# Summary, discussion and future perspectives

## SUMMARY, DISCUSSION AND FUTURE PERSPECTIVES

The number of liver transplantations performed globally keeps increasing every year (1). However, due to expansion of the donor pool with grafts from older donors, steatotic grafts, and DCD grafts, the quality of the average liver allograft is at risk. Therefore, transplant surgeons worldwide are trying to find thresholds to use these marginal grafts depending on their risk of postoperative complications, need for retransplantation and recipient mortality. In this thesis we have focused (I) on the additional morbidity and risk assessment in DCD liver transplantation and (II) the increasing development of renal complications due to the use of such DCD and other marginal grafts.

### Comparing outcomes & risk assessment in DCD liver transplantation

**Chapter 2** provides a summary on the evolving use of (Maastricht type III) DCD liver grafts. Due to the additional warm ischemia in the donor, these grafts experience more hepatic IRI (2). Hence, DCD grafts are retrieved with a 'super rapid' surgical technique, speeding up the process to get the liver into the ice box for transport to the recipient (3). Nonetheless, the use of DCD grafts is associated with an increased incidence of specific complications, such as PNF, ITBL and AKI (4–6). This leads to impaired graft and patient survival rates, with previous studies showing mixed results in comparison to DBD grafts (7–11). To limit the risk, most centres have adopted selection criteria for the donors and recipients of DCD grafts, such as a maximum for age and BMI for the donor and relatively low recipient MELD-scores. Several centres have reported their DCD experience using propensity score matching. When DCD grafts were matched to their DBD counterparts by the donor and recipient risk factors, the outcomes of the DCD grafts proved worse compared to the unmatched studies (12–15). The results of these studies reveals the 'real' additional risk of DCD grafts and highlights the importance of careful donor and recipient selection when DCD grafts are used.

Previous studies evaluating the outcomes in DCD liver transplantation mainly assessed patient and graft survival or the development of specific complications, such as ITBL. However, the experience of the patient depends on the sum of all postoperative complications. Until recently, there has not been a method to comprehend all these events and therefore Clavien and colleagues from the Zurich University Hospital have developed the *Comprehensive Complication Index* (16,17). This novel tool combines all postoperative complications according to their Clavien-Dindo into one number, which can be used for comparison of outcomes between groups

(18). In **Chapter 3** we present our comparison study of recipient outcomes after liver transplantation with DCD and DBD grafts using the CCI. Interestingly, the CCI was comparable for recipients in both groups during hospital admission. Yet, after six months DCD recipients had a significantly higher CCI. Recipients of DCD grafts also required more retransplantations in the first six months, but long-term patient survival was comparable for both groups. Recipient BMI, duration of recipient WIT and DCD grafts were identified as risk factors for a complicated postoperative course (CCI >60 after six months). Our CCI >60 threshold has recently been tested in a Canadian transplant cohort of DCD, DBD and living donor grafts (19). Similar to our results, recipients of DCD grafts did not have a higher CCI after hospital discharge, but unfortunately the comparison was not repeated after six months in their study. Benchmarking is the next attempt to improve risk assessment in liver transplantation by the Zurich team. In a multicentre outcome analysis with >2000 low-risk cases, they defined a benchmark for liver transplantation recipients (20). The authors set the Benchmark cut-off for the CCI after six months at 37.2 points, clearly lower than in our DCD cohort (53.4 points). Bearing in mind, this benchmark study consists of recipients with the lowest estimated risks and we feel that it is essential to develop such a benchmark for DCD liver transplantation separately, to determine the best achievable results in this particular group of recipients.

In this context, we aimed to identify the specific period of DWIT that is responsible for the additional hepatic IRI in DCD grafts. Therefore, we analysed the course of the agonal phase during DWIT in **Chapter 4**. There is a wide variance in the duration of the hypoxic and hypotensive agonal phase between donors. In most countries, hypotension (SBP <50 mm Hg) is considered as the start of functional DWIT (21,22). However, based on clinical experience, we hypothesized hypoxia (SpO2 <80%) plays a more important role in the onset of warm ischemia in DCD donors. Our results showed that SpO2 dropped below the threshold after two minutes, compared to nine minutes for blood pressure, resulting in a longer hypoxic agonal phase. Only the length of this hypoxic phase was associated with severity of hepatic IRI, displayed by the peak transaminase levels after the transplant. Furthermore, recipients receiving a DCD graft with a hypoxic agonal phase of more than 13 minutes had more complications assessed with the CCI and 90-day and long-term graft loss. With this study, we are the first highlighting the importance of the early-onset hypoxia during DWIT. There is not much known about the exact pathophysiology of the hepatocyte injury during the agonal phase, but the pathophysiology of hypoxic hepatitis has a similar pattern. Up to 10% of the critically ill patients in ICU with cardiac/respiratory failure or septic shock have clinical signs of hypoxic hepatitis (23). Previously, hypotension was

considered the major contributor to the hepatic injury, but recent studies suggest that hemodynamic mechanisms of hypoxia, such as hypoxemia, dysoxia and hepatic congestion play a more important role, while shock is only present in half of the patients with hypoxic hepatitis (24). It will likely require intensive animal studies with a specific hypoxic and hypotensive agonal phase models to fully understand the pathogenesis of ischemia during this period in DCD donation.

To assist the transplant surgeons in matching the appropriate DCD donor and recipient, we have developed a new prediction model for graft loss in **Chapter 5**: the UK DCD Risk Score. Using the UK national database with more than 1000 DCD liver transplants we calculated this score that consists of the seven strongest predictors (functional DWIT, cold ischemia time, MELD-score, recipient and donor age, donor BMI and retransplantation). The UK DCD risk score had a better predictive value (C-statistic of 0.79) than the known DCD prediction scores from UCLA and King's College Hospital and the new score was validated in a large UNOS-database cohort and the local DCD population in of the Queen Elizabeth Hospital in Birmingham (25,26). The score was divided into three classes: low risk (0-5 points), high risk (6-10 points), and futile (11-27 points) and the new score significantly predicted graft loss caused by PNF or ITBL. The UK DCD Risk Score is easily calculated at the time of liver acceptance and therefore has a great potential to improve the decision making in DCD liver transplantation. Furthermore, by stratifying the risk into three groups, we suggest which donor/recipient combinations will not require additional graft treatment with machine perfusion (low risk), when graft treatment is recommended (high risk), and when the graft should be declined (futile), if no adequate machine perfusion is available.

*Balance of Risk & machine perfusion for DCD grafts*

There is a substantial difference in the approach to DCD liver transplantation between the US and European countries, like the UK and the Netherlands. The percentage DCD grafts of the total deceased donor liver transplants increased significantly to 24% and 30% in 2016 in the UK and the Netherlands, respectively (27,28). In contrast, the total DCD liver transplants in US only increased from 5% in 2006 to 6% in 2016 (29). This is likely the result of the use of more extended criteria DCD donors (older / higher BMI) in the two European countries (21). Furthermore, the UK has a centre allocation for DCD grafts, which enables the transplant surgeon to match DCD grafts to the appropriate recipient (30). Recently, there have been more efforts in US to balance the risk between donor and recipient, so more DCD grafts can be considered for transplantation (31).

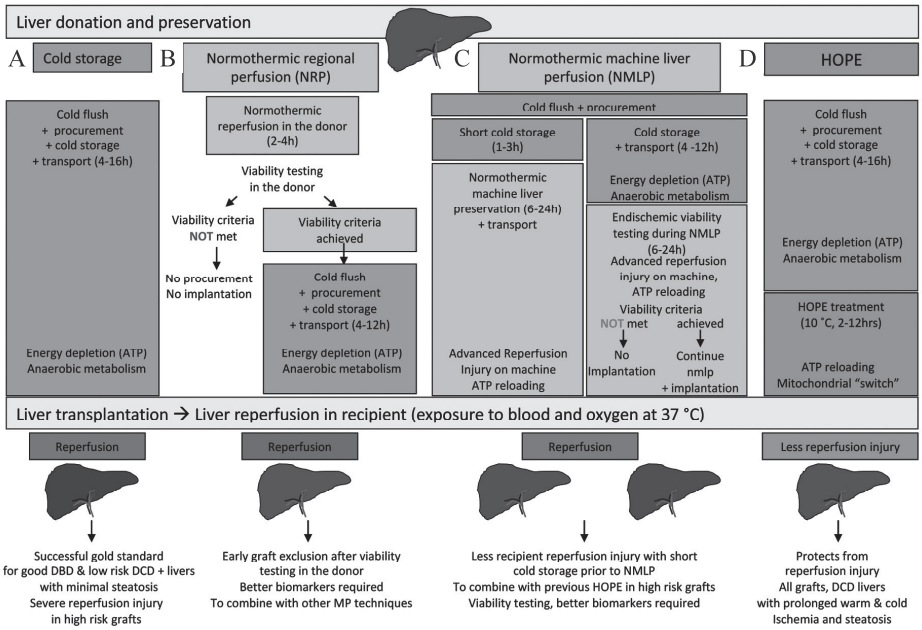


**Figure 1** – Mechanism of protection and injury through the three machine perfusion techniques
From Schlegel et al, Minerva Anestesiologica, 2018 (32).

Due to the marginality of DCD grafts, these organs are one of the main targets of machine perfusion in liver transplantation. Several machine perfusion techniques have been developed over the last years and three are currently tested in the clinical setting (**Figure 1**): (I) normothermic regional perfusion (NRP) in the donor, (II) and the ex-vivo techniques normothermic machine perfusion (NMP), and (III) hypothermic oxygenated machine perfusion (HOPE) (32). During NRP in Maastricht type III donors, an abdominal regional circuit is set up for perfusion through cannulation of the aorta/iliac artery and cross-clamp of the thoracic aorta with the regular super-rapid technique. An additional venous catheter for return of the fluid is inserted in the inferior vena cava. In-situ perfusion follows with donor blood, approximately for 2-3 hours (33). NRP was first introduced in Spain in uncontrolled (Maastricht type II) DCD donors to resuscitate the liver after the cardiac arrest prior to procurement (34). In the series from Barcelona, the one-year graft survival was satisfactory with 73%, but the utilisation of these grafts was only 12% (35). The first reports of NRP in Maastricht type III donors from Spain and the UK showed better results with 80-90% one-year graft survival rates (33,36). However, only 40-50% of the NRP grafts in these series were transplanted, so the assessment of graft function during NRP needs refinement to improve utilisation of these grafts without increasing the risk. In the first

report of NMP in humans (n=20), the grafts were connected to the machine directly after procurement, reducing the period of cold storage to a minimum, where after the grafts are perfused for 10-15 hours (37). The perfused grafts (of whom 4 DCDs) showed lower peak serum transaminase levels compared to matched cold-stored grafts, but no comparable graft survival rates after one-year. A similar Canadian study in a combined DBD/DCD cohort confirmed safety and feasibility of this technique, but did no clear benefit compared to static cold storage (38). Recently, the Consortium for Organ Preservation in Europe presented the results of their randomized controlled trial (39). The most noteworthy outcome of this trial is the lower discard rate of the machine perfused grafts, probably due to surgeon bias of a working organ on a machine, compared to simple cold storage, making a more confident call to use the organ. Also in this study, the peak serum transaminase levels were lower in the perfused group with subsequent lower EAD rates. However, the incidence of the more clinically significant biliary complications and graft and patient survival were similar in the machine perfused and non-machine perfused grafts. To date, there are no reports evaluating the outcomes of NMP-perfused DCD grafts separately.

Both NRP and NMP preservation techniques are relatively labour intensive and logistically challenging, as they require transport of additional equipment and staff to join the organ retrieval team. The end-ischemic HOPE technique is less demanding as the organ can be retrieved in the regular way and will be connected to the machine in the recipient transplant centre and perfused with oxygenated perfusion fluid for 2-3 hours. The Zurich University hospital has the largest experience with DCD grafts using HOPE, as a 10-minute 'no touch' period in DCD donation is imposed by the Swiss national law. This group has shown that the early outcomes of liver function of HOPE-perfused DCD grafts were comparable or better than their matched DBD counterparts from the same centre (40). Furthermore, HOPE has shown to be effective in reducing ITBL, compared to a matched cohort of unperfused DCD grafts from two other European centres, including Erasmus MC (41). The transplant group from Groningen published their initial experience with HOPE last year and the first results from this centre also indicate that HOPE is successful in reducing biliary strictures in DCD grafts (42,43). A multicentre trial comparing the outcomes of HOPE perfused DCD grafts with static cold storage has therefore been initiated in the Netherlands and is currently recruiting patients (NCT02584283).

**The kidneys at risk after liver transplantation**

Renal complications after liver transplantation have become a more serious issue over the last years due to (I) the 'sickest first' allocation of patients on the waiting list,

favouring patients with renal failure and (II) the expanding use of marginal grafts that have more severe hepatic IRI causing additional kidney damage in the early postoperative period (44–46). In **Chapter 6** we summarized the donor, recipient and surgical risk factors for AKI with a focus on the pathogenesis of the impact of graft quality on this complication. Postoperative AKI is associated with increased use of hospital resources and costs, graft loss and mortality (47–50) and recipients with AKI are at risk for developing CKD, especially when they require temporary RRT (51). Similar to AKI, post-transplant CKD has a multifactorial origin and is explained by the three-hit model (52). The first hit for the kidney is subsequent to the liver disease in patients with cirrhosis. Peri-operative events, such as extensive blood loss and reperfusion during the transplant procedure and postoperative complications are responsible for the second hit and finally, the third hit is a chronic process after liver transplant, due to the use of nephrotoxic immunosuppression and new-onset diseases, such as DM.

In **Chapter 7** we analysed the impact of the postreperfusion syndrome on development and severity of AKI after liver transplantation. PRS is the first manifestation of severe hepatic IRI after reperfusion and has previously been linked to severe renal failure with RRT and an increased mortality risk (53). Our findings show that the decrease in blood pressure after reperfusion has a linear relation with both the severity of hepatic IRI and postoperative AKI. Furthermore, if recipients experienced PRS, the odds of developing AKI showed a more than two-fold increase and long-term patient survival decreased significantly with the severity of AKI. Our results were recently confirmed in a large living-donor liver transplantation cohort from Korea (54,55). PRS can be used as an early warning sign for other problems in the early postoperative course and it is being used in the assessment of early graft function in machine perfusion as well (33,39). In addition, biomarkers that are expressed in case of severe reperfusion injury have been linked to postoperative AKI, highlighting the significance of PRS in the development of renal problems after liver transplantation (56,57).

To further explore the comprehensive impact of all the warm ischemia periods in DCD liver transplantation, we introduced a new period of warm ischemia time in **Chapter 8**; the combined WIT. This is the sum of the agonal phase and asystolic phase during DWIT and the recipient WIT. We evaluated the length of this combined WIT and the incidence of severity of AKI after DCD liver transplantation in the two cohort of the Erasmus MC, Rotterdam and the Queen Elizabeth Hospital in Birmingham. In both centres, the duration of combined WIT was associated with severity of AKI and recipients receiving a graft with more than one hour of combined WIT had

a more than two-fold increase in the risk of developing severe AKI. In addition, our results confirmed that recipients with the most severe form of AKI had the worst postoperative outcomes with longer hospital admission and higher retransplantation and mortality rates. The newly defined period of combined WIT could be useful in assessing the risk for other postoperative complications with the use of DCD grafts, such as PNF and ITBL.

Early identification of recipients at risk for post-transplant AKI is required for prevention of this serious complication and we aimed to develop a new prediction model for severe AKI. We choose severe AKI as the endpoint for this score, as this has the strongest relation with other recipient outcomes, described in our previous studies. We feel that the score is of most clinical use if it is available directly at the end of the transplant, so that preventive strategies can be undertaken to minimize further renal damage. The new AKI Prediction Score is presented in **Chapter 9**. Using the well-known Framingham Risk Scheme, we developed an easy-to-use prediction model, consisting of five donor, graft and recipient factors: Donor and recipient BMI, use of a DCD graft, FFP transfusion requirements during the transplant and the duration graft implantation. We identified three risk groups, to stratify the recipients with a low, intermediate and high risk for postoperative severe AKI. In case of an intermediate risk, we suggest a renal sparing immunosuppression protocol is considered (58,59). Early initiation of RRT has been proven to be effective in critically ill patients and therefore we would consider early RRT in high-risk recipients, according to the AKI Prediction Score (60). These potential helpful clinical applications make the new score unique. This is not the first prediction model for post-transplant AKI, but the previous scores did all use postoperative risk factors, including the use of nephrotoxic immunosuppression and postoperative inotrope requirements (61,62).

A logical consequence of the pre-transplant kidney problems in patients with ESLD and AKI in the peri-operative period is development of long-term renal impairment. On average, after 5 years 2% of the recipients is either RRT dependent or has received a kidney transplant. This number can increase up to 11% of the recipients who are still alive after 25 years (63). The evolving use of marginal grafts over the last years and the increasing burden of post-transplant AKI encouraged us to evaluate the impact of marginal grafts and development of CKD (46). In **Chapter 10** we show that recipients of marginal grafts (DCD grafts and marginal DBD grafts [long cold storage, higher BMI, older donors]) do not have an increased risk to develop CKD per se and the incidence of CKD is around 40% for recipients of standard, marginal DBD, and DCD grafts. However, those who experience severe AKI after the trans-

plant and require RRT have a significantly impaired long-term kidney function. Our results showed that recipients with RRT that had an additional complication requiring a reoperation in the early postoperative period were less like to have a full recovery of kidney function on the long-term.

## General conclusion

In **Part I** of this thesis we present the extra morbidity for recipients of DCD grafts with the novel CCI, identify prolonged hypoxia during DCD donation as the driving force of hepatic ischemia and present a new risk score to assist the transplant surgeon in making the decision for the best DCD graft and recipient combination and to help in deciding which graft will require additional therapy, e.g. machine perfusion. The results presented in **Part II** of this thesis highlight the impact of DCD grafts and other marginal grafts on postoperative AKI. Although no direct correlation was observed between these grafts and long-term kidney function, development of severe AKI with RRT-requirement should be avoided at all costs, as those recipients have an increased risk for CKD. Our new AKI Prediction Score could be useful to limit the risk for severe AKI and subsequent development of chronic renal impairment.

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