130	10.7	9.8	2.6
Japan [267]	2,4	JOTN	163	87.1	87.6	0.7

ETKAS: EuroTransplant Kidney Allocation System, JOTN: Japanese Organ Transplant Network, DD: deceased donors, pmp: per million population.

Circumstances of death

Death results from irreversible cessation of cardio-pulmonary or cerebral functions, leading to cardiac death or brain death, respectively. Cardiac arrest can occur spontaneously and suddenly outside the hospital (type 1) or in the accident and emergency department (type 2), or can be planed after removal of life-sustaining treatment in a patient who has a non-recoverable illness/injury with dependence on life-supporting therapy (type 3). Cardiac arrest in the presence of brain death is type 4.[7]

Donation in type 3 and 4 DCD gives the best post-transplant results[237,268] because death is anticipated and medically controlled. There is adequate time to approach the donor relatives, to organize medical staffs, and to fulfill legal formalities before death. Organ procurement is therefore undertaken with a relatively short warm ischemia time (WIT). Moreover DCD hemodynamic stability and respiratory function may be maintained until withdrawal of treatment, so the quality of grafts may be assured. Inversely, transplantation from type 1 and 2 DCD has worst results[237,268] because death occurs unexpectedly. There is time pressure to arrange logistic supports. Organ harvesting hence takes place in an uncontrolled manner with a longer WIT.

Warm ischemia

DCD kidneys are submitted to an inevitable period of procurement warm ischemia. The period of WIT is variable. It is the longest in type 1 and 2 DCD (90-120 minutes), and

shorter in type 3 and 4 DCD (15-20 min, rarely exceeding 30 min). **Figures 3.2.1 and 3.2.2** present the primary WIT intervals in each donor type with desirable time frames for successful KT. Good results are expected if primary WIT is less than 45-60 min.[14] Kidney from young and previously fit DCD may be allowed a longer WIT than those from older donors.[198]

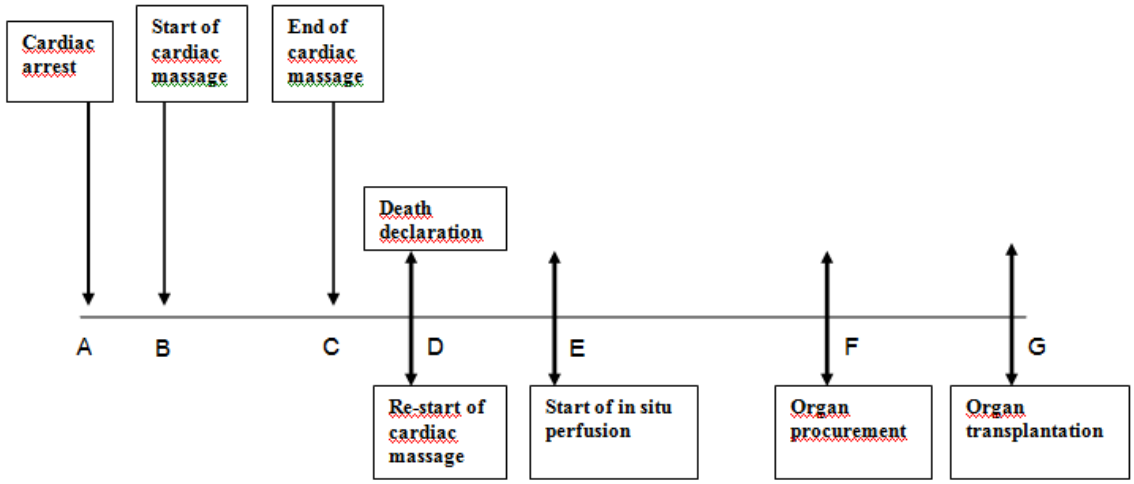

Figure 3.2.1. Procedure of kidney donation in type 1 and 2 uncontrolled DCD. **AB**: ***asystole time*** (time without cardiac massage) less than 15-30 min.[17,269,270] **BC**: ***assistance time*** with advanced cardio-pulmonary resuscitation (minimum 30 min).[17,62] **CD**: ***waiting time*** (no-touch period) between 2-10 min.[14,15] **DE**: ***catheter insertion period*** (less than 20 min).[46] **AD**: time between cardiac arrest and arrival to the hospital (less than 90 min).[271] **AE**: ***time between cardiac arrest and start of in situ perfusion or hypothermic ECMO*** (less than 150 min).[17,269,270] **EF**: ***in-situ perfusion period*** (less than 150 min)[263,272] or ***hypothermic ECMO period*** (maximum 240 min).[17] **EG**: ***cold ischemia time*** (less than 18 hr).[263]

Warm ischemia contributes to both primary non-function (PNF) and delayed graft function (DGF), and is perceived as the main barrier for the adoption of DCD programs in many transplant centers worldwide. For uncontrolled donors, various methods of kidney protection and harvesting have been advocated to decrease primary WIT: in situ intra-vascular cooling using the double balloon and triple lumen catheter (Maastricht protocol)[273,274], intra-peritoneal lavage and cooling (Washington protocol),[104] hypothermic and normothermic cardio-pulmonary bypass with extra-corporeal membrane oxygenation (ECMO) (Madrid and Barcelona protocol).[17] Additionally machine preservation methods may help to "resuscitate" the already compromised warm ischemic organs and may improve the organ quality and early graft outcomes.[50,51] Machine perfusion may also help to select transplantable kidneys and to discard nonviable ones (kidney viability testing). *The development of a DCD program is no*

longer acceptable if machine perfusion and viability testing are not available. [164] With regard to the logistic organization, two initiatives have been applied effectively in practice to reduce primary WITs: the "Maastricht box"[275] (a kit containing all the necessary equipment and instructions for in situ perfusion at the accident and emergency department) and the Madrid's "rapid identification and response system"[17] (highly qualified pre-hospital emergency services with response time within 7 min in urban areas and with the ability to perform advanced life support measures in mobile intensive care units).

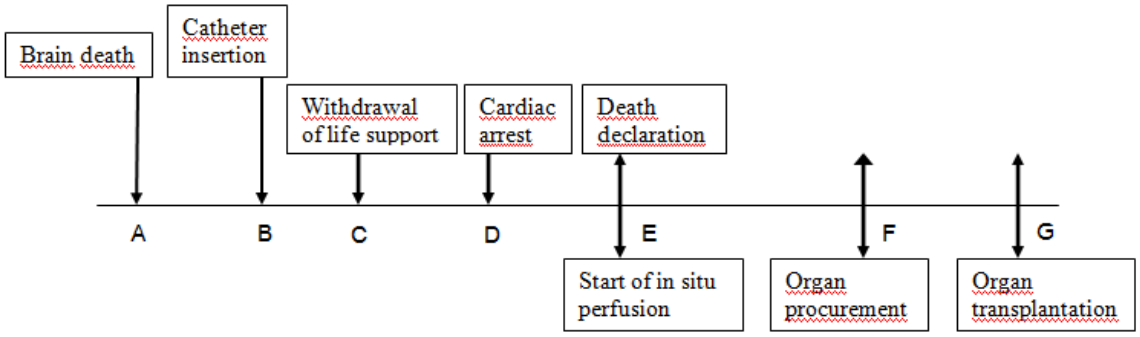

Figure 3.2.2. Procedure of organ donation in type 4 controlled DCD. DE: waiting period (no touch period).

For controlled donors, a super rapid recovery technique including rapid laparotomy and direct cannulation of the aorta has been proposed by the American Society of Transplant Surgeons[15] as the method of choice. However, if withdrawal of life-sustaining support is realized outside the operating room, the pre-mortem cannulation technique may be used to decrease the rush inherent with the super rapid recovery technique and WIT.[15]

A second WIT exists during vascular anastomoses of the graft, which also has impact on DGF. The time constraint on this part of the procedure is 40-45 min.[137,276]

Absence of brain death

Brain death due to a rapid increase in intracranial pressure provokes a cascade of changes in the hemodynamics, hormones and immune response, which have a negative impact on donor organ viability and transplant outcome.[277,278] In brain death, renal vaso-constriction due to excessive secretion of catecholamines and volume depletion leads to renal hypoperfusion and ischemic damage. Renal inflammatory and degenerative lesions appear on histological examination, including glomerulitis, periglomerulitis, vacuolization/atrophy and necrosis of proximal and distal tubules, proliferation of the arterial intima and glomerular

endothelium. Upregulation of circulating cytokines and chemokines, increased endothelial cell expression of adhesion molecules and major histocompatibility class I and II, as well as greater infiltration of T cells, macrophages and polymorphonuclear leukocytes into renal parenchyma, result in an increased renal immunogenicity and host allo-responsiveness. Consequently brain dead donor kidneys are at higher risk of rejection. The more rapid increase in intra-cranial pressure occurs, the degree of peripheral organ damage is more intense. In clinical transplantation, mechanisms involving donor brain death are quite varied and a relationship between donor cause of death and transplant outcomes (graft rejection, function and survival) has been confirmed in different types of solid organ allografts.[279]

Uncontrolled DCD whose cause of death is usually other than neurologic, do not undergo the process of brain death, while most controlled DCD have sustained irreversible cerebral injury. As a result, organs from controlled DCD are likely to suffer more from the harmful immunological, inflammatory and coagulatory effects than organs from uncontrolled DCD.[198,262,280] Events around the time of brain death may play a more important role in the genesis of renal damage than warm ischemia.[281] In addition, the impact of donor cause of death on DCD kidney transplant outcomes was also described.[179]

Allocation of DCD kidney grafts

Allocation of DCD kidney grafts varies according to countries and regulations. In Japan and in five countries belonging to the Eurotransplant International Foundation (Austria, Belgium, Luxemburg, the Netherlands and Slovenia), DCD kidneys are allocated in the same manner as DBD kidneys, through the Japan Organ Transplant Network (JOTN) and the EuroTransplant Kidney Allocation System (ETKAS), respectively. The legislation in Croatia and Germany (two other Eurotransplant countries) does not permit the procurement and transplantation of DCD kidneys.

In Spain and France, allocation of DCD kidneys is center oriented, i.e. to patients on the waiting list of the center that procured the DCD kidney. In a hospital in Madrid, 70% of transplanted kidneys were type 1 and 2 DCD grafts, and several DCD kidneys had to be sent to other transplant centers because of no available recipients. Patients began to be transplanted preemptively with DCD kidneys.[45] In the United Kingdom, in order to minimize cold ischemia time (CIT) and encourage new DCD programs, the policy is to transplant both DCD kidneys locally.[282] The United States reserves the allocation organization to Organ Procurement Organizations (OPOs).[131] Some OPOs distribute these kidneys using the

extended criterion donor (ECD) list, while others offer DCD kidneys to every recipient on the deceased donor waiting list and discuss the DCD status with the transplant center and candidate at the time of allocation. Recipients may refuse the allocated kidney without jeopardizing their chance of being offered another one.[6] However, the allocation policy should hasten the process of organ placement.[14] If there is no local suitable patient, DCD kidneys can be allocated by regional and national distribution.

As DCD organs have already been subjected to WIT injury, it is conceivable that additional CIT would have a greater adverse impact on the graft survival of DCD than DBD kidneys.[212] Kidneys considered as marginal are often turned down by multiple transplant centers prior to placement, resulting in prolonged CIT and increased DGF. The proper and rapid allocation of marginal kidneys could result in decreased CIT and DGF rates.[283] Among DCD kidneys, the incidence of DGF was reduced 15% if CIT was less than 12 hr, compared to CIT over 12 hr (25.2% versus 40.2%).[131] One-year graft survival of DCD kidneys was similar to DBD kidneys when shared locally (89.3% versus 89%, p=0.682) and slightly inferior when shared regionally (81% versus 87%, p=0.437) or nationally (82.7% versus 89.5%, p=0.0089).[212] Hence, Doshi supported the policy to favor local use of DCD kidneys.[212] Locke argued that DCD kidneys from donors younger than 50 years may function like standard criterion donor (SCD) kidneys and should be allocated using the standard deceased donor waiting list, whereas the ECD list should be used for DCD kidneys from donors older than 50 years.[131] Moreover these kidneys tend to be offered to non-sensitized recipients, hence the necessity for a pre-transplant cross-match is obviated and this may help to further shorten CIT.[237,263]

Clinical results of DCD kidney transplantation

Although DCD was the main donor source of cadaveric kidney grafts in the pioneer years, markedly inferior transplant outcomes led to the abandon of this practice during the mid 1970s in favor of DBD. However, since the resurgence of interest in DCD in the early 1990s due to the growing discrepancy between graft demand and supply, there has been significant medical progress in organ preservation, surgical techniques, immuno-suppressive drugs, treatment of post-transplant complications, histo-compatibility testing and allocation of donor organs. Thanks to these developments, long-term KT outcomes from DCD have been significantly improved over time, and now can be considered comparable to those from DBD.

The finding that DCD- and DBD-KT outcomes are comparable in the long term has several important implications in clinical practice: *firstly* it supports the use of DCD-KT despite the worse short-term outcomes, and emphasizes the interest of the development of DCD programs; *secondly,* to a certain extent, DCD kidneys should not be considered suboptimal; *thirdly* DBD and DCD kidneys should be allocated through the standard kidney allocation system; and *finally,* the use of such donor organs could considerably increase the donor organ pool and therefore, could have an important impact on the organ shortage.

In general, early graft function and survival (within the first 3 months post transplant) is worse in DCD kidney recipients than in DBD kidney ones, manifested by significantly higher rates of PNF, DGF, and lower renal function. Afterwards, comparable long-term results continue up to 10 and 15 years post-transplant. Better transplant outcomes are obtained in controlled rather than uncontrolled DCD.

Primary non-function

Primary non-function is defined as inadequate renal function after transplantation that necessitates continuation of dialysis. It is the consequence of ischemic cortical necrosis secondary to ischemia and reperfusion injury. Studies using type 3 and 4 DCD kidneys showed no significant difference in the rate of PNF compared to DBD kidneys (between 0% and 13%).[40,91,197,198,237,248,253,268,284-286] This is due to the fact that kidney grafts from controlled DCD have relatively short WIT (rarely exceeding 30 minutes). Their post-transplant results may be similar to DBD kidneys without requirement for machine preservation and viability testing.[77,237,287]

By comparison, the PNF rate of kidneys from uncontrolled DCD is significantly higher than from controlled DCD,[198,268,284] and may vary between 13% and 25%.[198,268,284,288] A lower PNF rate (less than 6%) has also been reported[45,285,288] and was explained by adopting restrictive DCD acceptance criteria (donor age <45-55 years, exclusion of donors with co-morbidities), improving donor management (rapid in situ cooling), preserving and choosing viable organs on the basis of machine perfusion. Up to one-third and one-half of kidneys from uncontrolled DCD were discarded due to poor perfusion parameters during machine perfusion or other reasons,[237,289,290] a policy which may help to keep the PNF rate of uncontrolled DCD kidneys at acceptable levels (less than 10%).[284] Therefore, the development of a successful uncontrolled DCD program may be not feasible if machine perfusion and viability testing were not existing. Transplantation of nonviable kidneys results

in unnecessary risk of surgery and immune-suppression, and immunologically sensitizes the recipient for future transplants.[291] Moreover in most cases, KT is not directly life-saving, but a procedure that improves quality of life and life expectancy.[284] Thus, a cautious approach to uncontrolled DCD-KT is necessary.

Mixed studies including both controlled and uncontrolled DCD demonstrated a PNF rate between 6% and 15%.[198,209,211,268,284] Snoeijs presented a PNF rate of up to 21% because more older DCD (donor age up to 74 years) and a relative high percentage of uncontrolled DCD were recruited in the study.[291] A recent outcome meta-analysis comparing (controlled and uncontrolled) DCD and DBD showed the PNF incidence may be 2.4 times higher in DCD-KT.[206]

Cho[179], Rudich,[251] and Locke,[131] when analyzing deceased donor KT outcomes from the UNOS database during different time periods, confirmed that DCD kidneys had a higher PNF incidence compared to DBD kidneys. However, no statistically significant difference was found between DCD kidneys from donors younger and older than 50 years[131] as well as under and above 65 years.[291]

Delayed graft function

Delayed graft function is commonly defined as the need for dialysis in the first post-transplant week, with subsequent recovery of renal function, except dialysis treatments to correct hyperkalaemia or volume overload.[242] The etiology of DGF is multifactorial. In the clinical setting, DGF can mask the presentation of acute rejection[292] and serial transplant biopsies may be recommended to rule out subclinical acute rejection as a cause of graft dysfunction until resolution of DGF.[292,293] Early effects of DGF include prolonged hospital stays, additional diagnostic radiology, repeated renal biopsies, need for supportive hemodialysis during DGF, as well as treatment of complications related to biopsy or inappropriate immune-suppression. The final inevitable consequences are increases in costs and patient dissatisfaction.[93]

All studies agree that DGF is more frequent after DCD-KT. The DGF rate of type 3 and 4 DCD kidneys may vary from 40% up to more than 70%,[91,197,198,237,248,253,268] and uncontrolled DCD kidneys develop even higher DGF rate (from 60% up to more than 80%).[45,188,268,288] In mixed studies, the incidence of DGF was prone to be higher when higher proportion of uncontrolled donors compared to controlled donors was included.[198,209,211,291] The UNOS database from 1998 to 2004 suggests a 2.5 fold adjusted relative risk for DGF

among DCD- compared to DBD-KT.[14] Similar results were also presented by Cho,[179] Rudich,[251] Locke,[131] Doshi,[212] and Gagandeep[285] when analysing the UNOS database at different periods of time. A recent meta-analysis of KT outcomes for all DCD types and DBD showed the incidence of DGF may be 3.6 times higher after DCD-KT.[206]

Another interesting aspect is that the negative effects of DGF on graft survival in the recipients of DBD kidneys may not be observed in DCD.[245,246] In several studies, survival of kidney grafts with DGF was better in the DCD compared to DBD groups.[45,131,179,209,212,285] DCD kidneys may tolerate DGF better than DBD kidneys, with 23–52% decrease in graft loss risk.[131] Several factors seem to make DCD kidneys less vulnerable to lasting injury, as the absence of donor's brain death, in association with more favorable donor characteristics and less co-morbidity.[17,212] Kusaka hypothesized that the long-term functional consequences of DGF may be more related to the injury of brain death than to ischemia reperfusion[294].

Acute rejection

Many studies demonstrated that DCD kidneys, despite showing greater DGF rates, do not have a greater incidence of acute allograft rejection, compared to DBD kidneys.[197,209,211,237,251,268,288] The acute rejection rate during the first year was not significantly different in DCD versus DBD kidneys, both in single center reports[197,209,211,237,288] and in large studies using national databases,[212,251] as well as in a recent meta-analysis of all DCD types,[206] except in Cho's study[179] which showed DCD kidneys had higher rate of acute rejection than DBD kidneys (19% vs 14%, p=0.04).

Most acute rejection episodes occur in kidneys with DGF, and the incidence of acute rejection in transplants with DGF and the incidence of severity of rejection may be comparable for DCD and DBD groups.[197,211] Sanchez-Fructuoso found DBD transplants with DGF had a higher incidence of acute vascular rejection than DCD transplants with DGF (57.9% vs 27.9%), and brain death emerged as a clear risk factor for vascular rejection.[280] Rudich's study suggested that transplants from DCD sources have less graft loss from acute and chronic rejection episodes compared with conventional DBD organ sources (22.2% graft losses at 6 months in the DBD group, versus only 16.9% of graft losses in the DCD group were attributable to acute rejection).[251]

Renal function

In clinical transplant practice, renal function is determined by serum creatinine levels or estimated glomerular filtration rate (eGFR) via Cockcroft-Gault formula or MDRD (modification of diet in renal disease) equation. DCD kidneys recover slower than DBD kidneys, and fail to optimize their function in the early post-operative period. Given higher incidence of DGF, DCD kidney function is often poorer at the time of hospital discharge and at 1-month post-transplant, but the difference diminishes with time and become statistically insignificant from 3 months to 1 year post-transplant.[188,268,295] Kidneys from different Maastricht categories may recover at different rates although their function may be similar at 3 months. Recovery may be more rapid for category 4 DCD kidneys, and slower for category 2 DCD kidneys.[268]

A recent meta-analysis of DCD- and DBD-KT outcomes showed that serum creatinine levels at 3 and 12 months may be similar in both groups.[206] One year after transplantation, DCD kidneys function well, suggesting that survival rates will be similar to DBD kidneys.[179] Chapman[247] examined outcomes of DCD-KT which functioned for at least 1 year post-transplant, and had a mean follow-up of 2-5 years. DCD and DBD graft loss was approximately 3% at 5 years, and both groups showed a similar decline in GFR after 1 year (-1.3 ml/min for DCD vs -1.4 ml/min for DBD). This means that DCD kidneys have a reduced functioning glomerular mass because of initial ischemic damage, but once transplanted there is no evidence of accelerate deterioration.[198] Comparable renal function between 2 groups has been proved up to 15 years post-transplant in a single center report.[211] However, interpretation of this study should be cautious as the number of patients in each group was small (112 DCD and 164 DBD kidneys), and as general analysis showed that serum creatinine levels were significantly higher in DCD kidneys recipients.

Graft survival

Short-term graft survival at 1 year post-transplant was similar between DBD and type-3 and -4 DCD kidneys and varied between 80% and more than 90%,[40,91,197,198,237,248,253,268,296] despite greater graft loss during the first 30 days and 3 months post-transplant in DCD than DBD kidneys.[197,248,286] Kidneys from uncontrolled donors had 1-year graft survival between 70% and more than 80%[45,188,198,268,288] and was significantly lower than kidneys from controlled donors.[198,268]

Most studies considered long-term outcomes as the outcome beyond the first year post-transplant, which can be calculated as graft survival (according to Kaplan-Meier method)

or graft haft-life with or without death censoring. Many factors have been shown to have impact on the long-term outcome after KT, both immunological and non-immunological injuries. Five- and ten-year graft survival of kidneys from controlled DCD was 60-80% and 50-60% respectively. The same percentage was observed in kidneys from uncontrolled donors. There is no difference in graft survival between DCD and DBD kidneys up to a follow-up period of 5, 6 and 10 years. Two studies published recently had a follow-up of 15 years and again showed no significant difference in the 5-, 10- and 15-year allograft survival between DCD and DBD.[211,286] Nevertheless, there was a tendency of better graft survival in the DBD group.[211,286] In unpublished data, Snoeijs reported the long-term outcome of viable DCD kidneys is equivalent to DBD kidneys up to 25 years of follow-up.[48]

Studies using UNOS database found that survival of DCD kidneys at 1-, 2- and 3-years were nearly comparable to SCD (p=ns) and superior to *ECD (p <0.001). ECD kidneys* and extended criteria DCD kidneys had no significant difference in graft survival.[14] With regard to graft survival at 5 years, DCD kidneys from donors younger than 50 years performed as well as SCD kidneys, while DCD kidneys from donors older than 50 years functioned as well as ECD kidneys (**Table 3.2.2**).[131] Gagandeep found the same long-term outcome up to 5 years post-transplant between uncontrolled DCD, controlled DCD and DBD.[285] A recent meta-analysis of outcomes of all types of DCD and DBD renal transplants confirmed graft survival of DCD kidneys is somewhat inferior to DBD kidneys from 3 months up to 6 years post-transplant but this difference may become non-significant at 10 years.[206]

Median graft survival was 96-126 months in the DCD vs 159 months in the DBD group.[211,253]

The comparable DCD and DBD long-term graft survival is supported by histological data that show kidneys from DCD do not have higher rate of allograft fibrosis than those from DBD[297] and the rate of development of chronic allograft nephropathy in DCD transplant does not exceed that associated with DBD transplants.[8]

Surgical complications

Likewise no statistical difference in the rate of technical complications has been demonstrated between DBD and DCD kidney recipients.[253,286] However, when the ureteral fistula and stenosis rates were combined, the difference was statistically greater in the DCD group (15% versus 7%) for urological complications.[253] By analyzing the UNOS database

between 1993 and 2000 from 708 DCD- and 97,990 DBD-KT, Rudich showed that surgical and urological complications, thromboses, and infections are not a greater cause of graft loss in DCD- than in DBD-KT.[251]

Table 3.2.2. Clinical KT outcomes according to deceased donors categories (UNOS database)

Donor category	PNF	DGF	Graft survival		References
			1 year	5 years	
SCD (standard criteria donors)	0.7	21	90	79.9	[14,131]
ECD (extended criteria donors)	1.82	33	83	66.9	[14,131]
DCD (donors after cardiac death)	1.71	40	89	81.6	[14,131]
exDCD (extended donors after cardiac death)	1.33	55	81	65.9	[14,131]
cDCD (controlled donors after cardiac death)	< 2	41	89	66.9	[285]
uDCD (uncontrolled donors after cardiac death)	**< 3**	**51**	**-**	**-**	[212,285]

Conclusion

The results of DCD and DBD kidney transplantation should be comparable if careful donor selection and management are respected. As a result, *DCD program* should be continued and expanded. *DCD donors* are potential donor source that may partially solve the imbalance between the growing number of end-stage kidney disease patients on the waiting list and the limited number of available kidney grafts. *DCD kidneys* do not always mean sub-optimal organs and merit to be shared equally as DBD kidneys on the renal allocation system.

4

Results of Liver Transplantation from DCD

4.1 DCD liver transplantation in Liège and Belgium

Submitted as

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Liver Transplantation from Donation after Cardiac Death: Belgian Experience 2003–2009

Submitted for publication in 'Transplantation'

ABSTRACT

Objectives: The Belgian multicentric experience with donation after cardiac death (DCD) liver transplantation (LT) was retrospectively updated to evaluate patient and graft survivals, and biliary complications.

Patients-Methods: From 2003 to 2009, 111 DCD-LTs have been performed in Belgium. Characteristics of donors, recipients and transplant procedure as well as transplant outcomes were retrospectively reviewed. Mean donor age was 47.6±15.5 years. Mean total WIT was 24.4±13 min and mean CIT was 367.3±128.9 min. Rates of local and national sharing were 72.1% and 19.8%, respectively. Mean recipient age was 55.9±11.2 years. The most frequent indications for LT were end-stage liver disease (49.5%) and HCC (39.6%). Mean MELD score at transplant time was 16.6±7.5 points.

Results: Overall patient and graft survival was 88.3% and 80.1% at 1 year, 74.4% and 64.9% at 3 years, 70.0% and 60.4% at 5 years, respectively. PNF rate was 4.5% (5 patients). Thirty-seven patients (33.3%) developed biliary complications with ITBL encountered in 14 patients (12.6%). Thirteen patients (11.7%) underwent re-transplantation, six urgently for PNF (4) and HAT (2), and seven for intractable biliary stenoses. Donor bilirubin levels and duration of donor hepatectomy were associated with an increased risk of graft loss while CIT, MELD score and donor bilirubin levels appeared as risk factors for biliary complications in a multivariate analysis.

Conclusion: Although DCD organ donors are a valuable source of viable liver grafts, they are associated with increased incidence of PNF and cholangiopathy that could be reduced with further identification and prevention of associated risk factors.

Introduction

Organ donation after cardiac death (DCD) has been reconsidered for use since the early 1990s to alleviate the serious shortage of donation after brain death (DBD) source. Although the use of DCD donors could decrease the mortality rate on liver transplantation (LT) waiting lists and increase the availability of organs for transplantation, it is associated with a higher risk of early graft dysfunction,[58,60,212,298] more frequent vascular and ischemia-type biliary lesions (ITBL),[299] higher rates of re-listing and re-transplantation[300,301] and lower graft survival,[57,59,89,302] which are the consequences of the combined effect of warm ischemia and cold ischemia-reperfusion injury.

A DCD-LT program using Maastricht category-III donors has been initiated in Belgium since 2003 after being approved by different institutional review boards and the Belgian National Council of Physicians.[173] Preliminary results during the 2003-2007 period, which had been published in 2010, appeared promising with overall patient and graft survival rates of 91.3% and 84.4% at 1 month, 83.3% and 72.4% at 1 year, and 66.9% and 48.8% at 3 years, respectively. The primary non-function (PNF) rate was 3.4% and ITBL developed in 32.7 % of liver allografts. Re-transplantation was necessary in 13.8% of liver recipients.[303] The aim of this retrospective study was to update the results of the Belgian multicentric experience in DCD-LT with regard to patient and graft survival, and biliary complications and to define risk factors associated with decreased graft survival and biliary complications.

Patients and methods

This retrospective review assembled the experience of six Belgian transplant centers in DCD-LT from January 2003 to December 2009. Among 111 liver grafts, one hundred and three were procured from Maastricht category-III donors, two from Maastricht category-IV and six from euthanasia donors. No category-II DCD-LT was performed despite active category-II DCD procurement programs in some Belgian centers. The acceptance criteria for DCD liver grafts were center-dependant. Donor causes of death were stroke (36.0%), head trauma (31.5%), anoxia (26.1%), euthanasia (5.4%) and other (0.9%). With the approval of EuroTransplant (ET) and of the Belgian Liver Intestine Organ Procurement Committee (BLIC), liver grafts were allocated in a center-oriented manner in order to shorten the cold ischemia time (CIT). The recipients were chosen according to the urgent need for transplantation and his (her) chances to receive a liver graft in a timely manner according to

the regular patient-oriented rules, including patients with extended criteria hepato-cellular cancer criteria. If no adequate candidate was available, the DCD liver graft was offered to other centers in Belgium and the Netherlands, two ET countries that allow DCD procurement and transplant activity. The rate of local, national and international sharing was 72.1%, 19.8% and 8.1%, respectively, in our series.

Organ procurement

In Maastricht category-III donors, withdrawal of life support was performed by a non-transplant physician in the operative room. Intravenous heparin was given in most cases (91%) before cessation of circulation. Phentolamin (Regitin®), epoprosterol (Flolan®) and streptokinase were utilized in 28.8% of liver donors. Organ recovery started 2–5 min after declaration of death, by cannulation of the femoral vessels or by rapid midline laparotomy and sternotomy with aortic and/or caval cannulation. Once the cold flush with University of Wisconsin (UW) or histidine–tryptophan–ketoglutarate (HTK) solutions was initiated, the aorta was cross-clamped in the chest just above the diaphragm, whereas the abdominal and thoracic cavities were filled with ice-crashed fluid for topical cooling. HTK was the most common used preservation solution (84.7%). After completion of the aortic flush, organs were removed and cold-stored until transplantation. Mean warm ischemia time (WIT) was 24.4 ± 13 min (range: 8 - 109). This time period comprised the withdrawal phase (from treatment discontinuation to cardiac arrest, mean: 13.5 ± 11.4 min, range: 1 - 98) and the acirculatory phase (from cardiac arrest to initiation of aortic cold perfusion, mean: 11 ± 5.6 min, range: 4 - 38). Mean CIT was 367.3 ± 128.9 min (range: 105 - 719). CIT was defined as the time interval from aortic cold perfusion until removal of the liver graft out of the cold preservation solution for implantation. Mean suture time, which was the vascular anastomosis time calculated from the removal of a liver graft out of iced preservation fluid to its reperfusion, was 47.8 ± 15.1 min (range: 22 - 135). The euthanasia procedure for organ donation has been described elsewhere.[12,231]

Recipients Characteristics

Mean recipient age was 55.9 ± 11.2 years (range: 10 - 73). Indications for LT were end-stage cirrhotic liver disease in 55 patients (B and C viral infection: 12, alcohol dependency: 32, primary biliary cirrhosis: 4, non-alcoholic steato-hepatitis (NASH): 1, hemochromatosis: 1 and cryptogenic cirrhosis: 5), hepato-cellular cancer in 44 patients

(cirrhotic livers: 39, non-cirrhotic livers: 5), and miscellaneous causes in 7 cases (primary sclerosing cholangitis: 3, familial amyloid poly-neuropathy: 1, neuro-endocrine liver metastases: 1, and biliary atresia: 2). In five cases, DCD-LT was performed for high-urgent (HU) patients (ET status equivalent to UNOS status 1a, UNOS: United Network for Organ Sharing) due to fulminant hepatic failure (2), liver failure after resection for Klatskin tumor (1) and urgent re-transplantation (2). Mean laboratory MELD (model for end-stage liver disease) score at transplantation was 16.6 ± 7.5 (range: 6 - 40).

Study Endpoints

Primary endpoints of the study were graft and patient survival rates, and symptomatic intra- and extra-hepatic biliary complications requiring invasive management (endoscopy, surgery or re-transplantation). Graft survival was defined as the time from LT to graft loss and/or patient death. Patient survival was considered from first transplantation to patient death. Early patient death was defined as any event within the first 3 months post-transplant. We also calculated graft and patient survival rates censored for recipient death unrelated to the quality of the graft (malignant tumor, accident…) in order to better estimate the risk of DCD-LT. Patients were followed up until September 30, 2010. Secondary endpoints were first-week peaks of transaminases and total bilirubin, occurrence of PNF, hepatic artery thrombosis (HAT), length of intensive care unit (ICU) and hospital stays, and need for re-transplantation.

Statistical Analysis

Continuous variables were presented as mean ± standard deviation (SD) and categorical variables as percentage. Differences between groups were evaluated by Student t-test or non-parametric Mann Whitney U/Wilcoxon Ranked Sum test for continuous variables and Fisher's exact test or Chi-square test for categorical variables. Survival rates were estimated by the Kaplan–Meier method and compared by the log rank test with graft failure and patient death as events. Univariate and multivariate logistic regression analyses were used to identify potential risk factors for graft loss and biliary complications. All tests were two-tailed and p-values < 0.05 were considered as significant. All analyses were performed using the SPSS statistical software, version 11.0 for PC Windows.

Table 4.1.1. Evolution of donor, recipient and transplant characteristics over time

Variables	2003-2009	2003-2007	2008-2009	p value
Donor age (years)	47.6 ± 15.5	44.3±14.6	51.3±15.8	**0.018**
Donor gender: M/F (%)	71/40 (64/36)	39/19(67/33)	32/21(60/40)	-
Donor BMI (kg/m^2)	25 ± 4.2	24.7±3.4	25.3±4.9	0.472
Donor ICU stay (days)	6.1 ± 6.3	4.7±3.8	7.5±8	**0.023**
Natremia (mEq/L)	142.6 ± 6.2	142.4±6	142.9±6.4	0.609
ALT (U/L)	44.3 ± 74.1	47.8±94.2	40.3±39.9	0.585
GGT (U/L)	72.9 ± 114.5	60±91.3	87±135	0.229
Total bilirubin (mg/L)	5.5 ± 3.6	5.9±3.9	5.1±3.4	0.229
Withdrawal phase (min)	13.5 ± 11.4	14.9±14.5	12.2±7.1	0.232
Acirculatory phase (min)	11 ± 5.6	10.2±5.6	11.9±5.2	0.129
Total WIT (min)	24.4 ± 13	24.6±15.5	24.2±10.1	0.869
CIT (min)	367.3 ± 128.9	395.6±139.7	341.9±116.4	**0.031**
Suture time (min)	47.8 ± 15.1	50.6±17.4	44.9±11.7	**0.045**
Total ischemia time (min)	439.1±132.6	466.1±138.3	409.7±120.7	**0.027**
Recipient age (years)	55.9 ± 11.2	54.9±11.6	57±10.9	0.344
Recipient gender: M/F (%)	85/26(77/23)	46/12(79/21)	39/14(74/26)	-
MELD score at transplant	16.6 ± 7.5	16±8,2	17.2±6.9	0.413
Recipient serum creatinine (mg/L)	10.2±4.1	10.1±4.1	10.2±4.1	0.833
Peak AST (U/L)	2409± 2929	2797±3727	1998±1673	0.156
Peak total bilirubin (mg/L)	58.8 ± 56.5	64±64.6	53.4±46.6	0.331
ICU stay (days)	6.9 ± 10.5	6.6±7.9	7.4±12.7	0.710
Hospital stay (days)	29.5 ± 29.1	31.8±34.3	26.9±22.1	0.379

M/F: male/female. BMI: body mass index. ICU: intensive care unit. ALT: alanine amino-transferase. AST: aspartate amino-transferase. GGT: gamma glutamyl transpeptidase, WIT: warm ischemia time. CIT: cold ischemia time. MELD: model of end-stage liver disease.

Results

During the 7-year period (from 2003 to 2009), there have been 111 and 1546 liver transplants from controlled DCD and DBD donors in Belgium, respectively. The number of DCD liver transplants increased steadily over the study period and contributed up to 6.7% of the deceased donor (DD) liver pool (**Figure 4.1.1**).

Patient and graft survivals

No patients were lost during the study period (mean of patient follow-up: 29.0 ± 21.5 months, range: 1 day to 91 months). Overall patient and graft survival rates were 91.0% and 85.6% at three months, 88.3% and 80.1% at one year, 74.4% and 64.9% at three years, and 70.0% and 60.4% at five years, respectively. Death-censored patient and graft survival rates

were 92.8% and 87.4% at three months, 92.8% and 84.5% at one year, 88% and 78.3% at three years and 82.8% and 72.9% at five years, respectively (**Figure 4.1.2)**. Causes of early death were per-operative cardiac failure (2), PNF (1), hepatic artery thrombosis (HAT) with following liver insufficiency (1), biliary sepsis (1), acute respiratory distress syndrome (1), multiple organ failure (3) and patient suicide (1). Seventeen other patients died later, including one from intractable biliary sepsis while awaiting re-LT, four from de novo cancers (melanoma: 1, lymphoma: 1, pulmonary tumor: 1, donor-transmitted sarcoma: 1), and four from hepato-cellular carcinoma recurrence, three from cerebral vascular accidents, one from a car accident, one due to Alzheimer disease, and three from unknown reasons. Graft and patient survival was compared between the 2003-2007 and 2008-2009 periods and the latter era had better although not statistically significant outcomes (**Figure 4.1.3**). This may be explained by shorter cold and warm ischemia times, and total ischemia times despite higher donor age and longer donor ICU stay in the second era (**Table 4.1.1**).

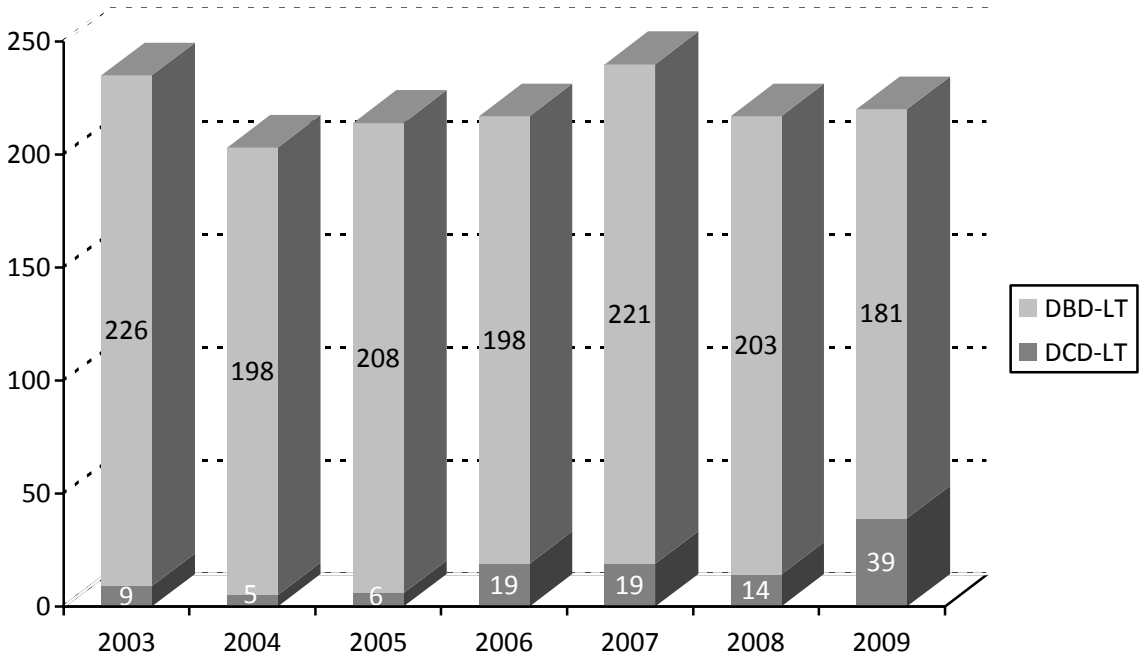

Figure 4.1.1. Evolution of donation after cardiac death (DCD) and donation after brain death (DBD) liver transplantation (LT) activity in Belgium over time

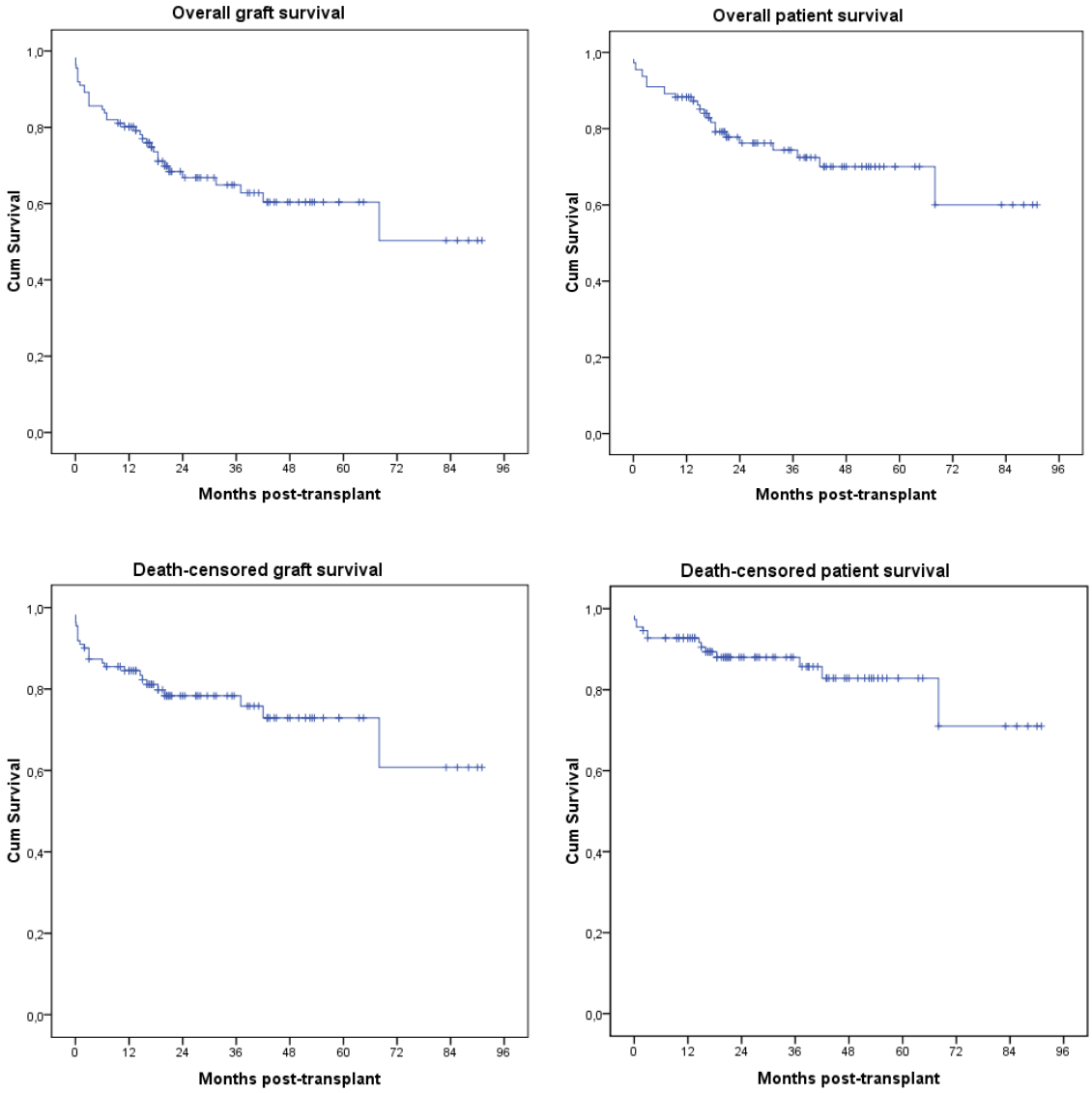

Figure 4.1.2. Overall and death-censored graft and patient survivals. Death-censored graft survival was 87.4% at three months, 84.5% at one year, 78.3% at three years and 72.9% at five years. Death-censored patient survival at corresponding points of time was 92.8%, 92.8%, 88% and 82.8%.

Post-operative evolution

Post-operative mean peak-AST was 2409.2 ± 2929.8 U/L (range: 43 - 21928) and mean peak-bilirubin was 58.8 ± 56.5 mg/L (range: 3.6 - 296). The rate of PNF was 4.5% (5 patients) and HAT 2.7% (3 patients). Mean ICU and hospital stays were 6.9 ± 10.5 days (range: 1 - 82) and 29.5 ± 29.1 days (range: 1 - 213), respectively. Thirteen patients (11.7%) underwent re-LT, six urgently for PNF (4) and HAT (2), and seven for intractable ITBL. In total, 37 DCD liver grafts were lost for reasons of re-transplantation or death at follow-up.

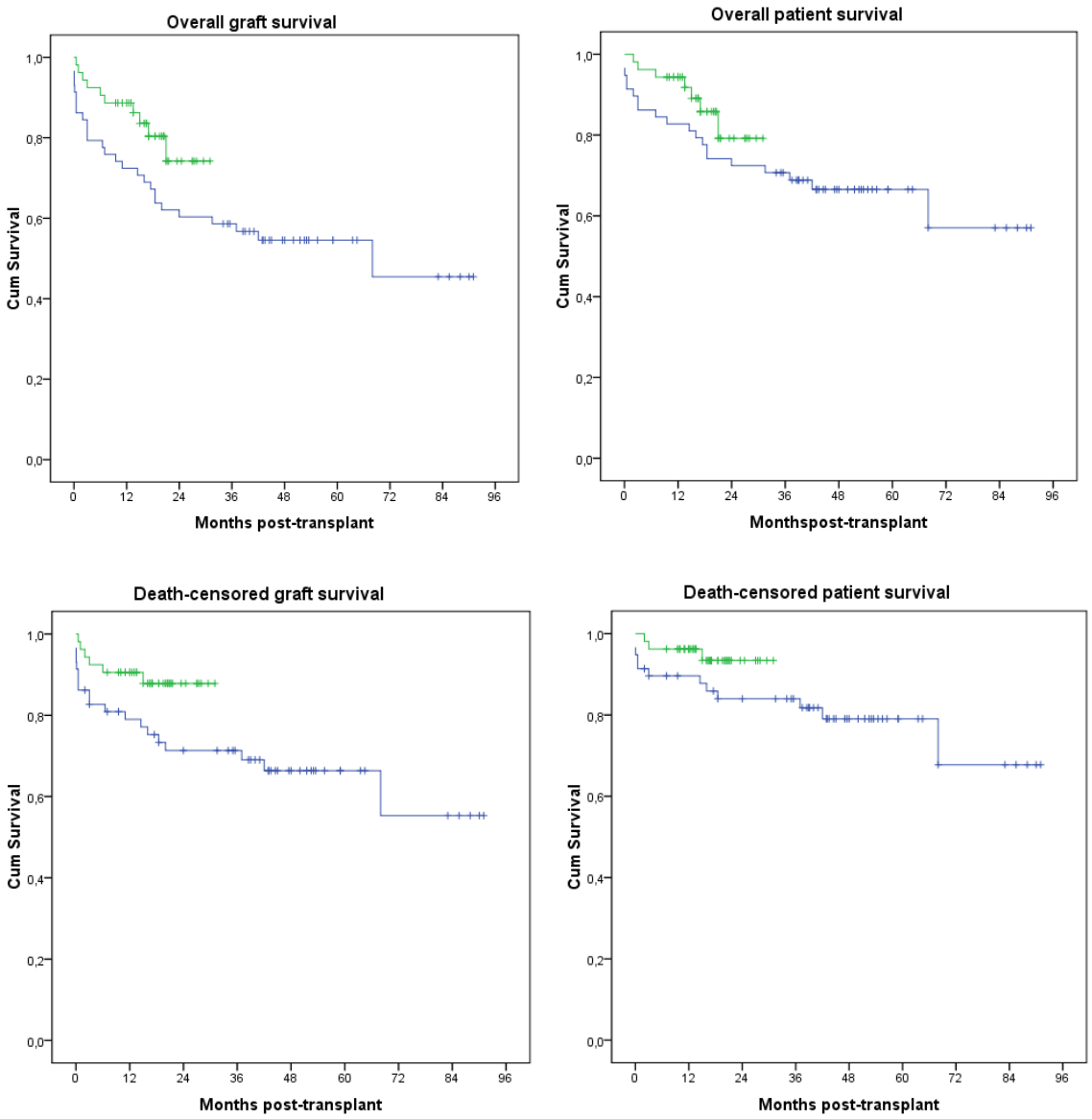

Figure 4.1.3. Graft and patient survivals during the 2 periods (blue line: 2003-2007 and green line: 2008-2009).

Biliary complications

Thirty-seven (33.3%) patients developed biliary complications in which thirty-five required various types of invasive treatment, either alone or in combination (endoscopy, surgery and re-transplantation). **Table 4.1.2** displays the diagnosis and treatment of these biliary complications. ITBL was encountered in 14 patients (12.6%) and re-transplantation was necessary in 7 (6.3%). Anastomotic stenosis occurred in 18 patients (16.2%) and biliary fistula in 4 (3.6%).

Table 4.1.2. Biliary complications (n=37)

Biliary complications		Data
Diagnosis		
Biliary fistula		4 (10.8)
Biliary stenosis	**Anastomosis**	14 (37.8)
	Anastomosis + ITBL	4(10.8)
	ITBL	10 (27)
	Without anatomic location of stenosis	2 (5.4)
Biliary tract compression by recurrent hepatic tumor		1 (2.7)
No diagnostic information		2 (5.4)
Treatment		
Endoscopy		19 (51.4)
Surgery		2 (5.4)
Endoscopy + Surgery		7 (18.9)
Re-transplantation		7 (18.9)
No intervention		2 (5.4)

ITBL: ischemia-type biliary lesions

Potential risk factors for graft loss and biliary complications

Univariate analysis showed a higher risk of graft loss in case of increasing donor age (p=0.04), donor bilirubin (p=0.03), CIT (p=0.01), suture time over 50 min (p=0.01), no use of heparin prior to treatment discontinuation (p=0.03) and hyper-urgent indication for LT (p=0.02). However, only donor bilirubin (OR=0.06, 95%CI 0.01-0.38, p=0.00) and duration of donor hepatectomy (OR=0.15, 95%CI 0.02-0.94, p=0.04) became statistically significant in the model of multivariate analysis.

Similarly, increasing donor ICU stay (p=0.02), donor bilirubin (p=0.02), WIT (p=0.02), CIT (p=0.01) and non local sharing of graft livers (p=0.03) were associated with increased risk of biliary complications in a univariate analysis. Nonetheless multivariate model revealed only donor bilirubin (OR=5.1, 95%CI 1.74-14.84, p=0.00), CIT (OR=12.8, 95%CI 2.16-75.74, p=0.00) and MELD score at transplant time (OR=5.28, 95%CI 1.21-23, p=0.02) as significant risk factors for biliary complications.

Discussion

This Belgian multi-centric experience in DCD-LT shows that controlled DCD donors constitute an alternative source of liver grafts enabling to alleviate the shortage of the DBD liver graft pool. However, the overall transplant outcomes appear inferior to DBD liver grafts

and are in accordance with previously reported results. Our results seemed particularly comparable to those at the Mayo clinic[304] regarding the number of graft losses and re-transplantation as well as one-year graft and patient survival, given the fact that the two studies are similar to each other in terms of study design, number of patients, warm and cold ischemia time, recipient age and MELD score at the transplant time, except that our donors were older than in Mayo clinic's study. Furthermore, our multivariate analysis demonstrated that better outcomes might be obtained through careful donor and recipient selection with low bilirubin at procurement and low MELD score, and short CIT at transplantation.

Graft and patient survivals in this series are comparable to those in other studies, and better results were however achieved in the latter 2008-2009 period. Transplant outcomes similar to those obtained from DBD-LT have been sporadically reported in select centers through careful donor selection, optimization of CIT, use of invasive techniques to optimize organ recovery before declaration of death[144,304-306] and appropriate graft and recipient matching.[59,212] Several authors could demonstrate that even if graft or/and patient survival is lower with a DCD liver, this DCD option is still better than continuing to wait for a DBD liver, as the patient's choice is frequently not between 'marginal' livers (including DCD) and standard livers but between marginal livers and no livers.[94] The benefit of earlier access to LT provided by a DCD graft could outweigh the risks of prolonged waiting for a standard graft.[95] Better knowledge of the risks of DCD-LT failure, and particularly the limitation of warm and cold ischemia, may offer better results in the future.[303]

Since the introduction of LT, biliary complications have always been and still are regarded as the 'Achilles heel' and as a major cause of morbidity and graft failure in liver recipients.[307] This study once again confirms the higher incidence of overall biliary complications and particularly ITBL in DCD-LT in comparison to DBD-LT. Fifty per cent of our ITBL patients needed to be re-transplanted. A recent meta-analysis revealed that DCD recipients had a 2.4 times increased odds of biliary complications (95% confidence interval - CI = 1.8–3.4) and a 10.8 times increased odds of ITBL (95% CI = 4.8–24.2) versus DBD recipients. On average, biliary complications were present in 29% of DCD compared with 17% of DBD recipients and ITBL in 16 % of DCD versus 3% of DBD recipients.[299]

In controlled DCD donors, the PNF rates are usually reported between 0% and 12%. Matched analyses[60,298] and registry data[58,212] showed a higher rate of PNF in controlled DCD

than DBD donors, although no difference was found in most comparative studies except one.[304,305,308,309 310] The increased risk of PNF in DCD-LT recipients was also confirmed in a recent meta-analysis (odds ratio - OR = 3.6, 95% CI = 2.1–6.4).[299] Case-series reports of controlled DCD-LT also had a rate of PNF between 0% and 10%.[303,311-315]

Early HAT is usually defined as the occlusion of the hepatic artery within the first 30 days post-transplant.[316] The frequencies of early HAT after DCD-LT varied from 0% to 16.6% and did not seem significantly higher than those after DBD-LT in most studies[10,60,94,144,298,301,304-306,309,317,318] except Yamamoto's study (33.3% versus 0%).[308]

DCD recipients more often require re-transplantation, as 21.6-42% versus 8.8-16% of DCD and DBD recipients were listed for re-transplantation, respectively.[300,301] The re-transplantation rate ranged from 7.6 to 31% in DCD-LT compared to 2.5-12% in DBD-LT.[10,58,60,144,212,298,300,301,304,309,310,318,319] DCD livers exhibited a 2.1 times greater risk of graft failure, a 2.5 times greater risk of re-listing, and a 3.2 times greater risk of re-transplantation compared with DBD livers.[301] The majority of re-listing and re-transplantation in the DCD group were a consequence of biliary complications, especially ischemic cholangiopathy, but not due to an increased incidence of PNF, HAT or technical complications.[300,301]

Conclusion

DCD liver grafts carry an increased risk of graft failure and post-operative morbidity, especially biliary complications and ITBL are worrisome. Patients who are potential candidates for a DCD liver transplant should be fully informed of the benefits and risks so they can determine their options. For the time being, these grafts should be reserved only for patients in whom current allocation schemes do not provide sufficient chances to be transplanted with a regular DBD graft in a timely manner. Further improvements and better identification of risk factors will allow wider and safer use of DCD liver grafts.

4.2 DCD liver transplantation in the world

Published as

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Donation after Cardio-Circulatory Death Liver Transplantation

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ABSTRACT

Objectives: The critical organ shortage has forced many transplant centers to reconsider the use of donation after cardiac death (DCD) since 1990s as an alternative donor source to the insufficient donation after brain death (DBD). This review aimed to examine the clinical and experimental experience in DCD liver transplantation (LT) in the world in order to help LT programs to develop DCD-LT and to better allocate DCD liver grafts.

Methods: We conducted a systemic review of all mono- and multi-centric DCD-LT studies over the past 20 years, and evaluated the short- and long-term results of DCD-LT in terms of initial graft function (primary non-function-PNF and initial poor graft function-IPF), graft and patient survival, rejection, and post-transplant surgical complications.

Results: DCD livers are a valuable organ source that helps to decrease the mortality rate on the waiting list and to increase the availability of organs for transplantation despite a higher risk of early graft dysfunction, more frequent vascular and ischemia-type biliary lesions, higher rates of re-listing and re-transplantation, and lower graft survival. Experimental strategies intervening in both donors and recipients at different phases of the transplantation process have focused on the attenuation of ischemia-reperfusion injury and already gained encouraging results, and some of them have found their way into clinical reality.

Conclusion: The future of DCD-LT is promising. Concerted efforts should concentrate on the identification of suitable donors (probably Maastricht category III DCD donors), better donor and recipient matching (high risk donors to low risk recipients), use of advanced organ preservation techniques (oxygenated hypothermic machine perfusion, normothermic machine perfusion, venous systemic oxygen persufflation), and pharmacological modulation (probably a multi-factorial biologic modulation strategy), so that DCD liver grafts could be safely utilized and attain equivalent results as DBD-LT.

Introduction

The first human liver transplantations (LT) were performed from donation after cardio-circulatory death (DCD) in the 1960s.[320-323] DCD-LT was nonetheless almost universally abandoned in the following two decades, given the well-recognized Harvard brain-dead concept in 1968 and given the better results of LT originating from donation after brain death (DBD).[324] In 1983, LT was approved as a therapeutic modality for end-stage liver diseases after a long period considered as an experimental procedure. The renewed interest in DCD donors started in the 1990s following the limited success of the transplant community to expand the DBD organ supply and following the request of potential DCD families.

If DCD kidneys are increasingly accepted around the world,[238] the use of DCD livers remains limited in experienced transplant centers due to higher risks of primary graft dysfunction and biliary complications as well as a lack of a reliable viability testing prior to liver implantation. However the number of DCD-LT increased rapidly over the past decade. In the United States, 276 DCD liver transplants were performed in 2008 compared to only 23 cases in 1999, making up 5% of the deceased donor (DD) liver transplants.[69,325-327] The same trend was observed in the United Kingdom,[83,328,329] Spain,[330] Netherlands,[331] and Belgium.[173,331] Netherlands had the highest rate of DCD- over DD-LT in the world (22.5% in 2008).[331] France has just initiated its DCD-LT program since 2010.[332] In Japan, although DCD donors were the essential DD source, its use was reserved mainly for kidney, pancreas and islet transplantation.[333] Using a mathematical model to analyze the potential impact of a DCD policy on LT programs, Chaib reported if 1%, 5% and 10% of deceased individuals became DCD donors, there would be 8%, 27%, and 37% relative reductions in the size of waiting list, respectively.[85] The use of DCD livers could increase the supply of transplants by 53%.[304] Centers with active DCD-LT programs usually reported 4-10% rates of LT from the DCD source.[203] The potential impact of DCD use on the DBD availability is also a controversial issue. Controlled DCD programs might negatively influenced DBD activity in Belgium, Netherlands and United Kingdom while uncontrolled DCD donors seemed to be a clear additional source of organs for transplantation in France and Spain.[19]

Most countries use Maastricht-category-3 DCD donors for LT, except France and Spain, where categories 1 and 2 are exclusively used due to legal interdiction of discontinuation of therapy in irreversibly brain-injured individuals.[4,332,334] German law prohibits any DCD organ procurement and transplant activity. In Italy, death of a human being must be declared 20 min after cardiac arrest using continuous electrocardiography. The

procedure therefore will enable, at best, retrieval of only a few marginal kidneys and some tissues, and will not be helpful for patients on LT waiting lists.[335] This article aimed at reviewing mono- and multi-centric DCD-LT outcomes, experimental strategies on animal models to optimize the utilization of this donor source and its future development.

Differences between DCD and DBD donors pertinent to LT outcomes

Generally results of DCD-LT are inferior to those from DBD-LT with regard to both short-and long-term graft and patient survival as well as post-transplant morbidity. Expected DCD-LT outcomes could be explained by inherent differences between DCD and DBD donors in circumstances of death, warm ischemia time (WIT) and donor cause of death. Consequently, a different strategy of DCD use in terms of logistics of organ retrieval and preservation, allocation and recipient selection appears necessary to guarantee acceptable results. These differences will be briefly discussed prior to considering results of DCD-LT in detail.

Circumstances of death and consequent WIT

In DCD, donor death is diagnosed on the basis of irreversible cessation of cardio-pulmonary function instead of conventional neurologic criteria. As a result, organs from DCD donors are subjected to a period of hypotension, hypoxia and acirculation prior to organ procurement and this WIT adversely affects tissue viability and graft function after transplantation.[336] An international classification of DCD donors into 4 categories was first proposed in 1995 and widely accepted up to now.[7] New DCD categories have been recently suggested in Spain,[10,337] Italy,[11] and Belgium.[12] The length of WIT varies greatly according to the type of DCD process. It is longest among uncontrolled category -1 and -2 (usually 90–120 min) and shorter among controlled category -3 and -4 DCD donors (usually 20-30 min). In brain death, issues related to donor warm ischemia are eliminated because DBD donors have an effective natural organ perfusion and a potentially well-preserved organ function and WIT is thus nearly equal to zero.

However, WIT is heterogeneously defined among authors.[57] In the controlled DCD context, the commonest definition is the time interval between withdrawal of both ventilator and cardiac support to start of cold flushing of the organ.[14,60] This definition includes the no-touch period and the time of death declaration and is proposed to have two phases (withdrawal and acirculatory phases). Other authors used a blood pressure (BP) or oxygen

saturation threshold below which would be defined as the beginning of true WIT (systolic or mean BP < 35 - 60 mmHg, oxygen saturation < 25 - 70% or unreadable).[15,27,301,314,338-341] De Vera did not use a BP threshold to define the start of WIT because tissues are still hypoxic in a DCD donor who maintains a BP but has ceased to ventilate.[60] It is unknown at what BP or oxygen saturation the liver parenchyma and biliary system undergo irrecoverable injury.[305] The first international Non-Heart Beating Donor workshop in Maastricht in 1995 suggested WIT should be calculated from the moment of cardiac arrest until the start of hypothermic flush-out.[189] This definition may be useful for consistency but is inaccurate at the cellular level. Hypoxia starts when the blood flow or oxygenation no longer meets cellular metabolic needs.[339] The start of WIT may be chosen prior to asystole, and the end of WIT may be at or after aortic flushing.[342] Apparently a well-accepted definition of donor organ ischemic times is needed to standardize nomenclature and allow accurate comparisons of individual DCD studies (**Figure 4.2.1**).[36,37]

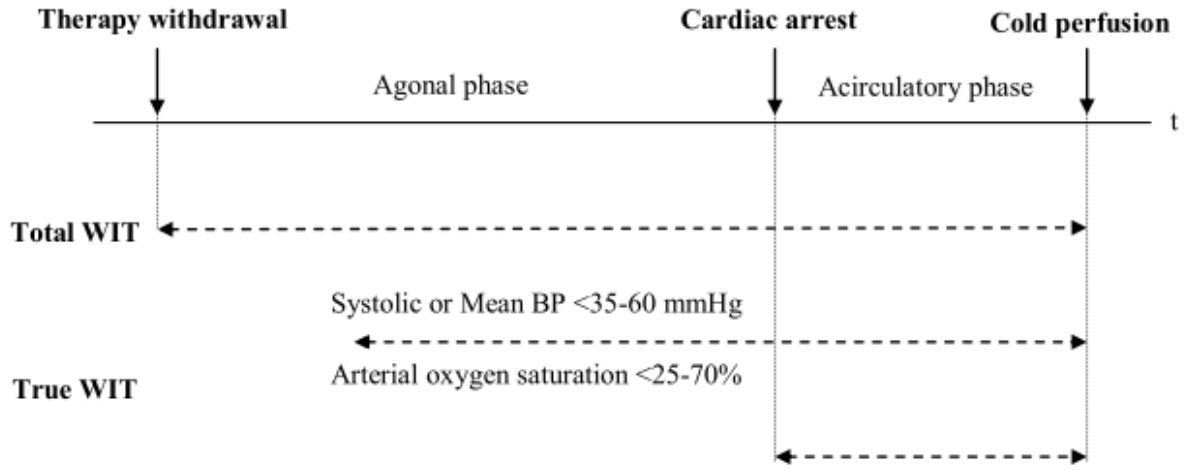

Figure 4.2.1. Different ways of WIT definition in the controlled DCD setting (see text for more details). WIT: warm ischemia time. BP: blood pressure, t: time. Total WIT is also called overall WIT. True WIT is also called complete or functional WIT. Agonal phase is also called withdrawal phase.

In transplant practice, WIT should be minimized as much as possible. For controlled DCD donors, the possibility to predict whether a potential donor will or will not expire in a time frame consistent with donation is extremely important, because prolonged time to asystole, likely resulting in suboptimal organ perfusion, is a common reason for non procurement of DCD grafts.[343,344] Time between therapy withdrawal and cardiac arrest usually does not exceed 1 hour in most DCD donors. However, if a DCD donor has a period of relatively hemodynamic stability after life-support withdrawal, this period may be extended

beyond 1 hour without additional warm injury to the organs.[345] Some authors emphasized during the withdrawal phase, time to a systolic BP < 50 mmHg should be < 30 min[304] and the hypotensive period (mean BP < 50 mmHg) < 15 min.[144] Manara proposed the so-called functional WIT, which is measured from the donor's systolic BP < 50 mmHg, the arterial oxygen saturation < 70%, or both, to the start of cold perfusion, should not exceed 30 min and may be limited to 20 min in suboptimal donors.[16]

Several factors have been identified as predictors of rapid death following treatment withdrawal and include the DCD tool of University of Wisconsin[30], donor Glasgow coma scale, inotropic use, BP at treatment discontinuation, high FiO_2 and mode of ventilation.[31,34] Withdrawal of therapy is preferably occurred in the operating room with a donor surgical team immediately available. Prior to cessation of the ventilator and organ perfusion support, the donor may be already prepared and draped, and the surgical instruments, preservation solution and tubing are set up to facilitate rapid organ recovery. The super rapid recovery technique is preferable and organs may be removed en bloc.[15,345] For uncontrolled donors, in-vivo organ preservation techniques, like in-situ intravascular cooling using a double balloon and triple lumen catheter or hypo- and normo-thermic cardiopulmonary bypass with extracorporeal membrane oxygenation (ECMO), should be employed. With regard to the logistic organization, two frequently mentioned initiatives are the "Maastricht's box" and the "Madrid's rapid identification and response system".[238]

Donor cause of death

DCD donors do not experience the brain dead process. Brain death provokes a cascade of changes in hemodynamics, hormones, and immune response, which negatively affect donor organ viability and transplant outcomes.[346,347] Hemodynamic instability may have deleterious effects on liver function, although the liver has a high tolerance to marked hypotension and a large physiological reserve. Only a few histological changes were observed in the liver both on light and electron microscopic examination during the brain dead process.[348,349] The most important changes are the increased liver immunogenicity with subsequent increased host allo-responsiveness and the occurrence of apoptosis of hepatocytes.[350] Clinical findings in livers from DBD donors revealed significantly higher leukocyte infiltrates, up-regulation of adhesion molecules (intercellular adhesion molecule - ICAM, vascular cell adhesion molecule - VCAM) and pro-inflammatory cytokines (interleukin-6 (IL-6), IL-10, IL-1β, interferon γ and tumor necrosis factor-α), along with an increased expression of major histo-compatibility

complex-II (MHC-II) relative to livers from living donors.[277,351] The peak time of cytokine expression and cell infiltration is during brain death and organ procurement but not after reperfusion.[277] These changes may amplify ischemia-reperfusion injury (IRI) during the transplant procedure and accelerate graft rejection after transplant.[352] In reality, donor brain-death mechanisms are quite varied and large differences may exist in the degree of impaired organ quality and transplant outcomes. The impact of donor cause of death on transplant outcomes has been recently confirmed in a UNOS (United Network for Organ Sharing) registry analysis, in which the cerebro-vascular accident presented as a predictor of worse graft survival across all organs relative to other donor modes of death.[279]

Uncontrolled DCD donors whose cause of death is usually other than neurologic do not undergo the process of brain death, while most controlled DCD donors have sustained irreversible cerebral injuries. As a result, organs from controlled DCD donors are likely to suffer more from the harmful immunologic and inflammatory effects of acute brain injury than those from uncontrolled DCD donors.[239]

Allocation policy

It is reported that organs that have already subjected to warm ischemic injury have an increased susceptibility to damage during cold storage.[353] The incidence of PNF was 2.5 times less in patients with cold ischemia time (CIT) ≤ 8h versus those with CIT > 8h (5% versus 13%).[60] The incidence of graft failure within 60 days of transplantation was 10.8% if CIT < 8h and substantially increased to 30.4% and 58.3% if CIT > 8h and > 12h, respectively.[58] Proper and rapid allocation of DCD livers thus appears pivotal to minimize CIT. One-year graft survival of DCD livers shared regionally was less good than those shared locally (67% versus 77%)[212] and the relative risk of graft failure from nationally shared DCD livers was 31% higher than locally or regionally shared ones[300]. Thus a policy to favor local use of DCD livers seems reasonable.[58,212] However, parallel (backup) offers should also be made to expedite organ placement.[14] The exchange of DCD livers between transplant centers has been successfully done but requires a more efficient and rapid referral system due to a lower tolerance of these allografts to cold storage.[311]

Regarding recipient selection criteria, DCD livers could be routinely discussed and offered to all recipients on the waiting list[304,311,318] or selectively reserved to uncomplicated cases to ensure short CIT (by avoiding cases with extensive history of abdominal surgery or portal-vein thrombosis).[304,338] An expected long surgical procedure exceeding 8 h of CIT,

logistical reasons for an extended CIT, combined organ transplantation, recipients with high MELD (Model for End-Stage Liver Disease) scores or a large age difference between donors and recipients could all result in the refusal of a DCD liver.[144] Patients with stable cholestatic liver disease or re-transplantation were also excluded from DCD programs because of problems related to the quality of life in primary biliary cirrhosis and to the fear that pre-existent warm ischemic biliary damage could trigger the recurrence of primary sclerosing cholangitis.[298] Using DCD livers in re-transplanted patients might increase the CIT associated with a difficult hepatectomy. Recently LaMattina has demonstrated the feasibility of simultaneous liver and kidney (SLK) transplantation using DCD donors and shown short-term results comparable to those of SLK transplantation using DBD donors, making it a valid approach to safely expanding the donor organ pool for patients with end-stage liver and kidney disease.[354]

It is still controversial whether it is better to transplant such grafts into healthy or sicker recipients (i.e. according to the recipient liver disease severity). UNOS database reviews advocated utilizing DCD livers in 'low-risk' recipients.[57-59] De Vera also observed better graft survival when DCD livers were utilized in patients with MELD scores ≤30, but simultaneously could demonstrate that 'sicker', high-risk recipients (at MELD scores >30 or on organ-perfusion support, like mechanic ventilation or hemodialysis) had a greater patient and graft survival benefit from the transplantation of DCD livers compared to patients who are not as critically ill.[60] Risk classification for DCD donors and DCD-LT recipients is summarized in **Table 4.2.1**. Other groups of patients that may have a true survival benefit from DCD-LT include MELD 'disadvantaged' patients (hepato-cellular carcinoma patients beyond the Milan criteria or who are listed in areas with long waiting times, patients with low MELD scores that do not adequately reflect their level of illness and their critical need for a transplant).[60,298]

Studies about the effect of DCD liver grafts on hepatitis-C virus positive (HCV+) recipients' transplant outcomes were inconsistent. Nguyen and recently Hernandez-Alejandro found a negative effect of HCV on DCD livers, but a formal contraindication for the use of DCD liver allografts in HCV+ recipients was not justified except for older donors.[342,355] In fact, while single-center series reported no significant difference in graft and patient survival rates of HCV+ recipients and graft loss from HCV recurrence between DCD and DBD groups,[60,95,304,356] as well as no deleterious effects of DCD liver grafts on the disease progression (fibrosis) in comparison with DBD liver grafts in HCV+ recipients,[95] the most

recent UNOS registry data showed inferior graft survival but similar patient survival of HCV+ recipients with DCD donors compared to ones with DBD donors. Furthermore, DCD livers on HCV disease do not fare worse than DCD livers on non-HCV disease. DCD livers thus appeared to be important source of LT for HCV patients.[357] Split livers from DCD donors have also been reported in recent years with acceptable results.[358,359]

Table 4.2.1. Risk classification for DCD donors and DCD-LT recipients

Authors		Donors	Recipients
Mateo[59]	Low risk	Both WIT ≤30 min and CIT ≤10 h	RCRR ≤1.5
	High risk	WIT >30 min and/or CIT >10 h	RCRR >1.5 Re-transplantation and/or On life-support and/or A combination of ≥ 3 risk factors: Hospitalization or in ICU Serum creatinine >2 mg/dL On dialysis Age >60 years
Lee[57]	Low risk	Donors with no identified donor risk factors	Recipients with no identified recipient risk factors
	High risk	Donors with at least one identified donor risk factor: Donor age >45 years WIT >15 min CIT >10 h	Recipients with at least one identified recipient risk factor: Previous transplantation Life support at transplantation
De Vera[60]	Low risk	-	MELD scores ≤30
	High risk	-	MELD scores >30 On life support (mechanical ventilation, hemodialysis)

RCRR: recipient cumulative relative risk. MELD: model for end-stage liver disease.

Transplant outcomes

Currently one-year patient survival after DBD-LT and to a certain extent after controlled DCD-LT is about 85-90% in comparison to 60% in the early eighties and around 30% in the early days of LT and at 5 years post-transplant patient survival rate remains over 70%. Medical progress over the past 40 years in the field of organ preservation, surgical techniques, immunosuppressive drugs, treatment of post-transplant complications and organ allocation has permitted DCD to become reality in the modern era. Although there are concerns about the quality of such organs, with evidence that a prolonged WIT causes a raised incidence of primary non-function (PNF) and biliary complications as well as suboptimal

graft and patient survival when compared to DBD livers, DCD livers may be life-saving for those who would die waiting for a DBD liver[212] and do increase the number of organs available for LT. With careful donor/recipient selection and matching, minimization of ischemia and good post-operative care, acceptable results can be achieved. Essential results of most important publications in the last decade in DCD-LT are presented in **Tables 4.2.2a, 4.2.2b, 4.2.3a, 4.2.3b and 4.2.4**.

Primary non-function

PNF is usually defined as unrecoverable hepato-cellular dysfunction leading to patient death or re-transplantation within the first week post-transplant after excluding other causes of graft failure such as vascular thrombosis, biliary complications, rejection or recurrent disease.[360-363] Initial studies using uncontrolled DCD donors reported a rate of PNF as high as 50%.[364] Currently only a few transplant centers in the world (like Spain, France) used this kind of donors because of aforementioned reasons. By using different in-vivo organ preservation methods to maintain DCD donors and by strictly applying donor selection criteria, authors in Madrid,[318] Barcelona,[10] and La Coruña[317,365-367] could obtain promising results from Maastricht category I and II donors with a PNF rate of 10-25%. The discard rate nevertheless was high up to 50-75%.[10,318] In controlled DCD donors, the PNF rates are 0% to 12%. Matched analyses[60,298] and registry data[58,212] showed a higher rate of PNF in controlled DCD than DBD donors, although no difference was found in most comparative studies[304,305,308,309] except one[310]. The increased risk of PNF in DCD-LT recipients was also confirmed in a recent meta-analysis (odds ratio - OR = 3.6, 95% confidence interval - CI = 2.1–6.4).[299] Case-series reports of controlled DCD-LT also had a rate of PNF between 0% and 10%.[303,311-315]

PNF is the consequence of severe IRI with the initial period of warm ischemia playing a crucial role. Experimental evidence supported that donor WIT should be less than 30 min to minimize PNF.[368] This warm ischemia (WI) period increases graft susceptibility to damage during cold preservation and CIT was a main contributing factor to PNF,[58,60] therefore, both periods of ischemia must be kept to a minimum. Many laboratory tests have been developed both in animal models and in human to predict the probability of occurrence of PNF post-transplant, but none is yet clinically efficient.[369] Recently Dahaba proposed bispectral index monitoring as an early intra-operative indicator of early graft dysfunction.[370]

Biliary complications

Since the introduction of LT up to now, biliary complications are always regarded as the 'Achilles heel' and a major cause of morbidity and graft failure in patients after LT.[307] The most common biliary complications are bile leakage and bile duct stricture.[371,372] Strictures involving the donor bile duct (>1 cm above the biliary anastomosis) and requiring endoscopic or radiological dilatation/stenting or surgery in the face of a patent, non-stenotic hepatic artery was referred to as ischemic-type biliary lesions (ITBL), based on the radiologic resemblance of those occurring after hepatic artery thrombosis (HAT).[144,309,372]

Abt first mentioned the significantly higher incidences of overall biliary complications as well as ITBL in DCD-LT recipients,[306] the finding which was later confirmed in both matched[60,298] and comparative[144,304-306,309,317] studies except Fujita's and Manzarbeitia's series.[94,319] The rates of overall biliary complications and ITBL were 10.5 - 53% and 8.3 - 38%, respectively in DCD-LT compared to 8.3 - 22% and 0 - 8%, respectively in DBD-LT. Especially Jimenez-Galanes reported only a 5% incidence of ITBL in their patients receiving livers from uncontrolled DCD donors under normothermic ECMO.[318] A recent meta-analysis revealed that DCD recipients had a 2.4 times increased odds of biliary complications (95% CI = 1.8–3.4) and a 10.8 times increased odds of ITBL (95% CI = 4.8–24.2) versus DBD recipients. In average, biliary complications were present in 29% of DCD compared with 17% of DBD recipients and ITBL in 16% of DCD versus 3% of DBD recipients.[299] Furthermore DCD recipients who developed ITBL experienced a fairly rapid clinical deterioration, characterized by a relatively short mean time from transplant to first endoscopic retrograde percutaneous cholangio-pancreatography (ERCP), from first ERCP to relisting and from relisting to re-transplantation (within 180 days).[300,301] ITBL results in re-operation, multiple endoscopic and percutaneous biliary interventions, re-transplantation and even patient death with markedly increased medical care costs.[64] The relative risk (RR) of developing graft loss with ITBL formation was 3.02 (95% CI = 1.9 –5.3) and graft survival was significantly decreased in patients with non-anastomotic strictures, compared to patients without it.[317] Up to 50% of all occurrences of ITBL lead to death and/or re-transplantation.[373]

ITBL is usually a reflection of severe IRI in relation to various factors. In animal models, irreversible biliary tract damage has been observed after 40 min of cardiac arrest although hepato-cellular function could be preserved.[374] Clinical observations showed that total WIT >30 min and chaotic donor physiology before asytole may increase the risk of post-transplant biliary stricture.[14,375] The mechanism could come from the stasis of blood and clot

formation in the peri-biliary micro-circulation whose blood is solely supplied by the hepatic artery.[313] Many multivariate analyses recognized DCD liver grafts as an independent risk factor for the appearance of ITBL (RR = 47.1).[144,317] Biliary epithelium is also known to be sensitive to cold preservation-reperfusion injury and the correlation between the incidence of ITBL and the duration of cold ischemia has been well documented. Li demonstrated that the rate of ITBL is significantly increased in livers with increased preservation injury, as reflected by post-transplant peaks in serum transaminases.[376] Other variables implicating in the mechanisms of ITBL may include injury of the peri-biliary vascular plexus, bile salt toxicity and potential immunological etiologies (ABO incompatibility, liver diseases with autoimmune component like autoimmune hepatitis and primary sclerosing cholangitis).[371] Chan found donor age >50 years, donor weight ≥100 kg and total ischemia time ≥9 h were predictive for the development of ITBL.[305] Patients who underwent LT from DCD donors >60 years had a markedly high rate of biliary complications (67%), with a RR of 5.6 (95% CI = 0.98–32.2).[60]

Due to serious consequences of ITBL on the patient's quality of life and healthcare cost, preventive measures seem to play a pivotal role in the safe expansion of DCD liver use. Attempts to minimize biliary duct damage may include the use of normothermic ECMO for donor maintenance[10,318,377] and machine perfusion for liver grafts, choice of preservation solutions (HTK versus UW),[378-382] use of anticoagulation and thrombolytic agents,[313] extensive irrigation of the donor bile duct and pressure perfusion of the hepatic artery during organ retrieval and/or at back table,[378,383,384] early porto-caval shunt to reduce portal hypertension in the recipient, choice of reperfusion techniques (concomitant versus sequential reperfusion of portal vein and hepatic artery)[385] and certainly the most important thing is always minimizing warm and cold ischemia period.[386]

Hepatic artery thrombosis and stenosis

HAT is a thrombo-embolic occlusion of the hepatic artery that can occur early or late after LT. Most authors used the first 30 days post-transplant as a time point to distinguish between early and late HAT.[316] Early HAT results in fulminant hepatic failure, bile duct necrosis and leaks, relapsing bacteremia and ultimately graft loss and recipient death. The frequencies of early HAT after DCD-LT varied from 0% to 16.6% and did not seem significantly higher than those after DBD-LT in most studies[10,60,94,144,298,301,304-306,309,317,318]

except Yamamoto's study (33.3% versus 0%).[308] Risk factors for early HAT have been well analyzed in a recent systemic review.[387] Few detailed studies discussed late HAT.

The incidence of hepatic artery stenosis (HAS) was not consistently found higher in DCD than DBD grafts (12.8-16.6% versus 0-5.4%).[298,309] It is possible that hepatic arteries are susceptible to WI during DCD organ retrieval, resulting in subsequent scar and stenosis. Moreover the increased susceptibility of DCD livers to post-operative arterial ischemia might be responsible for more biliary strictures in DCD than DBD recipients with HAS (83% versus 37%) as well as shorter time to the development of biliary strictures after HAS in the DCD group.[309] Inadequate surgical technique, vascular trauma by clamps, graft rejection, recurrent hepatic disease… might also play a role in the mechanisms for HAS.[298,388]

Graft and patient survival

Graft survival is defined as the time from transplantation to either re-transplantation or patient death, with 'early' and 'late' graft failure occurring within and beyond 1 year post-transplant, respectively.[60] Few studies reported experience with LT from uncontrolled DCD donors. Early results were poor with a PNF rate of 50% and one-year graft survival rate of only 17%[364] leading to a scarce usage of this donor category in the US. Subsequent series in Spain using advanced in-vivo organ preservation methods showed promising outcomes with one- and five-year graft survival rates of 50-80% and 49%, and one- and five-year patient survival rates of 70-85.5% and 62%, respectively.[10,317,318] LT from controlled DCD donors offered better results although they still appeared inferior to DBD-LT in matched studies,[60,298] registry data analyses,[57-59,212,300,302] and in some comparative studies.[301,309,310] One-, three-, five- and ten-year graft survival rates were 54-79.5%, 53-74.5%, 37.5-71% and 37.5-44%, respectively. Patient survival rates at corresponding time points were 61.9-91.5%, 62.8-89.5%, 42.9-89.5% and 42.9-57%, respectively. Transplant outcomes comparable to those obtained from DBD-LT have been sporadically reported in select centers through careful donor selection and optimization of CIT or through invasive techniques designed to optimize recovery before declaration of death.[144,304-306]

Significant risk factors for DCD liver graft loss have been identified by multivariate Cox regression technique in both single center studies and large data registry analyses.[57-59,212,300,389,390] Among donor risk factors, age >50 years, total WIT >30 - 35 min, CIT >6 h, body weight >100 kg and regional or national liver distribution had deleterious effects on graft survival.[57,59,390] There is a stepwise increase in the relative risk of graft failure among

donor age, WIT and CIT.[57,390] Strong recipient determinants of graft failure include age >55 years, history of previous transplantation, medical status at transplantation (ICU or non-ICU hospitalization, life support, dialysis, renal insufficiency), high MELD score (>30) and positive HCV serology.[57,59,390] In the DBD-LT model, it has been shown that a single risk factor lessened outcome marginally, however, the additive effect of multiple risk factors in a given donor-recipient pair were disastrous.[362] Grafts with ≥3 donor risk factors had significantly lower 1-year post-transplant survival than no or only 1 or 2 risk factors (58.3% versus 72.6%, 69.2% and 73.9%, respectively). No grafts with 4 risk factors survived within 1 year.[391] The relative risk of allograft failure from LT utilizing DCD donors was 31-87% higher than LT utilizing DBD donors.[58,212,300,302,389] Causes of early graft failure included PNF, biliary complications, HAT and deaths from sepsis/multi-organ failure. Late graft failure was often secondary to chronic rejection and recipient death with a functioning graft.

Although DCD livers may not be as good as DBD ones with potential inferior transplant outcomes, there are subgroups of grafts and recipients that could give favorable results through appropriate graft and recipient matching. Low-risk DCD grafts which are transplanted in low-risk patients lead to comparable graft survival rates with DBD livers. Livers from DCD donors transplanted into high-risk recipients fared poorly independent of the allograft quality.[59] Doshi showed DCD liver grafts were not inferior to DBD livers from older donors (≥60 years).[212] Given the ever increasing demand for LT, DCD livers appear to be a reasonable alternative to increasing use of older or split livers and are a reasonable option when death is imminent.[212] Even if graft or/and patient survival is lower with a DCD liver, it is still better than dying because of turning down a DCD offer and continuing to wait for a DBD liver on these days as the patient's choice is frequently not between marginal livers (including DCD) and standard livers but between marginal livers and no livers.[94] The benefit of earlier access to LT provided by a DCD graft could outweigh the risks of prolonged waiting for a standard graft.[95]

Re-transplantation

DCD recipients more often require re-transplantation. 21.6-42% versus 8.8-16% of DCD and DBD recipients were listed for re-transplantation, respectively.[300,301] The re-transplantation rate ranged from 7.6 to 31% in DCD-LT compared to 2.5-12% in DBD-LT.[10,58,60,144,212,298,300,301,304,309,310,318,319] DCD livers exhibited a 2.1 times greater risk of graft failure, a 2.5 times greater risk of re-listing, and a 3.2 times greater risk of re-transplantation

compared with DBD livers.[301] The majority of re-listing and re-transplantation in the DCD group were a consequence of biliary complications, especially ischemic cholangiography, but not due to an increased incidence of PNF, HAT or technical complications.[300,301] Particularly DCD livers had a temporally different failure pattern within the first year post-transplant that limited access to re-transplantation:[300,301] graft failure was more likely to occur within the first 180 days (18.1% versus 11.7%,[58] 10.2% versus 2.5%,[298] and 20.5% versus 11.5%,[300] of DCD and DBD grafts failed within 60, 90 and 180 days, respectively); at re-transplantation, DCD recipients waited longer and received higher risk allografts; and more DCD recipients remained waiting for re-transplantation with fewer removed for death, clinical deterioration, or improvement. Re-transplantation arouses controversy on medical, economic, and ethical grounds: patient and graft survival rates after a second LT are inferior to those after initial grafting, the procedure is more expensive and in the context of organ shortage, re-transplantation inevitably denies organs to first-time recipients.[392]

Utilization of DCD allografts for re-transplantation was rare (2.5% of initial DCD versus 3.1% of initial DBD) and outcomes from each group were comparable.[300] The general practice is to avoid re-transplantation with a DCD graft.[301] The use of DCD donors in the setting of re-transplantation resulted in an increased risk of recipient death (hazard ratio - HR = 2.1, 95% CI = 1.2-3.6).[392]

Acute rejection

The acute rejection rate did not differ significantly between DCD- and DBD-LT in most studies (1.9-29% versus 0.6-34%).[298,304,306,317,366] Foley reported a one-year rejection rate of 61% in the DCD group similar to that in the DBD group (56%). There were little data looking at the impact of DCD source on the risk of acute rejection.

Experimental strategies to improve DCD-LT outcomes

The progressively increased DCD liver procurement to solve the shortage of DBD organs and to alleviate the waiting-list mortality has raised many challenges to the transplant community and transplant policy makers.[375] A lot of experimental researches have been performed over the past decade, intervening in both donors and recipients at different phases of the transplantation process, at the aim of tackling some of these challenges and providing a deep insight into IRI mechanisms

Table 4.2.2a. Results of DCD-LT in single-center studies

Authors	Transplant center	Study period	Patient number	WIT (min)	CIT (min)	Mean follow-up	PNF %	Biliary complications %	ITBL %	HAT %	HAS %
Casavilla[364]	Pittsburgh, US	1989-1993	6 DCD_4 6 DCDc	37 23.8	10.6 h 11 h	32 m 17.5 m	50 0	-	-	16.6 33.3	-
Otero[366]	La Coruna, Madrid, Spain	1995-2000	20 DCD_2 40 DBD	108	647 405	>2 y -	25 3	30 8	-	0 0	-
Quintela[365]	La Coruna, Spain	1995-2004	9 DCD_2 + 1 DCD_4	80	561	57 m-	10	-	-	-	-
Suarez[317]	La Coruna, Spain	1994-2005	27 DCD_2 471 DBD	137	635 -	>3 m -	18 3	41.7 16.8	25.0 2.3	3.6 3.1	
Fondevila[10]	Barcelona, Spain	2002-2006	10 DCD_1 20 DBD	-	399 -	23 m -	10 0	10 0	-	10 5	-
Jiménez-Galanes[318]	Madrid, Spain	2006-2008	20 DCD_2 40 DBD	126	432 409	360 d -	10 2.5	5 -	5 0	0 0	-
Pine[298]	St. James, London, UK	2002-2008	39 DCDc 39DBD	13.4	352 593	2.5 y 6.6 y	5.1 0	33.3 10.2	20.5 0	2.6 5.1	12.8 0
De Vera[60]	Pittsburgh, US	1993-2007	141 DCDc 282 DBD	19.8	657 636	-	12 3	25 13	16.3 < 1	6 6	-
Yamamoto[308]	Stockholm, Sweden	1984-1988	24 DCDc 16 DBD	6	7 h 6.8 h	>20 y >20 y	8.3 18.7	37.5 6.3	-	33.3 0	-
Fujita[94]	Gainesville, Floria - US	1990-2006	24 DCDc 1209 DBD	12.8	7.6 h 8.1 h	-	0 2.8	25 20.5	12.5 -	8.3 4.1	-
Foley[309]	Wisconsin, US	1993-2002	36 DCDc 553 DBD	17.8	8.2 h 8.3 h	3 y 4.6 y	5.5 1.3	33 10	13.8 8.0	5.5 11.8	16.6 5.4
Manzarbeitia[319]	Philadelphia, US	1995-2002	19 DCDc 311 DBD	19.6	574 557	1000 d -	5.2 -	10.5 13.8	-	-	-
Abt[306]	Pennsylvania, US	1996-2001	15 DCDc 221 DBD	20.4	366 464	819 d 690 d	6.7 3.6	33.3 9.5	26.7 2.3	0 3.2	-
Nguyen[342]	Mayo Clinic, Floria - US	1998-2001	19 DCDc 234 ECD 214 SCD	16	6.7 h 7.1 h 7.5 h	> 4.5 y - -	5.3 4.7 1.7	26.3 22.6 15.9	10.5 - -	0 0 0	5.3 - -

Table 4.2.2b. Results of DCD-LT in single-center studies (continuing **Table 4.2.2a**)

Authors	Patient number	Rejection %	Retransplantation %	Graft survival %				Patient survival %			
				1 y	3 y	5 y	10 y	1 y	3 y	5 y	10 y
Casavilla[364]	6 DCD_4	-	83.3	17	-	-	-	67	-	-	-
	6 DCDc		33.3	50				50			
Otero[366]	20 DCD_2	27	25	80	-	-	-	80	-	-	-
	40 DBD	34	5	55				83			
Quintela[365]	9 DCD_2 + 1 DCD_4	-	10	100	-	-	-	100	-	-	-
Suarez[317]	27 DCD_2	17.4	-	-	-	49	-	-	-	62	-
	471 DBD	28.6				68				74	
Fondevila[10]	10 DCD_1	-	20	50	-	-	-	70	-	-	-
	20 DBD		5	75				80			
Jiménez-Galanes[318]	20 DCD_2	-	15	80	-	-	-	85.5	-	-	-
	40 DBD		0	87.5				87.5			
Pine[298]	39 DCDc	20.5	7.6	79.5	63.6	-	-	80	68.2	-	-
	39DBD	23.1	2.5	97.4	97.4			100	100		
De Vera[60]	141 DCDc	-	18	69	-	56	44	79	-	70	57
	282 DBD		7	82		73	63	85		76	64
Yamamoto[308]	24 DCDc	70.8	-	54.2	-	37.5	37.5	61.9	-	42.9	42.9
	16 DBD	56.2		43.8		37.5	37.5	63.6		54.5	54.5
Fujita[94]	24 DCDc	39.1	20.8	69.1	58.6	-	-	86.8	81.7	-	-
	1209 DBD	-	9.4	78.7	70.2			84	76		
Foley[309]	36 DCDc	61	19.4	67	56	-	-	80	68	-	-
	553 DBD	56	7.0	86	80			91	84		
Manzarbeitia[319]	19 DCDc	-	10.5	-	-	-	-	89.5	-	-	-
	311 DBD		8.7					84.2			
Abt[306]	15 DCDc	20.0	6.6	71.8	71.8	-	-	79.0	79.0	-	-
	221 DBD	21.3	3.6	85.4	73.9			90.9	77.7		
Nguyen[342]	19 DCDc	5.3	15.8	73.7	68.4	63.2	-	89.5	89.5	89.5	-
	234 ECD	33.3	8.5	-	-	-		85.0	78.6	72.3	
	214 SCD	33.2	19.6	-	-	-		84.3	80.7	76.5	

Table 4.2.3a. Results of DCD-LT in single-center studies

Authors	Transplant center	Publication year	Patient number	WIT (min)	CIT (min)	Mean follow-up	PNF %	Biliary complications %	ITBL %	HAT %	HAS %
Grewal[304]	Mayo Clinic, Floria - US	1998-2006	108 DCDc 1328 DBD	22.3	6.3 h 7.1 h	34.5 m 50 m	3.7 1.4	-	8.3 1.9	0.9 1.7	-
Kaczmarek[341]	Newcastle, UK	1999-2006	11 DCDc 164 DBD	34.6	7.6 h -	>14 m	0 -	45.4 16.4	18.2 0	0 -	-
Dubbeld[144]	Netherlands	2001-2006	55 DCDc 471 DBD	16.5	456 515	-	2.0 1.5	28 8.3	24 7.9	7 4.7	-
Chan[305]	Seattle, US	2003-2006	51 DCDc 334 DBD	-	-	3y -	0 3.3	23.5 8.9	13.7 1.2	0 4.8	-
Skaro[301]	Chicago, US	2003-2008	32 DCDc 237 DBD	15.8	5.5 h 5.2 h	-	3 1	53 22	38 2	9 3	-
Jay[64]	Chicago, US	2004-2008	28 DCDc 198 DBD	16.5	5.7 h 5.3 h	1.8 y -	3.6 0.5	57.7 21	44 1.6	10.7 3	7.1 6.1
Dezza[310]	Ghent, Belgium	2003 - 2006	13 DCDc 98 DBD	10	6.16 h 9.14 h	163 d 603 d	8 1	-	23.1 -	-	-
Maheshwari[312]	Johns Hopkins Baltimore,US	1997-2006	20 DCDc	33	8.7 h	7.5 m	5	60	50	5	-
Muiesan[311]	London, UK	2001-2004	31 DCDc	14.7	8.6 h	14.7 m	3.1	9.4	0	3.1	-
Abbass[315]	Michigan, US	2004-2008	26 DCDc	39	5.3 h	29 m	0	46	15.4	11.5	7.7
Detry[303]	Belgium	2003-2007	58 DCDc	25	451	23 m	3.4	38	32.7	3.4	3.4
Hernandez-Alejandro[314]	London, UK	2006-2007	10 DCDc	54.7	5.8 h	11 m	10	10	0	0	0
Hashimoto[313]	Cleveland, US	2005-2009	22 DCDc	21	422	27 m	4.5	27	9	0	0

Table 4.2.3b. Results of DCD-LT in single-center studies (continuing Table 4.2.3a)

Authors	Patient number	Rejection %	Retransplantation %	Graft survival %			Patient survival %		
				1 y	3 y	5 y	1 y	3 y	5 y
Grewal[304]	108 DCDc 1328 DBD	-	14.8 9.3	79.3 81.6	74.5 74.7	71.0 69.1	91.5 87.3	88.1 81.1	88.1 77.2
Kaczmarek[341]	11 DCDc 164 DBD	-	9.1 0	-	-	-	-	-	-
Dubbeld[144]	55 DCDc 471 DBD	-	18 10.4	74 80.4	68 74.5	-	85 86.3	80 80.8	-
Chan[305]	51 DCDc 334 DBD	-	9.8 -	79 85	79 77	-	83 88	83 78	-
Skaro[301]	32 DCDc 237 DBD	-	22 7	61 85	53 74	-	74 90	74 81	-
Jay[64]	28 DCDc 198 DBD	-	21.4 7.1	60 89	50 78	-	70 96	70 93	-
Dezza[310]	13 DCDc 98 DBD	-	31 12	54 79	-	-	62 86	-	-
Maheshwari[312]	20 DCDc	-	20	62	62	30	78	78	40
Muiesan[311]	31 DCDc	28.1	3.1	86.5	-	-	89.6	-	-
Abbass[315]	26 DCDc	26.9	23	77	-	-	92	-	-
Detry[303]	58 DCDc	-	13.8	72.4	48.8	-	83.3	66.9	-
Hernandez-Alejandro[314]	10 DCDc	-	10	-	-	-	-	-	-
Hashimoto[313]	22 DCDc	-	9	81	81	-	-	-	-

Table 4.2.4. Results of DCD-LT in UNOS data base registry

Authors	Study period	Patient number	WIT (min)	CIT (min)	PNF %	Retransplantation %	Graft survival %			Patient survival %		
							1 y	3 y	5 y	1 y	3 y	5 y
Abt[58]	1993-2001	144 DCD	12.7	8.1 h	11.8	13.9	70.2	63.3	-	79.7	72.1	-
		26856 DBD		8.9 h	6.4	8.3	80.4	72.1		85	77.4	
Mateo[59]	1996-2003	367 DCD	15.6	8.3 h	-	-	71	60	53	-	-	-
		33111 DBD		8.4 h			80	72	65			
Lee[57]	1996-2006	874 DCD	15.4	7.9 h	-	-	72.1	61.8	38.8	82.3	75.9	65.3
		43734 DBD		8.2 h			80.7	71.9	65.6	85.4	77.5	71.5
Doshi[212]	1998-2004	345 DCD	-	8.2 h	6.4	13.0	75	65	-	83	77	-
		20289 young-DBD		8.1 h	3.9	5.6	83	75		88	80	
		3604 old-DBD		8.2 h	5.3		76	64		83	73	
Merion[302]	2000–2004	472 DCD	-	7.9 h	-	-	70.1	60.5	-	-	-	-
		23598 DBD		8.1 h			83	75				
Selck[300]	2002-2007	855 DCD	-	-	-	21.6	73.8	57.6	-	-	-	-
		21089 DBD				8.8	84.4	74.4				
Mathur[390]	2001-2009	1567 DCD	16.1	7.5 h	-	13.6	-	-	-	78	64.9	-

min: minute. h: hour. d: day. m: month. y: year. DCDc: controlled donors after cardiac death. DCDu: uncontrolled donors after cardiac death. DCD_1, DCD_2 and DCD_4: Maastricht category-1, category-2 and category-4 DCD donors. DBD: donors after brain death. SCD: standard criteria donors. ECD: extended criteria donors. WIT: warm ischemia time. CIT: cold ischemia time. PNF: primary non-function. ITBL: ischemic-type biliary lesions. HAT: early hepatic artery thrombosis. HAS: early hepatic artery stenosis. Major symptomatic biliary complications include biliary leak, anastomotic and non-anastomotic stenosis. Red-coloured numbers denote the statistically significant difference between groups.

Donor pre-treatment

Various cyto-protective substances have been successfully administered into the donor prior to cardiac arrest for prevention of liver microcirculatory disturbance. Microcirculatory disturbance was the main obstacle to successful DCD-LT, which was due to four major mechanisms: deterioration of sinusoidal endothelial cells (SEC) caused by activated Kupffer cells, sinusoidal narrowing caused by some vasoconstrictors and swollen hepatocytes, leukocyte and platelet adhesion, and hyper-coagulability.[393] Up to now, only *Heparin and phentolamin* (an anti-coagulative substance and alpha-adrenergic antagonist) are allowed in clinical DCD organ procurement,[394] other substances remain in animal models. *Tacrolimus,* besides its powerful immunosuppression, enabled to prevent liver normothermic IRI by multiple mechanisms.[395] *Milrinone,* a type 3 phosphodiesterase inhibitor, attenuated graft injury caused by warm and cold ischemia via an increase in intracellular cAMP levels, protection of SEC, relaxation of hepatic stellate cells, inhibition of platelet aggregation and anti-inflammatory effect.[396] *Lazaroids*, an antioxidant designed to inhibit iron-dependent lipid peroxidation, ameliorated SEC viability via antioxidant effects and membrane stabilization.[397] *N-acetylcystein* has a direct effect on oxygen free radicals, but its usage had no effect in both graft viability and lipid peroxidation.[398]

Animal studies clearly showed the concept of pharmacological modulation of organ donors before procurement is feasible to improve the viability of marginal grafts. Nevertheless there are no definitive recommendations for the use of these drugs. Application of this method to clinical LT would require management of some practical problems and possible ethical conflicts.[399]

Organ preservation

Preservation of DCD livers by hypothermic machine perfusion (HMP) was shown superior to static cold storage (SCS) in many experimental studies.[400,401] Nonetheless a putative drawback of HMP for livers is to induce alterations at the vascular endothelial site, especially if HMP was performed for a long time or under suboptimal conditions.[402] Endoplasmic stress activation promoted cellular apoptosis via activation of caspase-12.[403,404] The efficiency of HMP was markedly increased by oxygenation of the perfusate.[405] The concern that high oxygenation might favor the generation of oxygen free radicals, which in turn could impair tissue integrity, was not justified. Several investigators could demonstrate the beneficial effect of oxygenated HMP in reducing the liver expression of pro-inflammatory

cytokines (TNF-α, IL-8), adhesion molecules (ICAM-1) and major histocompatibility complex class II antigens.[406-408] This benefit will likely be more pronounced in marginal grafts such as elderly, steatotic and DCD livers.[407] Cyto-protective agents can be added into the machine perfusion (MP) solution to ameliorate the efficiency of HMP organ preservation.[409]

The positive effects of HMP on warm-ischemically pre-damaged livers were observed even after a brief period of MP, before (pre-conditioning) or after SCS (post-conditioning)[406,410] and therefore, it was not necessary to require MP over a full preservation period and helped avoid side-effects of HMP on vascular endothelium.[404] The use of HMP as the initial method for organ preservation followed by secondary SCS during transportation combined the advantage of aerobic resuscitation (i.e. restitution of cellular homeostasis) with an ease of SCS for later surveillance and transportation.[404] Manekeller showed a post-conditioning of 1 hour after SCS can ameliorate the viability of marginal livers. The extension or abbreviation of post-conditioning time seems to have no further beneficial effects.[411]

Schon and St Peter reported advantages of normothermic machine perfusion (NMP) over SCS in pig DCD-LT models. Livers subjected to 1 hour of WI and then cold-stored for 4-24 hours were rendered completely nonviable while such livers under 4-24 hours of oxygenated NMP recovered function to a viable level.[353,412] Due to the complexity of the logistics of clinical multi-organ recovery and of the NMP device, a period of cold preservation prior to warm perfusion of the liver is unescapable. A brief period of cold preservation (1hour) prior to NMP could maintain the synthetic and metabolic function but resulted in significant hepatocellular damage, sinusoidal endothelial cell dysfunction and Kupffer cell injury.[413] Once this duration was prolonged to 4 hours, NMP completely failed to resuscitate porcine livers.[414] Normothermically perfusing DCD livers throughout the preservation period not only replenished cellular substrate, ameliorating the ischemic injury, but also provided a clear assessment of liver function and therefore could permit the use of severely injured organs with reassurance of function.[412,415]

Despite the aforementioned benefits of MP over SCS in liver preservation, only SCS is clinically approved up to now, MP is still in the pre-clinical stage and early clinical studies.[157] Tojimbara showed the impact of viscosity and temperature of initial flushing solutions on graft function. A low viscosity flushing solution was associated with lower vascular resistance, whereas a warm flush solution prevented cold-induced vasospasm and therefore improved the washout effect of the microcirculation.[416] HTK (histidine-tryptophan-ketoglutarate) solution possessing a low viscosity and low potassium is more preferable in the

DCD setting. The role of aeration of the cold-stored liver was also clarified. Oxygen provided either by surface diffusion (surface oxygenation) or intravascular diffusion (oxygen persufflation) helps improve the energy status of organs thus leading to earlier recovery. Surface oxygenation was not in use any more due to complicated technique, limited efficiency and risk of oxygen intoxication.[417] Venous systemic oxygen persufflation (VSOP) was shown to improve organ viability during hypothermic storage of the grafts and to be a feasible means for reconditioning of warm-ischemically pre-injured livers from DCD donors.[417-420] Experimentally even a short period of VSOP prior to long-term preservation of the liver by SCS may be sufficient for a relevant improvement of liver integrity upon reperfusion.[421] Gaseous persufflation with carbon monoxide was also tested in a DCD-LT rat model with enhanced liver graft viability.[422] However no additive or synergistic effect was noted when livers were persufflated with a mixture of gaseous oxygen and carbon monoxide.[423]

Pharmaceutical interventions during SCS aimed at conditioning marginal organs also increasingly gained attention. Different cyto-protective drugs have been added into the flush and/or preservation solution, like vasodilators (phentolamin, epoprosterol, dopamine),[424,425] anti-coagulants (heparin), fibrinolytic agents (streptokinase),[426] antioxydants (superoxide dismutase, edaravone),[427,428] antibiotics, hormones (glucagon, growth factors)[429]… In the DCD setting, vasodilators, anti-coagulants, thrombolytic agents and antibiotics seem particularly necessary because the organs tend to develop vasospasm, thrombus formation in the microcirculation and the risk of colonic bacterial contamination secondary to translocation of organisms during the WI period.[196,430]

Viability testing

Due to serious consequences of transplanting a DCD liver with potentially severe IRI (PNF, re-transplantation or even recipient death), it would be ideal if the viability of such livers could be predicted prior to rather than after transplantation. *WIT* is not always exactly known and thus cannot be a reliable parameter. *Light microscopic examination of biopsy specimens* was unable to uniformly predict liver function after transplantation.[431] Monbaliu showed the extent of parenchyma vacuolation predicted pig liver graft viability before LT.[432] Muiesan applied the mechanical digestion of liver biopsies with collagenase and assessed the viability of hepatocytes by trypan blue exclusion method.[311] However, the test was not helpful and the decision as to whether to use the liver was generally made on gross appearance, ease of perfusion, degree of steatosis and donor characteristics.[433]

Another approach is to evaluate the vascular resistance and enzyme release in the perfusate of HMP livers. Resistance index of the portal vein and hepatic artery showed no utility.[434] Biomarkers of liver cell damage, like transaminases, lactate dehydrogenase (LDH) and liver fatty acid binding protein (L-FABP), correlated well with WI duration and concomitant hepatocyte damage in pig DCD-LT models.[435] Possible other parameters are the ATP content and redox active iron status of the liver during HMP.[436] During NMP, the assessment of liver viability may be easier because the liver is in a normal metabolic state. Bile production was a good viability indicator besides the measurement of other liver functions (detoxification, metabolism or synthesis).[437] Recently Liu has tested the utility of magnetic resonance imaging and proton magnetic resonance spectroscopy to evaluate WI livers without success.[438]

Recipient treatment

Pharmaceutical strategies aimed at modulating IRI mechanisms were also applied successfully in animal recipients and generally did not impose ethical problems as donor pre-treatment. Such protocols without donor pretreatment will be favorable in clinical application. Most studies tested a single agent for a specific target of the IRI process. A multi-factorial approach acting on different pathways of the IRI process have been advocated and remarkably ameliorated transplant outcomes.[424]

Perspectives

The future of DCD-LT is promising. Concerted efforts should concentrate on the identification of suitable donors (probably Maastricht category III DCD donors), better donor and recipient matching (high risk donors to low risk recipients), use of advanced organ preservation techniques (oxygenated HMP and NMP, VSOP), and pharmacological modulation (probably a multi-factorial biologic modulation strategy) so that liver procurement and transplantation from DCD donors could be widely expanded and attain equivalent results as DBD-LT.

5

Revision of DCD classification

Published as

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Categories of Donation after Cardio-circulatory Death

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ABSTRACT

Objectives: This article aimed to review the various DCD (donation after cardio-circulatory death) descriptions in the literature and proposed an adapted DCD classification to better define the DCD processes, seeking to provide a better tool to compare the results of published reports.

Methods: We conducted a systemic review of all studies that discussed the use and classification of DCD organs during the past two decades in the world.

Results: The renewed interest in DCD in the early 1990s led to an increasing use of this donor source especially in the recent years. However, various DCD terminologies and classifications have been used, rendering it difficult to compare reported experiences.

Conclusion: The original DCD categories were efficient to expand this type of procurement, but a more complete categorization is now needed to define the various situations and to compare the clinical results encountered among different clinical groups and countries with active DCD programs. Modifications of the Maastricht classification presented here may be helpful in this matter and may be further modified in the future according to ongoing experiences as this field continues to progress.

Introduction

Deceased donor (DD) organ transplantation utilizes grafts procured from a deceased human being, the so-called "cadaveric organ donor." In the pioneering days of organ transplantation, the first DD organ procurements were performed after declaration of donor death based on cardio-circulatory arrest criteria.[320,439-441] In 1963, Professor Alexandre, from Brussels, Belgium, performed the first donation after brain death (DBD) in a patient whose death was declared based on neurological criteria.[172] The concept of brain death was confirmed in 1968 by the Ad Hoc Committee at the Harvard Medical School.[1] The wide acceptance of brain death in the Western world, and the better of DBD results due to the absence of warm ischemia (WI), led to the near complete abandonment of donation after cardio-circulatory death (DCD).

The interest in DCD was renewed in the early 1990s, as a means to partially overcome the shortage of DBD. In some European countries and in the United States, DCD has become an increasingly frequent procedure over this last decade,[19,240,326,442] including more than 40% of the DD pool in the Netherlands in 2008.[239] In Middle Eastern countries and in Asia, where DBD is rarely performed for legal, cultural, and/or religious reasons,[443,444] DCD is nearly the only type of organ procurement.[445] After several successful experiences with DCD kidney transplantation (KT),[45,91,173,238,239,288] these donors have recently provided other organs, including liver,[144,175,303,311,317,340,446] pancreas,[86,96] and lung.[99,100,447-451] Despite a first report of successful heart transplantation after procurement from DCD donors,[88] DCD heart transplantation has not reached (yet?) a significant clinical application.

To improve the results of DCD transplantation, it is important to compare the practices, experiences, and results of various teams involved in this field. It is therefore crucial to accurately define the different types of DCD. However, in the literature, different terminologies and classifications of DCD have been used, rendering comparisons difficult among the reports. The authors have presented herein an overview of the various DCD descriptions in the literature and have proposed an adapted DCD classification to better define the DCD processes, seeking to provide a better tool to compare the results of published reports.

Definition and classification of DCD donors

Cardio-circulatory death is defined as the "irreversible cessation of circulatory and respiratory functions".[15] In DCD donation, donor death is diagnosed by the cessation of

heartbeat and/or blood circulation, as assessed by electro-cardiography, monitoring of arterial pulses, or invasive arterial pressure. DCD donation does not exclude donor brain death. The term "non–heart-beating donation (NHBD)" was often used in the past (and is still sometimes used), but DCD is now preferred, as it more clearly implies donor death and can be compared with DBD. Both DCD and DBD donations imply organ procurement from a deceased donor, in contrast to a living donation. The initials "DCD" sometimes refer to "donation after cardiac death"; however, as DCD may be used in the future for heart transplantation,[88] a declaration of donor death based on irreversible cardio-circulatory failure may more accurately define the DCD process. Indeed it is difficult to understand or ethically justify the declaration of donor's death by "irreversible cardiac failure" if within minutes after the so-called "cardiac death," the donor's heart is procured for subsequent successful cardiac transplantation.[452,453]

The first DCD classification, proposed by the Rochester group in 1994, was based upon the possibility of planning donor cardio-circulatory arrest and the DCD surgical procedure.[15] Uncontrolled DCD involves organ procurement after unexpected cardio-pulmonary arrest and/or unsuccessful resuscitation.[15] In controlled DCD, the cardio-circulatory arrest is the consequence of a planned medical act of withdrawal of ventilatory and organ-perfusion support that can be performed either in the intensive care unit (ICU) or in the operating room (OR). In controlled DCD, procurement WI is recorded and minimized, as the procurement team is notified of the process and may be ready to start the surgical organ procurement within a few minutes after the declaration of death. In addition, cold ischemia (CI) may also be minimized as the potential organ recipients may be called into the hospital before the planned withdrawal of donor life support.

In addition, in 1995, after several years of extensive research and clinical experience in DCD KT, Pr Gauke Kootstra organized in Maastricht, Holland, an international meeting on NHBD. During this meeting, he proposed a DCD classification of four categories, which has been largely used over the last 15 years as the NHBD Maastricht classification (**Table 5.1**).[7] This classification has the advantage of characterizing the DCD processes that may have their own particularities, including ethical or surgical aspects. This classification also has the advantages of simplicity and usefulness, especially for KT.

Procurement WI

Table 5.1. Kootstra's 1995 Maastricht categories of donation after cardio-circulatory death[7]

Category	Description
1	Dead on arrival
2	Unsuccessful resuscitation
3	Awaiting cardiac arrest
4	Cardiac arrest while brain dead

Compared to DBD, DCD imposes an additional WI that induces a significant ischemic insult, increasing the risk of early post-transplant graft dysfunction. As a consequence of this procurement WI, DCD transplantation may be complicated by increased rates of primary non-function or chronic secondary ischemic lesions, leading to recipient death or re-transplantation when difficult and/or unstable conditions yield the organ. Indeed, the length of the WI during DCD may be variable according to the category of the DCD process, the longest being associated with the uncontrolled Maastricht category 1 DCD donation.

While WI during DCD is easily understood, its precise definition is difficult. At the cellular level, the WI insult to various organs is not identical, and does not start at the same time.[454] Particularly, the presence of air in the lungs may avoid pulmonary tissue ischemia in the early period after cardiac arrest.[455,456] The liver parenchyma, perfused in the majority by hypoxic portal flow, is used to a low oxygen level to some degree.[457] In uncontrolled DCD, the future donor undergoes resuscitation attempts that may provide some tissue oxygenation. However, these attempts are often not sufficiently efficient to avoid organ ischemia. Up to now, there has been no objective pre- or post-harvesting parameter that helps to determine whether a given donor or abdominal organ has suffered an irreversible WI insult that would exclude the possibility of organ transplantation. In uncontrolled DCD, WI is usually defined as the time between the first cardiac arrest and the cold flush of the organs. Controlled DCD processes may be defined in two phases: the withdrawal phase, the period between support withdrawal and cardiac arrest, and the acirculatory phase, defined as the period between cardiac arrest and aortic flushing (**Fig 5.1**). The acirculatory phase is composed of a "no-touch period," which is variable according to the ethical committee or legal requirements in various countries, (it is usually 2 to 10 minutes, but may be up to 20 minutes in Italy[11,15,19]) and the surgical period between declaration of death and cold organ perfusion. The exact measure of the duration of the two phases is easily adjusted in controlled DCD. However, if the time determining the end of WI and the beginning of CI is clear, the determination of the moment of the start of organ damage due to WI is difficult (or even impossible) since it is variable

among organs. The withdrawal phase is often marked by a progressive drop of oxygen saturation that is usually difficult to monitor as most pulse oxymeters are not calibrated to measure saturations below 90%. In addition, during the DCD process, the drop in arterial pressure is also not always progressive, with periods of relative hypotension followed by pressure normalization. In 1995, Kootstra defined DCD WI as the period between cardiac arrest and organ flush.[189] This definition is still used by the Eurotransplant organization in 2011.[458] For DCD kidney grafts, WI is now usually defined as the period between support withdrawal to aortic flush, meaning the whole DCD process.[238,284] In DCD liver transplantation (LT), most reports define WI as the period between support withdrawal and aortic cold perfusion,[58,60,95,303,305,459] but some authors have proposed to evaluate more precisely the period of real hepatic tissue WI. The American Society of Transplant Surgeons defined total WIT as the period between support withdrawal to aortic flush, and true WIT as the time between the drop in the mean arterial pressure below 60 mmHg and the initiation of perfusion.[15] But as shown in **Table 5.2**, many centers or procurement organizations use other criteria, often mixing (mean or systolic) arterial pressure and oxygen saturation criteria, to establish the beginning of "true" WI time in LT, without providing clear scientific evidence.[27,301,319,338,339,341] The same issue has also been raised in DCD lung transplantation.[100,447,460,461] There is clearly a need to standardize the nomenclature, but this problem is beyond the scope of this article.

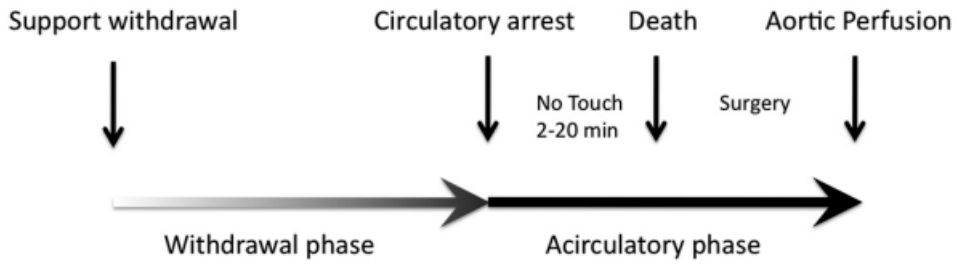

Figure 5.1. Process of controlled donation after cardio-circulatory death

Problems of these classifications and the modifications proposed in the literature

The Maastricht classification and the "controlled/uncontrolled" characterization of DCD are clearly current, useful standards. However, within the different types of DCD, clinical differences may lead to various post-transplant results presented in the literature. In Maastricht DCD categories 1 and 2, donor cardio-vascular death is an unpredictable event occurring outside or within the hospital, respectively. In these categories, DCD is, per

definition, an uncontrolled procedure with a prolonged period of DCD WI, if defined as the period between the first cardiac arrest to the flush of the potential grafts. Using one of the largest world experiences in category 1 and 2 DCD in Spain, Fondevila found it important to differentiate uncontrolled DCD with potential witnesses of the cardiac arrest and rapid attempt of resuscitation versus those that occur without any witness even in the hospital.[10] Experienced Spanish centers also have reported significantly worse results in category 2 DCD donors hospitalized in the ICU compared with those without an ICU stay.[9] The worst results of category-2 ICU DCD donors may be attributed to their long hospitalizations and to the cerebral damages that may be detrimental to donor organs due to significant pro-inflammatory and pro-coagulant responses.[462,463] In this report, the authors proposed to call these donors "category 5," despite the fact that they were clearly under the Kootstra's category 2 definition.[9] Category 5 has subsequently been used by other authors.[98,464,465] Recently an Italian group with limited experience in the field even proposed a category 6 for DCD patients on extra-corporeal membrane oxygenation.[11] In addition, some English groups have proposed to separate the Maastricht category 3 into 3A for controlled DCD performed in hospital and 3B for controlled DCD performed in hospice, due to worse results among the latter group despite equivalent WI and CI.[284,466] Moreover, in the literature there is also some misunderstanding in the characterization of Maastricht category 4 as controlled versus uncontrolled, as they can be both.[74,77,284]

Table 5.2. Definitions of procurement "true" warm ischemia in controlled DCD liver transplantation

Centers/PO	Year	Pressure (mm Hg)	Oxygenation (%)	Reference
ASTS	2010	MAP <60	NA	[15]
Philadelphia	2009	MAP <50	<70	[319]
Seattle	2005	MAP <35	<25	[339]
United Kingdom	2005	SBP <50	NA	[27,311,341]
Chicago	2009	SBP <50	<70	[301]
Miami	2003	SBP <35	<25	[338]

MAP: mean arterial pressure, SBP: systolic blood pressure.

In addition, in the recent years, a new type of DCD has been performed in Belgium (i.e., DCD after euthanasia).[12,231,467] There are now laws allowing physician-assisted suicide in the Netherlands, Belgium, and Luxembourg, under strict medical and legal conditions requiring the clear willingness of the patient with unbearable suffering to die in a humane

condition. Other countries have ongoing active political discussions on this subject. It is likely that in the future, other countries will establish laws on this practice. To our view, and to that of various Belgian university ethical committees that have been questioned on the subject, there is no ethical or legal objection to harvest organs after physician-assisted death following active, repeated requests of the patient who has been granted euthanasia. This is a clear voluntary donation by conscious people willing to help other human beings, despite the fact that their own medical condition may not be adequately palliated by modern medicine. These particular DCD donors may be a source of good organs, as these DCD donors have no recent brain damage at the time of the highly controlled cardio-circulatory arrest. The authors postulate that these DCD procurements after euthanasia may be more frequent in the future. Indeed, the Eurotransplant organization has officially recognized these DCD donations in their computerized organ donor forms. Clearly, these DCD donations are not included in the original Maastricht classification. Therefore, for all of these reasons, the authors consider the need to adapt the current classifications of DCD.

Proposition for an adapted DCD Maastricht classification

Table 5.3 shows the adapted DCD classification proposed herein. The authors consider that Kootstra's Maastricht classification should be conserved as the skeleton for further improvement, as it is simple and clear and classifies easily the various DCD types for ethical issues and for non-medical, non-specialized readers interested in the field. Up to now, other attempts to improve the Maastricht classification have added new categories based on various ischemic insults, potentially altering transplant results, despite the fact that the DCD situation was already included in the Maastricht classification. As an exemple, Sanchez-Fructuoso et al proposed to create category 5 for uncontrolled DCD occurring in the ICU,[9] despite the fact that these DCD donors are included in Kootstra's category 2 (unsuccessful resuscitation). Compared with Kootstra's 1995 Maastricht classification,[7] we have proposed herein to conserve the categories 1 to 4 but to divide them into a series of clinical situations. In addition, category 5 namely, DCD after medically assisted death, is added, since this category has clearly separate ethical and legal issues from those in categories 1 to 4.

As proposed by Fondevila,[10] category 1 (dead on arrival) may be divided into subcategories; 1A if there was no witness to the cardio-vascular arrest versus 1B, if the cardio-vascular arrest was witnessed and the potential DCD underwent some kind of unsuccessful resuscitation.

Kootstra's category 2 (unsuccessful resuscitation) includes rapid but failed attempts of in-hospital resuscitation. As the Spanish experience has reported significantly worse results in kidney transplantation from category-2 DCD occurring in patients hospitalized in the ICU,[9] we propose to divide the category into 2A (unexpected cardio-circulatory death in ICU) versus 2B (unexpected cardio-circulatory death in hospital including emergency room or ward).

Table 5.3. Modified DCD categories

Proposed adapted categories	Proposed definition	Controlled - Uncontrolled
1A	Cardio-circulatory death outside hospital without witnesses	Totally uncontrolled
1B	Cardio-circulatory death outside hospital with witnesses and rapid resuscitation attempt	Uncontrolled
2A	Unexpected cardio-circulatory death in ICU	Uncontrolled
2B	Unexpected cardio-circulatory death in hospital (ER or ward), with witnesses and rapid resuscitation attempt	Uncontrolled
3A	Expected cardio-circulatory death in ICU	Controlled
3B	Expected cardio-circulatory death in OR (withdrawal phase >30 min)	Controlled
3C	Expected cardio-circulatory death in OR (withdrawal phase ≤30 min)	Highly controlled
4A	Unexpected cardio-circulatory arrest in a brain-dead donor (in ICU)	Uncontrolled
4B	Expected cardio-circulatory arrest in a brain-dead donor (in OR or ICU)	Highly controlled
5A	Medically assisted cardio-circulatory death in ICU or ward	Controlled
5B	Medically assisted cardio-circulatory death in OR	Highly controlled

ICU: intensive care unit, ER: emergency department, OR: operating room.

In Maastricht category 3 (awaiting cardiac arrest), DCD procurement is a medically planned, controlled procedure in an ICU patient with a dreadful neurological prognosis, in whom further medical treatment is deemed futile.[196] WI and CI are precisely monitored and minimized. Category 3 represents a numerically significant source of transplantable kidneys, livers, pancreata, and lungs. Even cardiac procurement may be considered in this category 3.[88] But all categories 3 are not comparable in terms of ischemic insults to various organs. The WI may vary considerably according to the place and way in which one performs the withdrawal. If it is performed in the ICU, even with a double-lumen catheter,[47] the WI may be prolonged, as there is no efficient cooling of the body or topical application to the abdominal organs in

most cases; furthermore, the donor must be transported to the OR for the DCD procedure. We propose to name this category 3A (**Table 5.3**). When support withdrawal is performed in the OR among category-3 DCD, the procurement is performed within minutes after the declaration of death, using a rapid laparotomy technique. However, the period between support withdrawal and cardio-vascular arrest, the so-called "withdrawal phase" may vary considerably.[30] Moreover, some category-3 DCD donors display rapid respiratory and cardiac arrest due to a lack of spontaneous breathing due to destruction of the brain stem respiratory center or to partial or total suppression of its function by withdrawal of support.[15,68] The authors propose to separate these category-3 DCD OR donors into two groups: category 3B in whom the withdrawal phase is longer than 30 minutes versus category 3C in whom this phase in less than 30 minutes. It is possible that these categories 3C, highly controlled DCD donors may yield excellent liver, pancreas, or even heart grafts.

The Maastricht category-4 DCD of cardiac arrest while awaiting brain death is different in Western and Eastern countries. In Western countries, most category-4 DCD donors are brain-dead organ donors with unexpected and uncontrolled cardiac arrest after unsuccessful resuscitation. They mostly occur in the ICU during the preparation for DBD organ donation. Indeed the death of these donors is declared because of brain death and not of cardio-circulatory failure. This category does not require a "stand-off period." These donors may be urgently transported to the OR for organ procurement but their WI is usually long. We propose to classify these DCD donors as category 4A to differentiate them from the Eastern countries category-4B DCD donors. In Eastern countries, such as Japan,[468] and many Muslim nations, the concept of brain death is not widely accepted for cultural and/or religious reasons. Brain-dead donors may be transported to the OR for organ procurement after controlled respiratory support withdrawal. These highly controlled DCD donors might be a potential source of all transplantable organs. The category 4B DCD donation may also be (rarely) performed in Western countries if the family does not rely on the brain-death diagnosis and requests a controlled DCD donation.[311]

In addition to the four Maastricht categories defined in 1995, we propose to add a fifth DCD category, corresponding to organ donation after medically assisted death or euthanasia. As explained above, euthanasia was legally approved in a few countries. In Belgium, some individuals who had euthanasia expressed their willingness to have their organs procured after death. The authors propose to name these donations category 5 (**Table 5.3**), as they cannot be included in the Maastricht 1995 classification. Most patients who require euthanasia in

Belgium and in the Netherlands are cancer patients who clearly are not candidates for DCD donation. But a small proportion of these cases are patients with severe, stable neurological deficits, whose medical affectation cannot be transmitted through organ donation. These patients are potential DCD donors. Most euthanasias are performed at home by the regular family physician, but DCD donation after euthanasia requires one to perform the euthanasia in an OR (or in a preparation room close to the OR to allow the presence of the family at the time of death), in an ICU or in the ward, if requested by the patient and/or the family. In this condition, the authors propose to consider category 5A as medically assisted cardio-circulatory death in the ICU or ward with the donor rapidly transported to the OR after the death diagnosis. If the euthanasia is performed in the OR, the authors propose to name this DCD category 5B (**Table 5.3**).

Clinical interests of this adapted classification

The original Kootstra 1995 Maastricht classification separated DCD into four clear situations with common ethical and legal implications. This classification is still useful; the authors have herein added a category 5, which also has clearly different ethical and legal issues. However, as it is of primary importance to more precisely analyze clinical DCD results in the literature, the authors propose that the adaptation described herein presents important clinical issues.

Table 5.4 shows categories 2A, 3 (3A, 3B, 3C), and 4 in which the donor subjects may have experienced severe cerebral damage due to long ICU stays that may impair short- or long-term graft function.[238,239] In particular, this was the reported cause of inferior results of DCD kidney transplantation from category 2A donors.[9] **Table 5.4** presents possible WI to be expected in various situations. Total WI is defined as the period between the first cardiac arrest and the organ flush for uncontrolled DCD, and from withdrawal of support to organ flushing for controlled DCD. In controlled DCD (categories 3, 4B, and 5), CI may be reduced by hospital admission and/or surgical preparation of the recipient. CI may also be reduced in uncontrolled DCD situations by allocation of the DCD graft to a hospitalized potential recipient. All of these DCD categories may lead to different clinical results of transplantation.

Although this classification is more complicated, it is more complete than the 1995 Kootstra classification, while maintaining the same basic categories 1 to 4 (adding a fifth) that are now well-known and accepted criteria. Each category was divided into two or three subcategories: subcategory A is linked to longer WI (and worse results) than subcategory B;

and B versus C, respectively. In addition, subcategories A (2A, 3A, 4A, and 5A) are mostly linked to DCD processes occurring in the ICU, which helps to understand and memorize this classification (**Table 5.3**). Moreover, by keeping the original skeleton of the 1995 classification, space is left to add new subcategories in the future, if deemed clinically relevant. For example, category 1B (cardio-circulatory death outside hospital with witnesses and rapid resuscitation attempt) could one day be separated into 1B (resuscitation with human external massage and ventilation) versus 1C (resuscitation with mechanical reanimation as the cardio-compressor) versus 1D (resuscitation with ECMO), if clinically required by groups with the largest experience in this field.[147,469]

Table 5.4. Clinical differences according to the modified DCD categories, and some literature references reporting clinical use of these DCD organs in clinical transplantation

Categories	Proposed definition	Brain damage	ICU stay	Total WI	Kidney	Liver
1A	CCD outside hospital without witnesses	no	no	unknown	-	-
1B	CCD outside hospital with witnesses and rapid resuscitation attempt	no	no	long	[45]	[461]
2A	Unexpected CCD in ICU	variable	yes	long	[9]	[317]
2B	Unexpected CCD in ER or ward, with witnesses and rapid resuscitation attempt	no	no	long	[9]	[317]
3A	Expected CCD in ICU	yes	yes	>60min	[47]	[144]
3B	Expected CCD in OR (withdrawal phase >30 min)	yes	yes	>40 min	-	-
3C	Expected CCD in OR (withdrawal phase ≤30 min)	yes	yes	≤40 min	[91]	[175,240]
4A	Unexpected CCA in a brain-dead donor (in ICU)	yes	yes	long	-	[303]
4B	Expected CCA in a brain-dead donor (in OR or ICU)	yes	yes	≤40 min	[91]	[311]
5A	Medically assisted CCD in ICU or ward	no	no	≤40 min	-	-
5B	Medically assisted CCD in OR	no	no	≤20 min	[12,231]	[12,231]

CCD: cardio-circulatory death, CCA: cardio-circulatory arrest

Conclusion

Despite higher complication rates due to procurement WI, DCD organ transplantation is increasing. It will expand even further in the future, as a partial means to overcome the donor shortage. The original DCD categories were efficient to expand this type of procurement, but a more complete categorization is now needed to define the various situations and to compare the clinical results encountered among different clinical groups and countries with active DCD programs. We have presented modifications of the Maastricht classification that may be helpful in this matter and may be further modified in the future according to ongoing experiences as this field continues to progress.

6

Discussion and Future Prospects

6.1. Does the DCD source really contribute to the DD pool in Liège and Belgium? *(chapters 2.1 and 2.2)*

Before incorporating the potential of a DCD pool, it is important to emphasize that the goal of DCD transplantation is to increase the organ pool and decrease the patient death on the waiting list (urgently for vital organs), but not to obtain better herein or increase graft and patient survival.[470] During ten-year period (2002 - 2011), 71 cDCD procedures have been performed in Liège among 135 DCD referrals, supplying 176 organs for transplantation (including 62 livers, 104 kidneys, and 10 lungs) in addition to 1 liver and 1 pancreas for hepatocyte and islet preparation, and 43 hearts for homograft valve preparation and cryopreservation. On average, cDCD donors contributed 20.5% of the overall DD pool over 10 years and up to one-third of the yearly DD pool since 2009. In the same time period, the absolute number of DBD procurements slightly increased, translating into an increased number of DD organ retrievals and kidney and liver transplants.

In contrast, analyses on the DCD activity in Belgium during the same period (2000-2009) demonstrated although the number of DCD procurements, DCD kidney and liver transplants increased steadily over time, particularly from the year 2005 onward, there is no major rise in the Belgian DD donation and transplantation activity. In other words, some kind of donor-type redistribution within the DD pool might occur. Consequences of this possibility might be extremely worrisome because (i) total DD transplant activity will not be increasing due to the fact that DCD donors do not yield as many other organs besides kidneys as seen with traditional DBD counterparts; (ii) furthermore, transplant outcomes from DCD and DBD are not generally equivalent with regard to initial graft function, long-term complications and graft survival. Brook warned that the concentration of effort and resources on DCD may have resulted in a decline in the transplant rate from other, possibly better quality, sources.[79] Therefore, only when the contribution of this category of donors leads to an increase in the total number of DD pool available - and not to a 'substitution' - should its potential be considered.[80]

The alarming phenomenon of donor-type shift was firstly mentioned at the center level in the early 2000s, and then confirmed at the national level in some countries with active cDCD programs like the Netherlands and the UK. Several hypotheses have been suggested to explain the changing pattern of donation to a greater proportion of DCD: (i) improved road safety with a marked reduction in traumatic deaths; (ii) changes in neuro-surgical practice (de-compressive craniotomy and interventional radiology) that may delay or even prevent the

development of brain death after neurological disasters, and thus less patients fulfill brain-dead criteria;[75] (iii) donor family's choice between a cDCD and a DBD procedure with greater adoption of DCD to avoid unnecessary prolonged suffering for patients and families in case of unrecoverable neurological damage;[75] (iv) high pressure on the ICU bed triggering an eagerness among intensive care professionals to initiate a DCD procedure as soon as possible, rather than to wait up a brain-dead and heart-beating donation;[239] and (v) probably the limited intensive care resources making DCD the only or the main possibility of transplantation practices from DD and the way of progressing to self-sufficiency in transplantation.[19] Indeed, any suggestion that treatments should be continued primarily to promote the potential for DBD are likely to be met with considerable professional caution and resistance.[81]

In order to verify whether potential donors with irreversible catastrophic neurological injury are prematurely referred as DCD, before brain death has occurred, Saidi did examine the time intervals from hospital admission to organ recovery and from referral to organ recovery, and found no difference between cDCD and DBD groups, therefore eliciting the cDCD process is not moving more quickly and circumvents the brain death diagnosis.[75] We have recently conducted a similar analysis and the results were in line with Saidi's study (D. Ledoux, personal communication).

Obviously, cDCD might in fact jeopardize the practice of DBD. To effectively increase the DD pool without compromising the excellent results of transplantation, and without competing with DBD source, cDCD should be ideally reserved only to donors who have critical, irreversible brain injuries but who will never progress to brain death, and thus will never meet the neurological criteria for death diagnosis. cDCD should not be viewed as an option for clinical staff and families to support donation without the need for lengthy neurological evaluations and subsequent donor optimization.[16] The attending physicians and ICU care teams, as well as donors' family should be clearly explained on the differences between DBD and cDCD in terms of the quantity and quality of organs that can be transplanted from each type of donor.[471] When progression to brain death might occur if more time is allowed, it should be encouraged to maximize the opportunity of organ transplantation after brain death.

6.2. Is the use of DCD in Liège and Belgium worth the effort in terms of kidney and liver transplant outcomes in comparison with those from DBD in the literature?

Results of DCD-KT in Liège and Belgium (*chapters 2.2, 3.1 and 3.2*)

cDCD-KT program was initiated in Liège since 2005. During seven-year period (2005 - 2011), 80 DCD-KT have been undertaken, accounting for 24.2% of the DD kidney pool. The number of DCD kidney grafts increased steadily over time and comprised up to one-third of the yearly DD kidney pool since 2009. Overall and death-censored graft survival rates were 89.5% and 93.7% at 1 year, 85% and 90.8% at 3 years, and 81.3% and 90.8% at 5 years, respectively. Patient survival rates at 1, 3 and 5 years were 93.3%, 91.4% and 87.6%, respectively. No PNF grafts were observed. The DGF rate was 35.5%. The occurrence of DGF did not adversely influence graft survival, but did prolong the length of hospital stay.

In Belgium, the DCD-KT program was introduced in 2000. During ten-year period (2000 - 2009), 287 DCD-KT were performed (93% from cDCD and 7% from uDCD), comprising 7.4% of the DD kidney pool. Between 2000 and 2005, only 1.5% (range: 0.75 - 4.25%) of all transplanted DD kidneys originated from DCD, but from 2006 to 2009, this number increased to 16% (range: 12 - 16.5%). Death-censored graft survival rates at 1, 3 and 5 years were 95%, 91% and 86%, respectively. Patient survival rates at the corresponding time points were 97%, 94%, 87%, respectively. PNF occurred in 1% and DGF in 31% of cases. Machine-perfused kidneys experienced a numerically 9% lower DGF rate compared with cold-stored kidneys (27% vs 36%, $p = 0.07$). DGF rate in uDCD was higher compared with cDCD (65% vs 28.5%, $p = 0.001$); however, PNF rates were similar (0% vs 1%). Five-year patient and death-censored graft survival of uDCD were similar to cDCD (85% vs 93%, and 94% vs 95%, respectively).

Results of DCD-LT in Liège and Belgium (chapters 4.1 and 4.2)

cDCD-LT program in Liège was commenced in 2003. During nine-year period (2003 - 2011), there have been 56 DCD-LT, constituting 22.1% of the DD liver pool. DCD-LT activity increased rapidly over time and since 2009, made up more than one-third of the yearly DD liver pool. Global and death-censored graft survival was 92.6% and 92.6% at 1 year, 73.8% and 87.7% at 3 years, and 60% and 87.7% at 5 years. Patient survival at the corresponding time points was 92.6% at 1 year, 73.8% at 3 years and 60% at 5 years. Biliary complications were encountered in 14.3% of patients. There was no intra-hepatic bile duct stricture, no re-transplantation and no PNF.

The first Belgian DCD-LT were performed in 2003, following the successful development of DCD-KT in 2000. During seven-year period (2003 -2009), 111 DCD-LT

have been done, making up 6.7% of the DD liver pool. The number of DCD-LT also increased rapidly over time, and since 2009 contributed up to 20% of the yearly DD liver pool. Overall and death-censored graft survival rates were 80.1% and 84.5% at 1 year, 64.9% and 78.3% at 3 years, and 60.4% and 72.9% at 5 years, respectively. Patient survival rate was 88.3% at 1 year, 74.4% at 3 years, and 70% at 5 years, respectively. PNF rate was 4.5% (5 patients). 33.3% of patients developed biliary complications with ITBL encountered in 12.6%. 11.7% patients underwent re-transplantation for PNF, hepatic artery thrombosis, and intractable biliary stenoses.

Medical aspects of organ transplantation from DCD

Liège's experience in using cDCD donor source for KT is comparable to the national level in Belgium and does not differ from the general results in the world. DCD-KT resulted in good early graft function and excellent medium-term outcomes. The relatively low rate of DGF in Liège was essentially attributed to the short warm and cold ischemia times, and rather favorable donor factors (young age and few co-morbidities). DCD kidneys were routinely cold-stored in Liège. 13.7% were machine-perfused in the context of a Eurotransplant randomized controlled trial about the efficacy of HMP over SCS, and had less DGF than the cold-stored group (27.3% vs 36.9%), even the difference did not attain statistical significance.

In this Eurotransplant trial, HMP was shown to reduce the risk and severity of DGF and to improve one-year graft survival in all DD kidney types, and its benefit was greater when kidneys are more vulnerable to DGF (i.e. marginal kidneys: ECD and DCD).[51] However, the graft-survival advantage after HMP disappeared in the DCD subgroup after three-year follow-up, although remained significant in DBD and especially ECD kidneys, advocating a different mechanism of DGF in DCD compared to DBD kidneys.[472] To be beneficial from the machine effect, it has been suggested that kidneys should probably be pumped immediately following procurement until transplantation.[216,217] Immediate or delayed HMP requires further investigation because of its important logistical consequences.

It is worth noting that organs that have already subjected to warm ischemic injury have an increased susceptibility to damage during cold storage. The use of these marginal organs further stresses the importance of avoiding prolonged CIT without any appropriate medical reasons. CIT is subject to manipulation by the organ-sharing system and is the most modifiable factor. Many factors contribute to the cold storage time and include the distance between the procurement and transplant centers, organ transport system, weather,

communication between the donor and recipient surgical teams, the availability of the recipient and the OR, and the potential reallocation of organs for alternative patients...[473,474] Shortening CIT helps to improve graft survival and reduce costs in the early post-transplant period.[475]

In every transplantation from DCD, we make efforts to keep CIT <18 hr for kidneys and <6 hr for livers. Liège data demonstrated that for kidneys, mean CIT was 722 ± 279 min, 92% and 50% of the kidney grafts had the length of preservation time <18 hr and <12 hr, respectively; for livers, mean CIT was 265.6 ± 85.1 min, 87.5% and 44.6% of the liver grafts had the duration of cold storage <6 hr and <4 hr, respectively. Recipients are required to get to the hospital early before the scheduled time of organ arrival (or the planned withdrawal of donor life support) for the evaluation of medical status, dialysis requirement, anaesthesia examination, and possible surgical preparation. Transplantation usually starts upon the arrival of organs, even during the night. In DCD-LT, two teams of surgeons perform the donor and recipient operations virtually simultaneously. Upon declaration of death and after satisfactory hepatic visualization in the donor (weight, physical characteristics, perfusion quality, the presence of fatty change, and wedge biopsy), the second surgical team begins the recipient operation. We tend to reserve DCD liver grafts for uncomplicated cases by avoiding cases with extensive history of abdominal surgery or portal-vein thrombosis, re-transplantation, or combined organ transplantation, and livers are implanted in orthotopic position with standard or modified piggyback technique. The current Eurotransplant ‘center-driven allocation policy’ for DCD liver grafts further reduce the ischemia time and facilitates the better donor-recipient matching.

In some countries (the UK, France and Spain), DCD kidneys are locally attributed to patients on the waiting list of the center that has made the retrieval. This policy aims not only to minimize the CIT but also to encourage new DCD programs. Some transplant centers are prone to distribute these kidneys to low and non-sensitized recipients; hence, the necessity for a pre-transplant cross-match is obviated, which may shorten the CIT.[66,263] Moreover, the increased immunologic reactivity of sensitized and/or re-grafted recipients may compound the ischemic endothelial injury that up-regulates immunogenicity, thereby leading to increased early rejection activity that frequently goes undetected.[112] The Eurotransplant Senior Program allocates older donor grafts preferably to older recipients and omits HLA-typing in order to limit CIT.[476]

A welcome but unexpected finding in Liège's experience was the complete absence of PNF in DCD kidneys. PNF is a consequence of ischemic cortical necrosis and its absence may reflect the relatively short WIT (mean: 20.7 ± 7.5 min) incurred by kidneys from cDCD. In Liège policy, volatile anesthetics are administered for the purpose of confort therapy in an end-of-life patient given its pharmacological pre-conditioning effect and its analgesic and hypnotic properties. The ventilator switch-off in sedated DCD donors shortens the dying process. WLST takes place in the OR with the retrieval surgical team already in place to immediately perform laparotomy and directly cannulate the aorta after five-minute no-touch period and death declaration. Topical cooling by chilled physiological saline and crushed ice was promptly undertaken. The donor intervention is generally under experienced surgeons' responsibility. The experience of the attending recovery team play a crucial role because minimizing WIT demands rapid cold perfusion of the organs, and then swift but careful dissection to remove the transplantable organs in a cold bloodless field without injuring organ vasculature, especially aberrant vessels. Our protocol follows closely the recommendations of the American Society of Transplant Surgeons in which *acceptable total WIT*, defined as the time interval between WLST and initiation of cold perfusion, *should be <30-45 min for livers and <45-60 min for kidneys*; and *desirable true WIT*, defined as the time interval between significant ischemic insult after WLST (mean arterial pressure <60 mmHg or systolic blood pressure <50 mmHg) and initiation of cold perfusion, *should be <20-30 min for livers and <30-45 min for kidneys*.[15] Thus, no extra-renal organs will be used if the donors develop >15 min of hypotension prior to death declaration. A few centers use pre-mortem cannulation in conjunction with immediate post-mortem perfusion during the interval between death pronouncement and organ procurement, further facilitating unhurried organ procurement and possibly improving graft function.[147]

Apart from the criteria of WIT, DCD donors must meet identical standards to those used for selecting organs from DBD donors. In Liège, the upper age limit for kidney donation is set at 65 years, which is the age limit under the Eurotransplant protocol, but no age restriction in case of liver donation provided that there are no other associated risk factors (i.e. prolonged CIT, abnormal liver function tests, abnormal histological examination like steatosis or fibrosis). Donor age is limited to 55 years in France and Spain,[78,477] and 60 years in other countries because of the fear that the additional ischemic insult, when allied to an already marginal organ, will result in very poor transplant outcomes.[41] Consequently, ECD donors are often not considered for DCD.

Contrary to the favorable results of KT using older donors in living and heart-beating settings, KT using non-heart beating donors older than 65 years was associated with unacceptable clinical outcomes that can be considered below the standards for KT at the time (5-year overall graft survival of more than 60%).[291,478] Older kidneys suffer more IRI than younger kidneys, probably due to reduced functional nephron mass, atherosclerotic lesions and reduced regenerative capacity associated with greater age.[479] Therefore, the use of elderly DCD donors in order to increase the donor pool cannot be justified without the guidance of histological assessment of pre-transplant biopsies.[480] Limiting the cut-off donor age to 65 might also improve the discard rate.[199]

Preliminary results at our institute using older DCD liver donors (age ranging from 56 to 79 years) did not show any difference in early graft function, biliary complications, and graft and patient survival after one-year follow-up in comparison with the younger group.[481] A recent study comparing standard and extended criteria cDCD livers also found equivalent early transplant outcomes with a follow-up duration of 18.5 – 25 months. Advanced age (>60 years), higher BMI (>30 kg/m^2), longer true WIT (>30 min, time interval between MAP <50 mmHg or oxygen saturation < 80% and initiation of cold perfusion) and CIT (>8 hr) alone should not be an absolute contra-indication to LT with cDCD grafts, provided the recipients are selected carefully to avoid accumulation of other risk factors.[28]

Liège experience in DCD-LT is also as good and promising as that in DCD-KT. We showed that cDCD is really an additional source of transplantable liver grafts and transplant outcomes were apparently as good as those from DBD-LT. The absence of PNF and intra-hepatic biliary stricture at out center was the evidence of relatively short warm and cold ischemia times as aforementioned. Additionally, in accordance with the recipient selection criteria published by highly experienced transplant centers[60] and register data,[57-59] we preferentially offered DCD liver grafts to low risk patients (low MELD scores) and patients with hepato-cellular carcinoma beyond the Milan criteria.

An overview of the results of DCD-LT over the past two decades in the world revealed inferior graft and patient survival and higher risks of biliary complications and re-transplantation than DBD-LT, although comparable or equivalent results have been sporadically reported in select centers through careful donor and recipient selection and optimization of CIT, or through invasive techniques designed to optimize recovery before declaration of death. Nonetheless, we believe that even if graft or/and patient survival is lower with a DCD liver, it is better than dying because of turning down a DCD offer and continuing

to wait for a DBD liver on these days, as the patient's choice is frequently not between marginal livers (including DCD) and standard livers but between marginal livers and no livers.[94] The benefit of earlier access to LT provided by a DCD graft could outweigh the risks of prolonged waiting for a standard graft.[95]

Technical and logistical aspects of organ transplantation from DCD

Key considerations in establishing a cDCD program include the outcomes of DCD organs, the potential logistical difficulties relating to the process, and the difficulty in predicting death. The fear of high risks of DGF, PNF and other potential complications is not justified on the basis of good results of cDCD organ transplantation in Liège since the commencement of the program up to now. Therefore, these risks should not be considered as a medical barrier any more with careful donor and recipient selection and matching.

Kidneys from controlled Maastricht category-3 donors generally have a shorter and more predictable WIT than those from uncontrolled Maastricht category-1 and -2 donors, and thus more closely resemble those from the conventional DBD donors.[237] Broad experience in using cDCD kidneys clearly demonstrates that machine perfusion and viability testing is not obligatory for kidneys recovered from cDCD donors, hence simplifying the logistics of organ procurement and cold storage.

It is the policy at our center that withdrawal of multi-organ support occurs during the normal working hours in the OR (with the possibility of disrupting elective or emergency OR activity) and under the supervision of senior anesthesiologists. There are no major problems in getting their support because they closely collaborate with our department and actively take part in the DCD program. Moreover, our surgeons are willing to allow scheduled operating lists to be cancelled in order to make DCD procurement and transplantation, and hospital management is also willing to accept the loss of this other operating room activity.

On average 30-40% of intended DCD do not progress to death in a timely manner after WLST and therefore do not proceed to organ retrieval.[16,75] Reducing the number of 'stood-down' donations would avoid family distress, reduce the burden on hard-pressed ICU staff, and also enable more efficient resource utilization as the organ procurement process is costly and labor-intensive.[16] However, time between therapy withdrawal and cardiac arrest (so-called the withdrawal phase or agonal phase) is beyond the control of the procurement team. To be transplantable, the agonal time must not exceed 1 hr for extra-renal organs,[311 477] but may be extended up to 4-5 hr for kidneys without compromising the transplant outcomes

and increased the number of retrieved cDCD kidneys by 30%.[41] Obviously, it is possible to prolong the agonal time beyond 2 hr provided the retrieved kidneys pass viability assessment using machine perfusion, but the discard rate was high (13% if <2 hr; 33% if >2 – 5 hr and 45% if > 5 hr).[40] DCD kidneys from elderly patients, which are susceptible to ischemic injury, should also be used with caution if agonal times are protracted.[42] Furthermore, the importance of events (hypotension, hypoxia, acidemia) occurring during this time period need to be insisted on.[34,38]

Prolonged agonal time is linked to prolonged donor instability and increased risk of severe organ ischemia. It is labor-intensive and has important logistical consequences, including indefinite reservation of an OR, surgical staff on stand-by and unavailable for other duties, and transport delays.[34] Several factors have been identified as predictors of rapid death following treatment withdrawal.[34] Two predictive tools that have been validated and commonly used in the US are the University of Wisconsin[30] and UNOS scoring systems.[31] A novel predictive score, DCD-N score which incorporates the neurological status of the patient before WLST, has recently been introduced for specific use in neurological patients with catastrophic cerebral damage.[32] Prediction of time to death after WLST on the basis of clinical impression has proven inaccurate.[33] Therefore, improvement of the ability to identify good DCD candidates for donation remains the objective.

Our mean agonal time was 10.5 ± 6.8 min, ranging between 1 and 30 min. We accept this time period up to 60 min for organ donation. The use of volatile anesthetics as analgo-sedation treatment modality helps reduce the length of dying process,[177] ensuring the occurrence of patient death in the OR, and thus avoiding emotional stress, misunderstanding, or even confusion and intense workload due to stand-down for both OR medical staff and families.

Particularities of the DCD program in Liège

As previously presented, DCD activity in Liège was started before an official DCD protocol was established and approved by all interested parties in 2009. Immediately after the issue of this important document, we observed a significant increase in the number of DCD procedures in the following years. So what are the problems for the development of DCD programs in Liège prior to 2009?

When the first organ procurements from cDCD donors occurred in 2002, most of the medical and OR nursing staff was unaware of this procedure. The anesthesiologists on duty

were asked to terminate the patients'end-of-life care with little information about the patients' medical history and the decision-making process on the futility of treatment. They acknowledged feeling uncomfortable with the DCD process as did the OR nursing staff. In 2004, a meeting was held by the representatives of the Hospital Ethics Committee, ICU, and transplant team to inform the peri-operative staff about the procedure and reassure them. At the same time, another meeting between the Department of Anesthesiology and Intensive Care Medicine concluded that end-of-life care should be achieved in the OR by the intensive-care physician in charge of the patient or a willing anesthesiologist. Unfortunately, the involvement of the attending intensive-care physicians did not create a climate of confidence and serenity in the OR as expected. It was therefore decided to proceed to DCD procurements with the personnel knowledgeable about the procedure. Here are 1 of the 3 senior anesthesiologists in charge of the abdominal surgery and transplantation at our department. In the 2 main collaborating hospitals, end-of-life care is provided by one anesthesiologist intensivist invested in this program. However, problems persisted because of the inconsistency in the way of delivery of end-of-life care, death determination… between the 3 anesthesiologists at our center, as well as between collaborating donor hospitals. This lack of consistency induced malaise, unease, questions, or even suspicions in the ancillary medical staff that might limit the acceptance of DCD programs.[177]

Our experience in the implementation of DCD programs emphasizes the need for a detailed protocol, the necessity of extensive discussions among all staff that are likely to be involved in DCD about the ethical, moral, professional, and legal issues surrounding DCD. If a DCD program were to be successful, this would need to be addressed in a manner suitable to all parties involved.[482]

6.3. Could the current Maastricht DCD classification be ameliorated? *(chapter 5)*

As experience increases in parallel with a rapid expansion of the number of DCD retrievals and transplants, subtle differences in the transplant outcome appear as a result of differences in the mode and location of the donor death within the same Maastricht DCD category and of resultant various ischemic insults.[9,10] Furthermore, a new type of DCD with a substantial potential and good quality organs (i.e., DCD after euthanasia) emerged in Belgium and has not yet included in the original Maastricht classification.[232] For all of these reasons, we consider the need to adapt the current DCD classifications.

We conserve the Maastricht categories 1 to 4 but divide them into a series of clinical situations (1A, 1B, 2A, 2B, 3A, 3B, 3C, 4A, and 4B), and add a category 5, namely DCD after medically-assisted death, as this category has separate ethical and legal issues from those in categories 1 to 4. All of these DCD categories may lead to different clinical results of transplantation.

Although this classification is more complicated, it is more complete than the 1995 Maastricht classification, while maintaining the same basic categories 1 to 4 (adding a fifth) that are now well-known and accepted criteria. Each category was divided into two or three sub-categories: sub-category A is linked to longer WI (and worse results) than sub-category B; and B versus C, respectively. In addition, sub-categories A (2A, 3A, 4A, and 5A) are mostly linked to DCD processes occurring in the ICU, which helps to understand and memorize this classification. Moreover, by keeping the original skeleton of the 1995 classification, space is left to add new sub-categories in the future, if deemed clinically relevant.

In conclusion, DCD programs in Liège demonstrated that DCD donors are really an additional source of organs for transplantation. The medium-term transplant outcomes of DCD kidney and liver grafts are as good as those coming from DBD counterparts. These programs have no negative impact on the DBD activity and the public's perception. They partially meet the increasing demand of organs for transplantation and satisfy the request of the donors and/or their family. The use of this alternative donor source justifies the intense efforts and costly investments with regard to the growing number of patients on the waiting list of transplant.

6.4 Future prospects

DCD must progress in two directions: recovery and transplantation of more and different types of organs and improvement of outcomes. We have made evidence the expeditious rise in the number of organs retrieved and transplanted from cDCD in Liège over the past few years despite some impediments. With an active role of the procurement and transplantation coordinators, the full support and unanimity of all interested parties (ICU, Department of Anaesthesiology, operating room staff, Hospital Ethics Committee, Hospital Management Board), a favorable legal framework allowing maximal efforts to stimulate organ donation and transplantation (opting-out, legality of DBD, DCD, and living

donation), and a recent initiative of the GIFT-project about the 'donor facilitators',[221] this trend is likely to be consolidated in the future.

Broad experience of Spanish centers in Maastricht category-2 kidney and liver transplants[17,145] as well as promising results of the US and UK centers in Maastricht category-3 pancreas transplants[66,86,89,483] will certainly guide us for the establishment of similar programs in Liège when more patients are registered on the waiting list and the full potential of DBD is explored.

We acknowledge the beneficial effects of HMP in reducing early graft dysfunction rates and revitalizing marginal kidneys that should have been discarded if HMP were not available. HMP will certainly play a greater role in DCD kidney programs in Liège when donor selection criteria are expanded and more sub-optimal kidneys are accepted. Economic evaluations of HMP versus SCS suggested that the implementation of HMP of all common types of DD kidneys is likely to be cost-effective with lower costs per life-year and reduced costs per QALY (quality-adjusted life-year) compared to SCS.[54,55]

For DCD-LT, the identification of suitable donors (probably Maastricht category-3 DCD donors), better donor and recipient matching (high risk donors to low risk recipients), use of advanced organ preservation techniques (oxygenated hypothermic or normothermic machine perfusion, venous systemic oxygen persufflation), and pharmacological modulation (probably a multi-factorial biologic modulation strategy) could assure equivalent results to DBD-LT and thus expand the DCD donor source.

6.5 Applicability and feasibility of DCD programs in Viet Nam

The first related living donor KT was performed in Viet Nam in 1992. Until December 2010, after nearly 20 years of organ transplantation, there have been 400 kidney and 16 liver transplants mostly from related living donors. Just a few unrelated living donor grafts were accepted (between spouses and samaritan donors). In November 29th, 2006 the Law on Human Tissue and Organ Donation, Procurement and Transplantation was approved by the Vietnamese General Assembly, allowing the retrieval of tissues and organs from DBD donors for therapeutic purposes and scientific research. However, 3 years after the Law took effect on the first of July 2007, only 15 kidneys, 1 liver and 1 heart were retrieved from 8 DBD donors for transplantation and allocated locally for patients on the waiting list of transplant centers. Viet Nam has not yet had a national organ exchange organization.[484]

Estimates about end-stage organ disease patients showed Viet Nam had about 80000 end-stage renal disease (ESRD) patients; the incidence of ESRD was 6400 patients/year (until April 1st 2009, there were 86 million habitants in Viet Nam).[485] Approximately 10% of ESRD patients had access to hemo-dialysis or peritoneal dialysis (HD: 6000 patients, PD: >1000 patients in all over the country).[486] It is estimated that there have been 23000 cirrhosis and liver cancer patients. Alcoholism and virus B hepatitis were common causes of chronic liver disease, and followed by hepato-cellular carcinoma.[487] National statistics on the advanced heart and lung diseases did not exist; however, published data from some large hospitals were considerable [488] National investigation in 2008 demonstrated 5.7% of the population was diabetic in comparison to 2.7% in 2002. The rate of diabetes mellitus was 7.2% in big cities.[489]

Consequences of serious imbalance between the demand for and supply of organs available for transplantation led to a substantial number of patient deaths on the waiting list (no statistic data) and the development of transplant tourism abroad as well as illegal sales of organs. During the period of 1992 - 2005, 157 patients were transplanted in Viet Nam compared to 300 patients going abroad for transplantation.[490] Some suspected sales of organs associated with lethal outcomes have been mentioned by the mass media.[491] Therefore, the use of alternative donor sources other than living donors becomes necessary and urgent to solve the organ shortage in Viet Nam.

Although there has not yet been an audit of the DBD potential in Viet Nam, estimates from large hospitals showed this potential is enormous. At Viet Duc hospital, 800-1000 patients died each year because of traffic, labor or daily life-activity accidents, and about half of them were brain-dead patients.[492] One study at Viet Duc, Bach Mai, and Military No 103 hospitals demonstrated 80% and 20% of brain-dead patients were caused by head trauma and stroke, respectively.[493]

Despite a huge number of potentially ideal DBD donors, few cases proceed to organ procurement. Traditional belief of the Vietnamese people, 'as a man lives, so shall he die', has become the most important barrier to organ donation. The family wants to keep the deceased-donor body whole and intact so the dead person could be re-born perfectly in another world after death.[494] Some people agree to donate their organs while alive, but once dying, their next of kin are unwilling to realize the wishes of their beloved. It is remembered that Vietnamese Law relies on the ‘opting-in’ or ‘required consent’ principle. More concerted efforts at supporting bereaved families in understanding the donation process and in balancing the

emotions of giving the ‘gift of life’ with the perceived ‘sacrifice’ of organ donation may increase the number of families assenting to donation.[199]

Viet Nam has not yet Law on the DCD. Moreover, the current Law prohibits discontinuation of life-support therapy in patients with severe irrevocable neurologic injury and medically-assisted death. Until there are changes in the legislation, the most important and urgent mission now is to explore the huge pool of DBD that is largely underused. We acknowledge that although DCD is not yet feasible in the near future in Viet Nam, when compared to DBD, it helps us to better understand the deleterious impact of brain death on graft quality, the perplexing interaction between innate and adaptive immune system, the consequences of warm ischemia-reperfusion on early graft function, the necessity of better preservation solution and preservation techniques, the complex organization of the procurement and transplantation process, as well as the principles of organ sharing. The success of every deceased donor transplantation programs in Viet Nam could not be possible without these knowledge and experience.

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Summary

Through a series of clinical studies, this thesis aims to clarify the contribution of donation after cardiac death (DCD) to the deceased donor (DD) pool and results of kidney and liver transplantation coming from this donor source in Liège and Belgium. Additionally, an adapted DCD Maastricht classification is also discussed.

Chapters 2.1 and 2.2 summarize the DCD procurement and transplant activity in Liège and Belgium from 2000 to 2009 with an update on data up to 2011. In Liège, DCD really contributes to the DD pool and boosts the transplant activity of the center in both kidneys and livers by on average 30%. By contrast, the steady rise in DCD activity in Belgium does not lead to major increase in the DD donation and transplantation. In other words, some kind of donor-type redistribution within the DD pool might occur.

Chapters 2.2, 3.1, and 3.2 discuss the results of kidney transplantation (KT) from DCD. We demonstrate that Liège's experience is comparable to the national level in Belgium and does not differ from the general results in the world with regard to early graft dysfunction, medium-term graft function, graft and patient survival. The excellent results of DCD-KT are attributed to the relatively short warm and cold ischemia, favorable donor factors, and the role of hypothermic machine perfusion (in Belgian series).

Chapters 4.1, and 4.2 discuss the results of liver transplantation (LT) from DCD. Liège's results are encouraging and apparently as good as those from donation-after-brain-death LT because of short warm and cold ischemia times. Belgian results show an increased incidence of primary non-function and ischemic cholangiopathy which is in agreement with previously published data.

Chapter 5 proposes an adapted DCD Maastricht classification which maintains the original categories 1 to 4 that are now well-known and widely accepted, and adds a fifth category, so-called 'DCD after euthanasia'. Each category is divided into two or three sub-categories: sub-category A is linked to longer warm ischemia (and worse results) than sub-category B; and B versus C, respectively. In addition, sub-categories A (2A, 3A, 4A, and 5A) are mostly linked to DCD processes occurring in the ICU, which helps to understand and memorize this classification. By keeping the original skeleton of the 1995 Maastricht classification, room is left to add new sub-categories in the future, if deemed clinically relevant.

Résumé

Au travers d'une série d'études cliniques, cette thèse a pour objectif d'éclairer sur la contribution de donneurs à coeur arrêté (DCA) à l'accroissement du pool de donneurs décédés (DD) et sur les résultats de la greffe rénale et hépatique àpd de ce type de donneurs à Liège et en Belgique. En outre, une classification adaptée de DCA de Maastricht a été aussi discutée.

Les chapitres 2.1 et 2.2 résument l'activité de prélèvement et transplantation àpd DCA à Liège et en Belgique de 2000 à 2009 avec une mise à jour des données jusqu'à 2011. À Liège, la DCA a contribué au pool de DD et augmenté l'activité de transplantation rénale et hépatique en moyenne de 30%. Au contraire, l'augmentation progressive de l'activité de DCA des autres centres Belges ne conduit pas à une augmentation significative du don et de la transplantation àpd DD. Comme ci, il existait une sorte de redistribution du type de donneur.

Les chapitres 2.2, 3.1 et 3.2 discutent les résultats de la greffe rénale àpd DCA. On montre que l'expérience Liégeoise est comparable au niveau national et international en termes de dysfonction primaire du greffon, de fonction du greffon, de survie du greffon et du patient à moyen-terme. Les excellents résultats de la greffe rénale àpd DCA sont attribués à l'ischémie chaude et froide relativement courte, aux caractères favorables du donneur, et à l'effet bénéfique de la machine de perfusion (en série Belge)

Les chapitres 4.1 et 4.2 discutent les résultats de la greffe hépatique àpd DCA. Les résultats Liégeois sont encourageants et comparables à ceux de la greffe hépatique àpd donneurs en mort cérébrale grâce à l'ischémie chaude et froide relativement courte. Les résultats au niveau des centres Belges montrent cependant une augmentation de l'incidence de non-fonction primaire et de cholangiopathie ischémique, conforme aux données publiées antérieurement.

Le chapitre 5 propose une classification adaptée de DCA de Maastricht qui maintient les catégories originales de 1 à 4 et y additionne une cinquième, sous le nom 'DCA après euthanasie'. Chaque catégorie est subdivisée en deux ou trois sous-catégories: sous-catégorie A est liée au temps de l'ischémie chaude plus longue (et résultats moins bons) que sous-catégorie B, et B versus C, respectivement. En plus, les sous-catégories A (2A, 3A, 4A, and 5A) sont essentiellement liées aux procédures de DCA aux soins intensifs. Grâce au maintien de la structure initiale de la classification de Maastricht (en 1995), les potentialités sont ouvertes pour ajouter de nouvelles sous-catégories à l'avenir, si elles s'avèrent cliniquement justifiées.

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