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DE DOCTEUR EN MEDECINE

Comparaison de l'incidence des syndromes d'ischémie reperfusion et des complications postopératoires précoces en transplantation hépatique entre 2 groupes de receveurs : greffons issus de donneurs en mort circulatoire contrôlée (Maastricht 3) versus greffons issus de donneurs en état de mort encéphalique, une étude rétrospective monocentrique.

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Avertissement

La Faculté n’entend donner aucune approbation aux opinions émises dans les thèses : celles-ci sont propres à leurs auteurs.

Sigles

ABM	Agence de la biomédecine
CRN	Circulation régionale normothermique
cDCD-LT	*Liver transplantation from controlled donation after circulatory death*
DBD-LT	*Liver transplantation from donation after brain death*
DDAC	Donneur décédé après arrêt cardiaque
EME	Etat de mort encéphalique
ERO	Espèces réactives de l'oxygène
etCO$_2$	*End Tidal CO$_2$*
ICU	*Intensive Care Unit*
INR	*International Normalized Ratio*
LATA	Limitation et arrêt des thérapeutiques actives
M3	Maastricht 3
PAM	Pression artérielle moyenne
PRS	Post-reperfusion syndrome
PTP	Pore de transition de perméabilité
ROS	*Reactive oxygen species*
SIR	Syndrome d'ischémie-reperfusion
TH	Transplantation hépatique
WLST	*Withdrawal of Life Sustaining Treatment*

Sommaire

Préambule

Le travail scientifique présenté dans cette thèse de médecine fait l'objet d'une publication d'article international en anglais. Il suit le plan suivant :

- Une introduction longue en français, qui poursuit deux objectifs : présenter le contexte médical avec une orientation principalement pédagogique, et présenter le contexte scientifique et l'objectif, comme le fait également l'introduction de l'article en anglais
- L'abstract en anglais, tel qu'il sera soumis en complément de l'article reproduit juste après.
- L'article en anglais, tel qu'il sera soumis à une revue scientifique internationale. Cet article suit le plan classique, dans le format imposé par le journal (introduction, matériel et méthodes, résultats, discussion)
- Une discussion en français, qui reprend pour l'essentiel la discussion en anglais de l'article

Le document est structuré ainsi en application de la circulaire Toubon[1].

Les références présentées en fin de document, ainsi que les listes de figures et tables, résultent de la fusion des parties en anglais et en français. La numérotation est donc incrémentée dans l'ensemble du document, que les parties soient anglophones ou francophones.

[1] Circulaire du 19 mars 1996 concernant l'application de la loi no 94-665 du 4 août 1994 relative à l'emploi de la langue française. JORF n°68 du 20 mars 1996 page 4258. NOR: PRMX9601403C

Introduction

1 Contexte

1.1 Transplantation hépatique

La transplantation hépatique représente actuellement le traitement curatif de nombreuses pathologies hépatiques en phase terminale. Cependant, le nombre croissant de candidats à la greffe se heurte à une insuffisance de greffons disponibles. Pour pallier cette problématique, un nouveau type de donneur est envisagé : le donneur décédé après arrêt cardiaque (DDAC).

La classification de Maastricht, établie en 1995, a permis de définir 4 catégories de décès après arrêt circulatoire. Elle sépare les décès « non contrôlés » (catégorie I, II et IV), et les morts « contrôlées » (catégorie III):

- Catégorie I : Arrêt circulatoire en dehors d'une prise en charge médicalisée, décédée à la prise en charge
- Catégorie II : Arrêt circulatoire avec mise en œuvre d'une réanimation, mais sans récupération d'une activité circulatoire
- Catégorie III : Arrêt circulatoire après décision de limitation et d'arrêt des thérapeutiques actives
- Catégorie IV : Arrêt circulatoire en cours de prise en charge en réanimation des patients en mort encéphalique.

L'arrêt circulatoire soulève la problématique d'un temps d'ischémie chaude prolongé et mal contrôlé. Pour rappel, l'ischémie chaude correspond à la phase d'absence de circulation efficace, et donc de mal perfusion du greffon (lors d'un arrêt circulatoire ou lors du clampage artériel, avant la conservation hypothermique). Une fois explanté du donneur, le greffon est conservé dans une solution à 4°C. Le temps d'ischémie froide est le délai entre le clampage de l'artère de l'organe, et le déclampage de cette même artère après réalisation des anastomoses.

La catégorie III implique un arrêt des thérapeutiques actives, et donc une mort circulatoire « programmée », ce qui permet de mesurer de manière fiable le temps d'ischémie chaude, et donc d'assurer la qualité du greffon.

Ainsi en France, le prélèvement de foie de donneurs en mort circulatoire est autorisé depuis 2008, de rein depuis 2005, de poumons depuis 2014, et de pancréas depuis 2018.

Dans son rapport de février 2024, l'Agence de la Biomédecine (ABM) rapporte une augmentation de 5,7% de l'activité de prélèvement sur donneurs décédés par rapport à 2022. Les deux tiers de la croissance du nombre de greffes observé entre 2012 et 2019 sont liés à la greffe d'organes issus de donneurs Maastricht III.

1.2 Maastricht 3: protocole national

1.2.1 Donneurs et receveurs

Selon le protocole de l'ABM [1], les donneurs doivent être âgés de moins de 71 ans [2], et l'organe candidat au prélèvement ne doit pas souffrir d'une atteinte aiguë ou chronique.

Les receveurs doivent être inscrits sur liste pour une première greffe, et ne doivent pas être instables sur le plan hémodynamique, afin de ne pas accroître le risque de lésions du greffon qui seraient liées à des anomalies de perfusion. Les greffes HLA incompatibles sont exclues.

1.2.2 LATA

La procédure Maastricht 3 concerne principalement des patients admis dans les suites d'une pathologie avec lésions cérébrales irréversibles, faisant discuter un arrêt des thérapeutiques actives, conformément aux lois Léonetti et Claeys Léonetti [3,4]. La discussion du prélèvement d'organe avec les proches du patient ne doit intervenir qu'après la décision de LATA.

1.2.3 Procédure de prélèvement

La phase agonique s'étend de la mise en œuvre de l'arrêt des thérapeutiques, jusqu'à l'arrêt circulatoire. La phase d'ischémie chaude fonctionnelle débute lorsque la pression artérielle moyenne (PAM) devient inférieure à 45 mmHg. Après l'arrêt

circulatoire, 5 minutes de « no touch » doivent être respectées. Le patient est ensuite déclaré décédé. En France, le prélèvement du foie impose la mise en place d'une circulation régionale normothermique (CRN). Les canules artérielles et veineuses sont posées après la déclaration du décès, et un ballonnet intra-aortique est placé dans l'aorte thoracique, afin d'empêcher la perfusion cérébrale et cardiaque.

En France en 2022, 83% des procédures de LATA ont eu lieu en chambre de réanimation, 14% au bloc opératoire [1].

Dans le cadre du prélèvement hépatique, différents délais maximaux doivent être respectés (la procédure est résumée dans la Figure 1) :

- Phase agonique inférieure à 3 heures.
- Phase d'ischémie chaude fonctionnelle inférieure ou égale à 45 minutes.
- Phase d'asystolie inférieure ou égale à 30 minutes.
- CRN supérieure à 1h
- Ischémie froide inférieure ou égale à 8 heures.

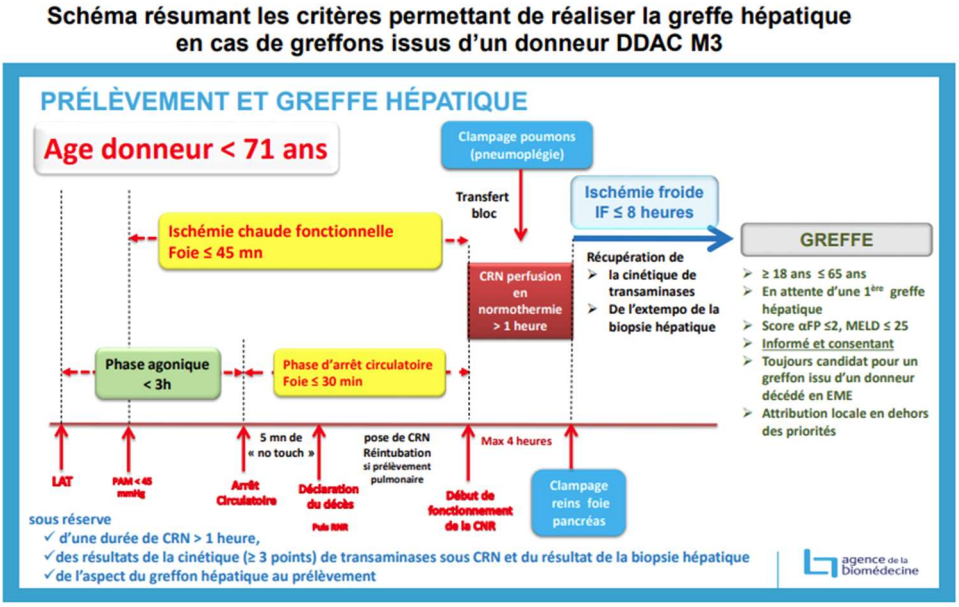

Figure 1. Protocole de prélèvement de foie dans le cadre d'un donneur DDAC, d'après l'ABM [1]

1.3 Donneurs en mort circulatoire versus donneurs en état de mort cérébrale en transplantation hépatique : premiers résultats.

Les premières études comparant la transplantation de greffons hépatiques provenant de donneurs Maastricht 3 (DDAC M3) et de donneurs en état de mort encéphalique (EME) retrouvaient une moindre survie des greffons. En 2008, Selck et al. décrivaient plus de dysfonctions de greffon et de réinscriptions sur liste de greffe dans les 180 jours chez les patients ayant reçu un greffon issu d'une procédure Maastricht 3 [5]. En 2011, Foley et al. retrouvaient une survie significativement plus basse dans le groupe Maastricht 3, ainsi que plus de perte de greffon à 1, 5, 10 et 15 ans [6]. En 2021, une méta-analyse regroupant 13 études ne retrouvait pas de surrisque de mortalité après ajustement sur le biais de publication, en revanche un surrisque de perte de greffon [7]. Une autre méta-analyse s'intéressant à 21 études ne retrouvait pas de différence sur la survie du greffon [8].

La littérature tend à converger sur un surrisque de complications biliaires et de cholangiopathie ischémique [8–14] dans le cas de greffons provenant de DDAC. La cholangiopathie ischémique semble associée à l'âge du donneur, à un temps d'ischémie froide supérieur à 8h [6], et à la durée d'ischémie chaude [15].

Par ailleurs, en 2014, Lee et al. décrivaient également un risque accru de dysfonction précoce de greffon, définie par la présence d'un des critères suivants dans les 7 premiers jours postopératoires: bilirubine ≥ 10 mg/L; INR ≥ 1,6; ASAT/ALAT ≥ 2000 UI/L [16].

Sur le plan physiopathologique, ces complications peuvent être expliquées par le collapsus à l'arrêt des thérapeutiques, responsables d'une hypoxie et de la formation de microthrombi [9]. Par ailleurs, les greffons sont soumis à une période de conservation à 4°C, provoquant des lésions liées à l'hypothermie. Une nouvelle agression se surajoute lors de la réoxygénation à la reperfusion du greffon. L'ensemble de ces lésions s'inscrit dans le processus d'ischémie-reperfusion.

2 Syndrome d'ischémie-reperfusion

2.1 Physiopathologie de l'ischémie-reperfusion

L'ischémie reperfusion est provoquée par la succession d'une obstruction partielle ou complète des vaisseaux sanguins, suivie de la restauration d'un flux sanguin.

L'ischémie est responsable d'une inadéquation entre les apports en oxygène et en substrats énergétiques, et les besoins de la cellule. Du fait de la moindre disponibilité de l'oxygène, le métabolisme aérobie diminue, et la glycolyse anaérobie devient la principale source de production d'ATP. Au cours de la glycolyse anaérobie, la formation de lactate à partir de pyruvate consomme des ions H^+, induisant une surcharge intracellulaire en protons. Du fait de l'acidose intracellulaire, l'échangeur Na^+-H^+ est activé, provoquant une entrée de sodium dans la cellule. Ce flux de sodium active un échangeur Na^+-Ca^+, aboutissant à une surcharge calcique intracellulaire (Figure 2) [17].

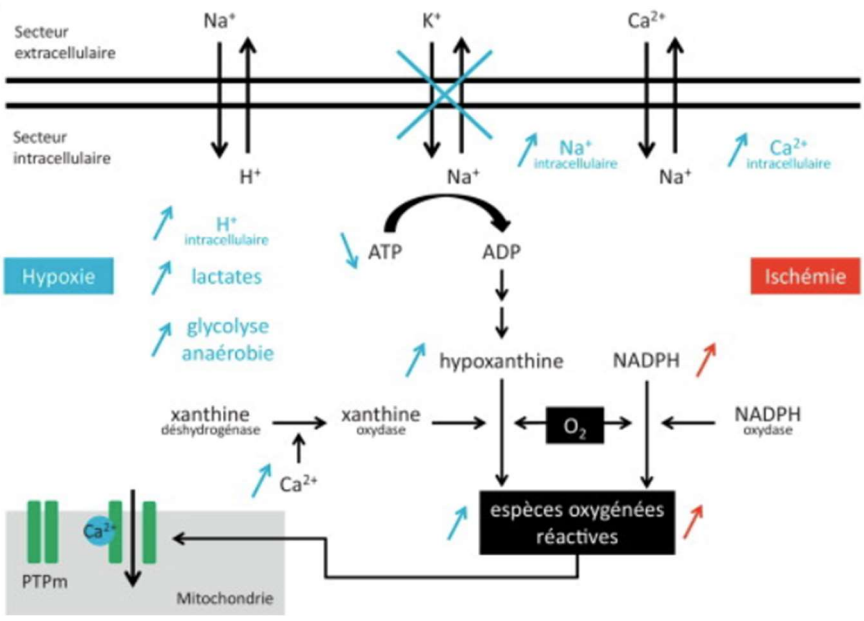

Figure 2. Formation de ROS au cours de l'ischémie-reperfusion, d'après Gennai et al. [17]

Pour rappel, en conditions normales, la membrane mitochondriale interne reste imperméable aux molécules électriquement chargées. Cela permet de maintenir un gradient de concentration de protons entre la matrice mitochondriale et le cytosol. Ce gradient de protons, entretenu par la chaîne respiratoire, permet la synthèse d'ATP. En condition de surcharge calcique, un canal situé sur la membrane interne (appelé pore de transmission de perméabilité, PTP) s'ouvre, entraînant un gonflement

mitochondrial par mouvement osmotique, et aboutissant à la rupture de la membrane externe, ce qui libère des molécules pro-apoptotiques dans le cytosol. Par ailleurs, le cytochrome C, maillon de la chaîne respiratoire situé dans l'espace intermembranaire, quitte cette chaîne et est libéré dans le cytoplasme, empêchant la synthèse d'ATP mitochondriale.

En transplantation, on distingue l'ischémie chaude (à 37°C) et l'ischémie froide (à 4°C). L'hypothermie peut être vue comme un phénomène protecteur, le métabolisme se ralentissant, entraînant une diminution des besoins cellulaires en ATP.

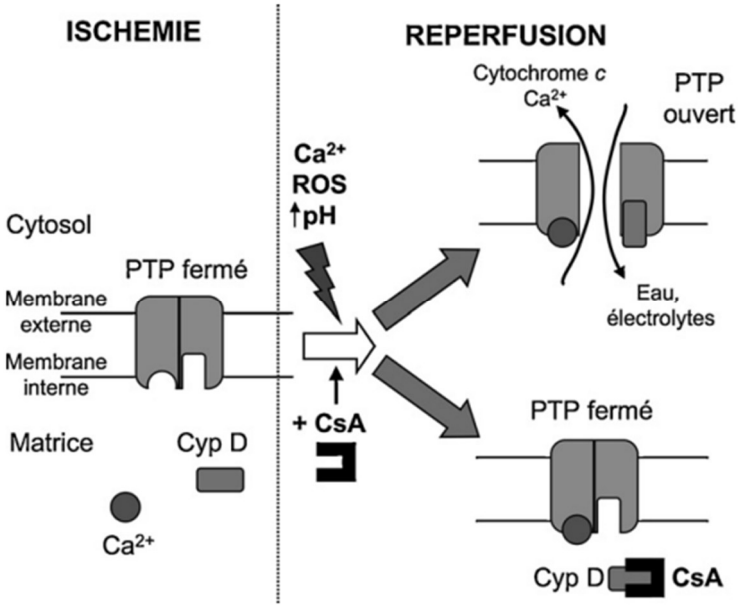

Figure 3. Transition de perméabilité mitochondriale, d'après Cour et Argaud [18].

Lors de la reperfusion, le flux sanguin est restauré, mais des lésions cellulaires peuvent être provoquées par plusieurs mécanismes :

- Génération d'espèces réactives de l'oxygène (ERO): la reperfusion réintroduit brutalement de l'oxygène à des cellules dont la chaîne respiratoire mitochondriale est endommagée. La mitochondrie produit alors des ERO, responsables de réactions oxydatives, notamment la peroxydation lipidique, responsable de lésions des membranes cellulaires.
- Entretien de la surcharge calcique et ouverture du PTP (Figure 2)
- Accumulation du produit de dégradation de l'ATP : l'hypoxanthine, qui participe à la formation d'ERO sous l'effet de la xanthine oxydase (Figure 1).
- Recrutement de macrophages et PNN par les médiateurs inflammatoires accumulés dans les tissus ischémiés

En transplantation hépatique, l'ensemble de ces phénomènes se traduit en pratique clinique par le syndrome d'ischémie-reperfusion, correspondant à une instabilité hémodynamique lors du déclampage de la veine porte.

2.2 Syndrome d'ischémie-reperfusion: définitions

Le syndrome d'ischémie-reperfusion (SIR) en transplantation hépatique est décrit pour la première fois par Aggarwal et al. en 1987, comme un collapsus cardiovasculaire suivant la revascularisation du greffon [19].

Cette instabilité hémodynamique serait causée par le relargage massif de radicaux libres, d'endotoxines et de cytokines inflammatoires. Aggarwal décrit ce phénomène comme une chute de PAM > 30%, durant au moins 1 minute, dans les 5 minutes qui suivent la reperfusion. Hilmi et al. distinguent le SIR « léger » et « significatif » [20] :

- La forme peu sévère est définie comme une chute de PAM ou de fréquence cardiaque de 30% (par rapport à la phase d'anhépatie) pendant moins de 5 minutes. Pour être considérée comme légère, l'instabilité hémodynamique doit répondre à l'injection d'1g de chlorure de calcium en intraveineux, et/ou aux boli d'adrénaline (100µg) sans nécessiter de recourir à une perfusion continue d'agents vasopresseurs.
- La forme sévère correspond à une hypotension persistante (> 30%), une asystolie, ou des troubles du rythme mal tolérés sur le plan hémodynamique ; ou au besoin d'un support vasopresseur en perfusion continue en peropératoire. Cette forme concerne également l'apparition d'une fibrinolyse prolongée (> 30 minutes) ou récurrente (récidivant dans les 30 minutes), nécessitant le recours à des agents antifibrinolytiques.

Plus récemment, Fukazawa et al [21] détaillaient les différentes phases suivant la reperfusion du greffon :

- Phase 1 : les 5 minutes suivant le déclampage de la veine porte. Durant cette phase, on observe une hypotension brutale, menant à l'utilisation de vasopresseurs et de remplissage vasculaire.
- Phase 2 : jusqu'au déclampage de l'artère hépatique. Cette phase est marquée par la diminution progressive de la PAM.

- Phase 3 : de la reperfusion artérielle hépatique jusqu'à 240 minutes après la reperfusion porte.

Les patients développant un syndrome d'ischémie reperfusion avaient une chute significativement plus importante de la pression artérielle en phase 1, et une pression artérielle moyenne plus basse durant la phase 2.

2.3 Syndrome d'ischémie-reperfusion: conséquences

Le SIR est responsable de plusieurs complications :

- Insuffisance rénale aigue [22–27] avec un surrisque d'évolution vers une maladie rénale chronique [23].
- Un risque accru de mortalité péri-opératoire [22,26,28]
- Plus de transfusion de produits sanguins [25,28].
- Des non-fonction primaires de greffon [29]
- Un surrisque de perte de greffon et de nécessité de retransplantation [20].
- Un pic cytolytique plus élevé [24]

Le SIR semble plus fréquent dans le cas des DDAC [30].

Plusieurs facteurs de risque de SIR ont été identifiés, principalement : la durée d'ischémie froide [22,26,28] ; l'âge des donneurs [21,24], la durée opératoire [28], l'absence d'anastomose porto-cave [22], une PVC basse [21].

2.4 Apport de la CRN

Nous avons donc vu que le surrisque de complications postopératoires dans le cas des greffons DDAC semblait être lié à l'ischémie et au syndrome d'ischémie reperfusion.

En France, afin de réduire l'ischémie froide du greffon, l'utilisation d'une circulation régionale normothermique (CRN) est rendue obligatoire dans le cadre du prélèvement hépatique. Cependant, dans de nombreux pays (non européens), le prélèvement d'organe dans le cadre des procédures Maastricht 3 est effectué sans circulation extra corporelle, avec une préservation froide seule. En 2020, Lomero et al. [31] ont réalisé une étude de pratiques sur le territoire européen : parmi les 35 pays interrogés, 18

pratiquaient le prélèvement d'organe dans le cas de DDAC. Une CRN était utilisée dans 8 pays : la Belgique, la France, l'Italie, les Pays-Bas, la Norvège, l'Espagne, la Suisse et le Royaume-Uni. Aux Etats-Unis, une analyse récente commence seulement à acter de la sécurité et de l'efficacité de la CRN [32].

En effet, plusieurs études démontrent une diminution de la mortalité, des complications biliaires, du risque de cholangiopathie ischémique et de perte de greffons grâce à l'utilisation de la CRN chez les DDAC [33–35]. La durée de CRN ne semble pas avoir d'impact sur les complications périopératoires [36].

La circulation régionale normothermique semble donc bel et bien améliorer les résultats des greffes utilisant des transplants issus de donneur en arrêt circulatoire. Après étude de la littérature, nous n'avons toutefois trouvé aucune donnée sur l'évolution de l'incidence du syndrome d'ischémie reperfusion avec l'utilisation d'une circulation régionale normothermique chez les donneurs décédés après un arrêt circulatoire.

3 Objectifs

L'objectif principal de ce travail était d'estimer s'il existe une différence d'incidence du syndrome d'ischémie reperfusion selon le type de greffon en transplantation hépatique : greffons issus d'un donneur en mort circulatoire contrôlée avec CRN, versus greffons issus d'un donneur en mort cérébrale. Les objectifs secondaires étaient de déterminer l'impact du type de greffon et le rôle du syndrome d'ischémie reperfusion sur les complications périopératoires.

Article en Anglais

1 Introduction

Transplantation is currently the curative treatment for many end-stage liver diseases. To overcome the shortage of available grafts in the face of growing demand, donation after circulatory death (DCD) becomes increasingly common throughout the world. In France, DCD liver transplantation has been performed since 2008. Donations after controlled circulatory arrest (cDCD) accounts for two-thirds of the increase in transplants between 2012 and 2019. Early results showed poorer graft survival, more graft dysfunction, and more retransplantation [5]. Some studies even showed excess mortality [6]. Graft dysfunction was mainly due to biliary complications and ischemic cholangiopathy [8–14]. Collapse and circulatory arrest raised concerns of ischemia-reperfusion-induced tissue injury.

During the surgical procedure, this ischemia-reperfusion model translates clinically into hemodynamic instability during portal vein unclamping and graft reperfusion. Post-reperfusion syndrome was first described by Aggarwal et al. as a decrease in Mean Arterial Pressure (MAP) >30% lasting at least one minute within 5 minutes of reperfusion [19]. Post-reperfusion syndrome is responsible for complications: acute kidney injury (AKI) with risk of progression to chronic kidney disease, peri-operative mortality, transfusion, primary graft dysfunction, graft loss, higher transaminases release levels [22–29]. In France, the use of normothermic regional perfusion (NRP) is mandatory, in order to reduce graft ischemia. Several studies have shown a reduction in mortality, biliary complications, risk of ischemic cholangiopathy and graft loss with this perfusion technique [33–35]. However, we could not find any data on the relationship between NRP and post-reperfusion syndrome.

The main objective of this study was to assess whether there is a difference in the incidence of post-reperfusion syndrome (PRS) according to graft type in liver transplantation: liver transplantation from controlled donation after circulatory death (cDCD LT) using NRP versus donation after brain death liver transplantation (DBD-LT). Secondary objectives were to determine the effect of graft type and the role of ischemia-reperfusion syndrome on perioperative outcomes.

2 Patients and methods

Study design

Our study was a monocenter retrospective case-control study. The studied population included patients transplanted in Lille from January 2018 to June 2022. The data on transplanted recipients were collected from “CRISTAL”, the ABM French national database. The retrospective data were extracted from Lille University Hospital health data warehouse (Include project). Through this data warehouse, the per operative data were collected from the anaesthesia information management systems (AIMS) DIANE® (Bow medical, France). Follow up data were obtained from the hospital information system SILLAGE® (SIB, France) until one year after the transplantation. The study followed the STROBE recommendation.

cDCD Protocol and NRP technique

Surgical techniques were performed according to the center practice. The liver recovery during the Maastricht 3 procedure followed the ABM protocol. To qualify for a Maastricht 3 procedure, donors had to be < 71 years old, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) had to be <4N before the withdrawal of life sustaining treatment (WLST) and during the NRP procedure. The preimplantary biopsy had to show steatosis ≤ 20% and a fibrosis stage < F2.

After the patient’s death was established, arterial and venous cannulae were placed. Eventually, the lines were placed one day before the circulatory arrest. The NRP had to last between 60 minutes and 4 hours. The following terms were defined according to the ABM guidelines: warm ischemia time (WIT, time between life support withdrawal and the start of NRP); functional warm ischemia time (fWIT, when organ perfusion reaches a critical point with a MAP ≤ 45 mmHg until the start of NRP); agonal phase (time from withdrawal of ventilation to the absence of spontaneous respiration and circulation); asystolic phase; cold ischemia time (CIT, time during which organs were preserved in a hypothermic state or in static storage, or under hypothermic perfusion). The liver could be transplanted if fWIT was ≤ 45 minutes and time to circulatory arrest ≤ 30 minutes.

Patients

The inclusion criteria were patients aged 18 to 65 years awaiting their first liver transplantation, with a MELD score strictly below 26. Patients were excluded if they had complete portal thrombosis, hemodynamic instability, split transplantation, super-emergency transplantation, or combined transplantation.

Baseline characteristics included gender, age, BMI, ASA score, MELD score, Child-Pugh score, indication for liver transplantation, alcohol consumption, viral status for hepatitis and HIV, underlying liver disease, presence of diabetes or chronic renal disease, smoking status, transjugular intrahepatic porto-systemic shunt (TIPS), and medical condition before transplantation (need for mechanical ventilation or acute kidney injury requiring extra-renal epuration). We also collected donor age, donor length of stay in intensive care unit, steatosis and fibrosis stage of the graft. Regarding surgery, we collected surgery duration, blood loss, cold ischemia time, and warm ischemia time.

Perioperative patient management

The patient management was identical in both groups, regardless of the type of graft. Just before the unclamping of portal vein, patients received a perfusion of sodium bicarbonate at 8,4%. The immunosuppression protocol was as follows: methylprenidsolone 500 mg per surgery, 250 mg on day 1, and 20 mg/d, tapered from 30 days post-op; mycophenolate mofetil 500 mg per surgery. if patients weighed more than 80 kg, they received 500mg 4/d, followed as soon as possible by 1000mg orally twice a day. If patients weighed less than 80 kg, they received 500mg 3 times a day, then 750mg twice a day. If patients had a renal insufficiency, they received basiliximab 20 mg on the day of surgery and on day 4; and tacrolimus was delayed at day-3. Tacrolimus was started at 0.1 mg/kg/d on day 0 if renal function was normal. Immunosuppression protocol is detailed in Appendix 1.

Patients underwent a CT scan 5 to 9 days after the transplantation in order to check early surgical complication. After discharge from hospital, they were followed up twice a week in the first two weeks, then once a week until the first month, and twice a month until 3 months after the transplantation day. From the third month to the end of the first year, the follow up frequency went from every month to every 3 months.

Endpoints

The primary endpoint was the occurrence of the post reperfusion syndrome at portal vein unclamping. Postreperfusion was defined following the Aggarwal definition: as a drop in MAP of over 30% for at least 1 minute or circulatory arrest, or the need for epinephrine, in the 5 minutes following portal vein unclamping.

However, portal vein unclamping was often imprecisely identified in our AIMS. As patients systematically received a bicarbonate infusion a few minutes before unclamping, we chose the 10 minutes-period following the administration as the period of interest. We checked whether this time was correlated with a drop in the etCO2, which was a marker for a drop in the cardiac output.

The MAP was invasively monitored thanks to an arterial line, which enabled having a precise measurement at baseline and in the 10 minutes following the portal unclamping. If patients received epinephrine during that period, we considered that the primary endpoint was met.

The secondary endpoints included the impact of graft type on postoperative complications and events, as well as the role of postreperfusion syndrome on postoperative complications and length of hospital stay. Postoperative events were defined as follows: survival at one year, retransplantation, primary non-function, acute graft rejection, early allograft dysfunction, biliary complications, vascular complications, AST/ALT peak, time to peak transaminase levels (in days), acute kidney injury (according to the KDIGO definition and classification), and glomerular filtration rate at discharge. Additional events included anastomosis integrity at 7 days, surgical revision, endoscopic procedures, radiologic procedures, medical complications (including hemodynamic, respiratory, neurological, and psychiatric failures; systemic infection; venous thromboembolic events; adverse drug reactions), Clavien-Dindo score, six-month hospital readmission, length of stay in intensive care units (critical care unit, postoperative, gastroenterology), length of stay in conventional hospitalization, and total length of stay. During follow-up at three and twelve months, we assessed the occurrence graft loss, graft rejection and complications including: infectious events, surgery related complications, complications due to immunosuppression, neoplasia, liver disease relapse (detailed in Appendix 2).

Data Analysis

Categorical variables were expressed as frequencies (percentage). Quantitative variables were expressed as means ± standard deviation (SD) or medians [interquartile range (IQR)] in cases of non-normal distribution. Normal data distributions were checked graphically and by applying the Shapiro–Wilk test.

The association between graft origin (BDB vs. cDCD) and reperfusion syndrome was analysed using a logistic regression model. An additional analysis was performed, adjusted on age, portocaval anastomosis and MELD score. The odds ratio (OR) and its 95% confidence interval (CI) were expressed as measures of effect size. The association between graft origin and perioperative outcomes was evaluated using linear regression models for quantitative outcomes and logistic regression models for binary outcomes. Exceptions included death, surgical recovery, biliary complications and vascular complications, which were analysed using Cox proportional hazards models. The assumptions for statistical model were verified. For factors found to be significant at a threshold of $p<0.05$ supplemental analyses were performed, adjusting for age, portocaval anastomosis and MELD score. The same methodology approach was applied to study the associations between reperfusion syndrome and perioperative outcomes. Survival curves for the overall population and stratified by graft origin were realized using the Kaplan–Meier method. Statistical testing was conducted at the two-tailed P value of 0.05. The data were analysed using the SAS software version 9.4 (SAS Institute, USA).

Regulatory framework

Data collection and analysis has been declared to the CNIL, the French data protection authority, by declaration to the University hospital of Lille data protection officer (DEC23-079) in accordance with french legislation on retrospective non-interventional research on existing data. Lille University Hospital health data warehouse (Include project), through which the data were collected, has been approved by the French National Data Protection Authority (CNIL) from 2019 (authorization number: 1754053) (https://www.legifrance.gouv.fr/cnil/id/CNILTEXT000039292712). Include data warehouse ensures that researchers at Lille University Hospital can process end-to-end data in a secure, GDPR-compliant environment. Patients were informed to ensure that they had no objection to participating in the study. No patient refused.

3 Results

3.1 Flowchart

Between January 2018 and June 2022, 390 LT procedures were performed in our center. 261 patients underwent their first LT, were aged from 18 to 65 years old and had a MELD score ≤ 25. Among this population, we included 221 patients. Two groups were formed as previously described. The flow chart is shown in Figure 1.

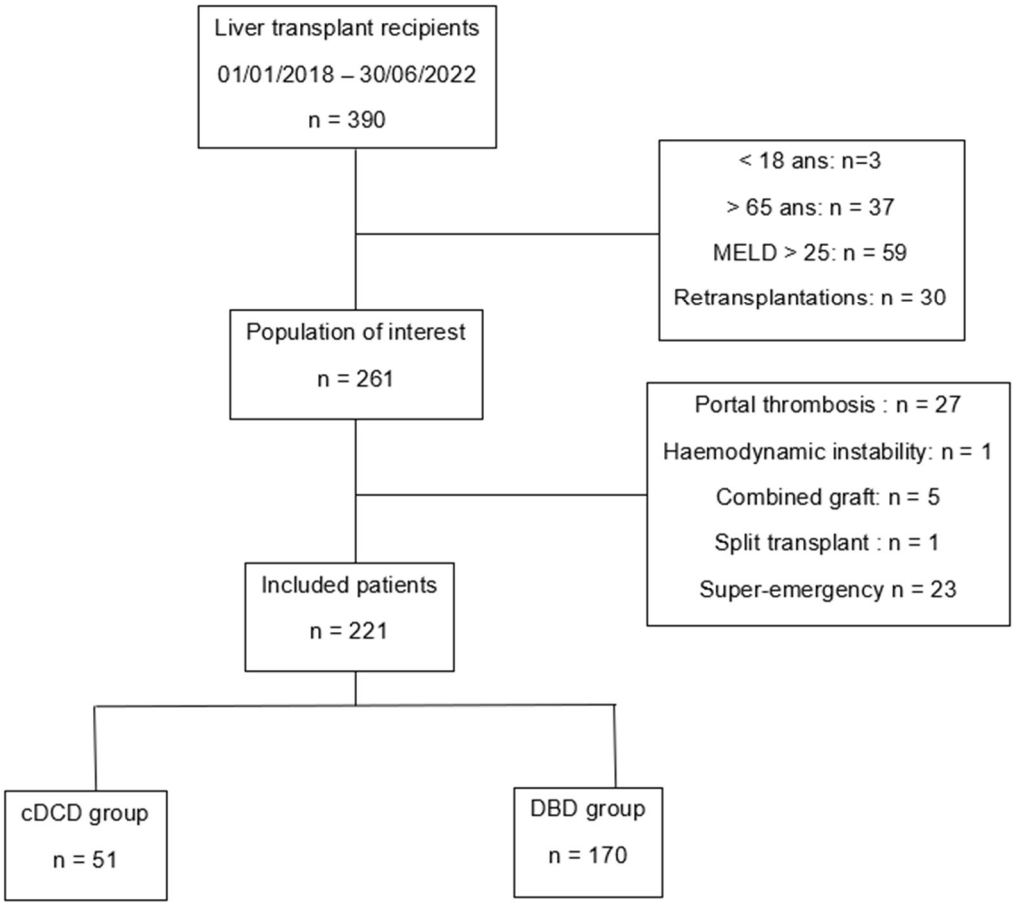

Figure 1. Flow Chart. cDCD, controlled donation after circulatory arrest. DBD, donation after brain death.

3.2 Patients

Recipients were predominantly male (73%), with an average age of 57 [IQR 48-61] years old. The median BMI was 27 [23-30] kg/m². The median ASA score was 3. The median MELD score at registration on waiting list was 14 [8;18], and the median Child-Pugh score was B8 [A5; C10]. 44% were transplanted for cirrhosis. 44% were

transplanted for hepatocellular carcinoma. The remaining 12% were transplanted for biliary diseases (sclerosing cholangitis, cholangiocarcinoma), polycystic liver disease, alpha-1-antitrypsin deficiency, Wilson's disease. Alcohol consumption was found for 142 (64%) patients. 11 patients (5%) were tested positive for HBV and 18 (8%) for HCV. 40 of them (18%) had a non-alcoholic steato-hepatitis (NASH). 69 (31%) were diabetics, including 41% treated by insulin.

79 (36%) were non-smokers, 46 (21%) were still actively smoking while being registered on the transplant list, whereas 96 (43%) had stopped. 15 (7%) were treated for chronic renal failure. 11 patients had undergone a TIPS. 202 patients (91%) were awaiting transplantation at home, whereas 8 (3,6%) were hospitalized, and 11 (5%) were admitted into an intensive care unit. No patient was under mechanical ventilation. Only one was under extra-renal-epuration due to an acute kidney injury. The median glomerular filtration rate just before the graft was 98 mL/min. We classified steatosis into the categories: < 5%, 5 to 33%, or > 33%. 103 (48%) grafts had a level of steatosis < 5%, 92 (43%) between 5 and 33%, and 19 (9%) superior to 33%. Stages of graft fibrosis were leveled from 0 to 3. Only two patients had respectively a level of fibrosis at 2 and 3. 136 grafts (64%) were labelled 0, and 74 (35%) 1. Median age of the donor was 57 [43; 67] years old. The donor's average length of stay in ICU was 4,5 [2; 6,5] days, although this data was only known for 56 patients (25%).

Baseline characteristics (shown in Table 1) were overall similar between groups. The LT indication did differ between groups: in the DBD group, patients were mainly transplanted for cirrhosis, whereas in the cDCD group, the main indication was CHC. More recipients in the DBD group had an "expert" component.

Table 1. Baseline characteristics

	cDCD N= 51	DBD N= 170	P
Male gender	37 (72,5%)	125 (73,5%)	0,89
Age (y)	59 [49;62]	57 [48;61]	0,11
BMI (kg/m²)	28,5 [24,5;30]	26,3 [22,9;30,4]	0,37
ASA score	3	3	0,93
MELD score	12 [8;16]	14 [8;19]	0,12
Child-Pugh score	B7 [A5; B9]	B8 [A6; C10]	0,048
TIPS	0 (0%)	11 (6,5%)	0,75
LT indication			
Cirrhosis	14 (27,5%)	84 (49,4%)	< 0,001
CHC	35 (68,6%)	62 (36,5%)	
Other	2 (3,9%)	24 (14,1)	
“Expert” component	12 (23,5%)	67 (39,4%)	0,04
Liver disease			
OH consumption	38 (74,5%)	104 (61,2%)	0,081
NASH	8 (15,7%)	32 (18,8%)	0,61
Biliary disease	5 (9,8%)	18 (10,6%)	0,87
Hemochromatosis	0 (0%)	1 (0,6%)	
Autoimmune liver disease	2 (3,9%)	20 (11,8%)	0,10
Viral status			
HCV	3 (5,9%)	15 (8,8%)	0,77
HBV	3 (5,9%)	8 (4,7%)	0,72
HIV	0 (0%)	0 (0%)	
Smoking status			0,65
Non smoker	16 (31,4%)	63 (37,1%)	
Active smoker	10 (19,6%)	36 (21,2%)	
Ancient smoker	25 (49%)	71 (41,8%)	
Chronic renal failure	4 (7,8%)	11 (6,5%)	0,75
Glomerular filtration rate before LT (mL/min)	99 [79;109]	97 [75,5;107]	0,38

Waiting place			0,12
Domicile	50 (98%)	152 (89,4%)	
Hospitalization	1 (2%)	7 (4,1%)	
ICU	0 (0%)	11 (6,5%)	
Extra renal purification before LT	0 (0%)	1 (0,6%)	
Mechanical ventilation	0 (0%)	0 (0%)	
Steatosis			0,081
<5%	28 (59,6%)	75 (44,9%)	
5-33%	18 (38,3%)	74 (44,3%)	
>33%	1 (2,1%)	18 (10,8%)	
Antifungal agent	20 (42,6%)	32 (19%)	0,003
CMV prophylaxis	8 (15,7%)	30 (17,9%)	0,72
Donor's age (y)	51 [38;62]	57,5[43;71]	0,028

Values are expressed as mean ± standard deviation, median [IQR], or n (%). cDCD controlled donation after circulatory death. DBD, donation after brain death. LT, Liver Transplantation. HCV, Hepatis C virus. HBV, Hepatitis B virus. HIV, human immunodeficiency virus. ICU, Intensive Care Unit. CMV, Cytomegalovirus.

3.3 Peroperative outcomes

Peroperative data in both groups is shown in (Table 2) The median operating time was significantly longer in the DBD group (384 [325;528] min; cDCD: 342 [299;386] min, p= 0,002). Cold ischemia time was shorter in the cDCD group (284 [232; 353] min; DBD: 439,5 [351;528] min; p <0,001) whereas warm ischemia time did not differ significantly between groups. More patients in the DBD group were under catecholamines support before portal vein unclamping than in the cDCD group (DBD: 155 (91,7%); cDCD: 41 (80,4%); p = 0,023). The need for norepinephrine was similar between groups. portocaval anastomosis was necessary for 45,1% of the patients in the cDCD group, and 33,5% in the DBD group. Most of the patients were extubated at the end of the surgery.

Table 2. Peroperative outcomes

	cDCD (n= 51)	DBD (n= 170)	P
Operating time (min)	342 [299;386]	384 [325;457]	0,002
Cold ischemia time (min)	284 [232;353]	439,5 [351;528]	< 0,001
Warm ischemia time (min)	46 [35;60]	43 [34;56,5]	0,31
Functional warm ischemia time (min)	21 [18;26]	-	
Agonic phase (min)[2]	21 [18;26]	-	
Asystolic phase (min)	5 [3;6]	-	
Portocaval anastomosis	23 (45,1%)	56 (33,5%)	0,13
Blood loss (mL)	1402 ± 707.0	1957 ± 1863	0,087
Labile blood products use	30 (58,8%)	120 (70,6%)	0,11
Cumulated norepinephrine (mg)	3,8 ± 3,8	4,9 ± 4,9	0,21
Catecholamines before unclamping	41 (80,4%)	155 (91,7%)	0,023
Catecholamines weaned	34 (66,7%)	106 (62,7%)	0,61
Orotracheal extubation	50 (98%)	153 (90%)	0,08

Values are expressed as mean ± standard deviation, median [IQR], or n (%). cDCD controlled donation after circulatory death. DBD, donation after brain death.

3.4 Post reperfusion syndrome

Postreperfusion syndrome occurred in 44 patients (20%). It happened for 6 (11,8%) patients in the cDCD group, and 38 (22,5%) in the DBD group. We identified potential cofounding variables, which were included in the multiple regression model: age; portocaval anastomosis and MELD score. The onset of PRS did not differ between the 2 groups (odds ratio (OR) = 0,46, 95% confidence interval (CI) = 0,18; 1,16, *P* = 0,10), neither after adjusting for cofounding variables (OR = 0,435, 95% CI = 0,17; 1,12, *P* = 0,085).

3.5 Postoperative outcomes

One-year survival did not differ significantly between groups (hazard ratio (HR) = 0,21; CI = [0,03;1,61]; *p*= 0,13 (Figure 2). One patient (2%) was dead at 12-month post transplantation in the cDCD group, whereas 15 patients (9%) had died in the DBD group.

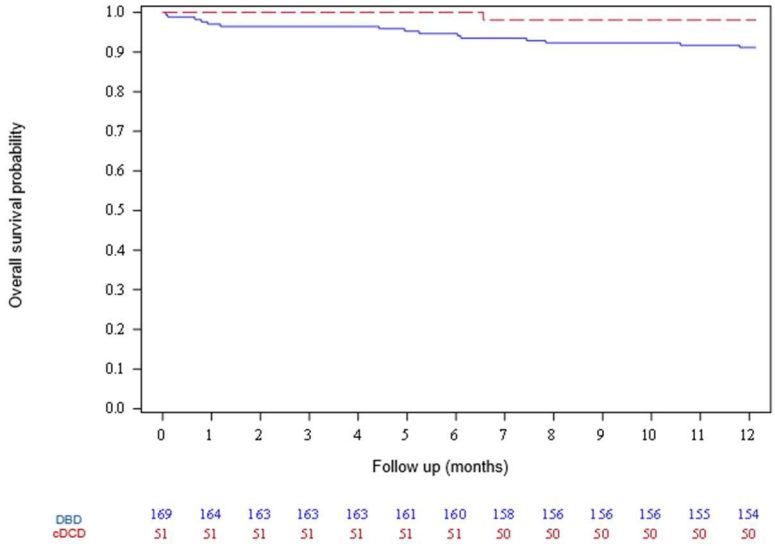

Figure 2. One-year survival. P=0,013. cDCD, controlled donation after circulatory arrest. DBD, donation after brain death.

Cause of deaths are presented in the Table 3. Deaths were mainly due to infections.

Table 3. Cause of deaths

cDCD patients (N=1)
Septic shock post pleural decortication of an infected hematoma (N=1)
DBD patients (N=15)
Refractory septic shock (N= 7)
Metastatic cholangiocarcinoma (N=2)
Right heart failure on pulmonary hypertension (N=1)
Unexplained peroperative cardiac arrest (N=1)
Mesenteric ischemia (N=1)
Meningoencephalitis (N=1)
WLST following uncontrolled epileptic disorder (N=1)
Unknown (N=1)

cDCD, controlled donation after circulatory arrest. DBD, donation after brain death. WLST, withdrawal of life sustaining treatment.

Postoperative outcomes in the two groups are shown in Table 4. After adjustment, the serum transaminase peaks were significantly lower in the cDCD group than the DBD group (cDCD AST= 632 UI/L [478;1199]; DBD AST= 910 UI/L [514;1977]; p = 0,001 and cDCD ALT= 443 UI/L [302;814]; DBD ALT= 607 UI/L [362;1275]; p = 0,004). Acute kidney failure was less frequent in the cDCD group (OR = 0,425 [0,22; 0,84], *p*= 0,01). Medical complications occurred less frequently in the cDCD group (OR = 0,42 [0,21;0,84], *p*= 0,01). Complications at 12 months follow-up were less common in the cDCD group (OR = 0,25 [0,11;0,605], *p*=0,002).

Total length of hospitalization was significantly shorter in the cDCD group (cDCD=12 days [10;17]; DBD = 15 [12;23], p=0,009), as well as length of stay in critical care unit (cDCD= 0.2 ± 1.3 days ; DBD= 2.4 ± 12.4 days, p= 0,04).

As primary non function, graft loss and necessity for an endoscopic procedure were rare events, no statistical analysis was possible.
Details of complications at 3 and 12 months post transplantation are shown in the Table 5 and Table 6.

Table 4. Postoperative outcomes

	cDCD N= 51	DBD N= 170	*unadjusted*		*adjusted* [1]	
			OR/HR[2] [IC95%]	P	OR/HR[2] [IC95%]	P
1-year mortality	1 (2%)	15 (8,9%)	0,21 [0,03;1,61]	0,13	-	-
Retransplantation	3 (5,9%)	7 (4,1%)	1,46 [0,36;5,85]	0,60	-	-
Primary non function[3]	0 (0%)	4 (2%)	-	-	-	-
Acute graft rejection	4 (7,8%)	14 (8,3%)	0,94 [0,30;3]	0,92	-	-
Early allograft dysfunction	12 (23,5%)	50 (29,8%)	0,73 [0,35;1,50]	0,39	-	-
Biliary complication	8 (15,7%)	29 (17,4%)	0,82 [0,36;1,87]	0,64	-	-
Vascular complication	9 (17,6%)	41 (24,4%)	0,68 [0,33;1,40]	0,30	-	-
AST peak	632 [478;1199]	909,5 [514;1977]	-	<0,001	-	0,001
ALT peak	443 [302;814]	607 [362;1275]	-	0,03	-	0,004
Time to AST/ALT peak (days)	0 [0;1]	1 [0;1]	-	0,073	-	-
Acute kidney injury	18 (35,3%)	95 (56,5%)	0,42 [0,22;0,80]	0,01	0,425 [0,22;0,84]	0,01
Renal replacement therapy	2 (5,7%)	20 (14,1%)	0,37 [0,08;1,6]	0,19	-	-
Glomerular filtration rate at discharge	96 [69;106]	92 [65,5;106]	-	0,67	-	-
Anastomosis integrity at 7 days	45 (88,2%)	137 (82%)	0,61 [0,24;1,56]	0,30	-	-
Surgical revision	9 (18%)	49 (29%)	0,65 [0,28;1,15]	0,11	-	-
Endoscopic procedure[3]	1 (2%)	5 (3%)	-	-	-	-
Radiologic procedure	1 (2%)	13 (7,7%)	0,24 [0,03;1,91]	0,18	-	-

Medical complication	26 (51%)	124 (72,9%)	0,39 [0,20; 0,735]	0,004	0,42 [0,21;0,84]	0,01
Clavien Dindo score	2 [1;2]	2 [2;3b]	-	0,003	-	-
6-month readmission	9 (18%)	54 (33%)	0,46 [0,21;1]	0,05	-	-
Total length of hospitalization	12 [10;17]	15 [12;23]	-	0,01	-	0,009
Stay in critical care unit	0.2 ± 1.3	2.4 ± 12.4	-	0,04	-	0,04
Stay in postoperative intensive care	10.5 ± 4.1	12.1 ± 5.7	-	0,06	-	-
Stay in gastroenterology intensive care	0.9 ± 2.7	2.0 ± 7.1	-	0,76	-	-
Stay in conventional care	3.7 ± 5.6	5.1 ± 8.0	-	0,60	-	-
3-months follow up						
Complications	20 (39,2%)	65 (40,1%)	0,96 [0,51;1,93]	0,91	-	-
Graft loss[(3)]	1 (2%)	4 (2,5%)	-	-	-	-
Graft rejection	5 (9,8%)	10 (6%)	1,65 [0,54;5,08]	0,38	-	-
12-months follow up						
Complications	7 (14%)	63 (38,9%)	0,26 [0,11; 0,60]	0,002	0,25 [0,11;0,61]	0,002
Graft loss[(3)]	1 (2%)	7 (4,3%)	-	-	-	-
Graft rejection	6 (12%)	18 (11,1%)	1,10 [0,41;2,92]	0,86	-	-

cDCD controlled donation after circulatory death. DBD, donation after brain death. Lengths of stay are expressed in days.

[(1)] Adjusted for: age, portocaval anastomosis and MELD score. Adjustment was performed for factors found to be significant at a threshold of p <0,05.

[(2)] Odds ratio, except for 1-year mortality, surgical revision, biliary and vascular complications, for which Hazard ratios were realized.

[(3)] As primary non function, graft loss and necessity for an endoscopic procedure were rare events, no statistical analysis was possible.

Table 5. Complications at 3 months post transplantation

	cDCD N= 51	DBD N= 170
Infection	7 (13,7%)	23 (13,7%)
Immunosuppression induced	11 (21,6%)	27 (16,1%)
Surgical	3 (5,9%)	19 (11,3%)
Recurrence of liver disease	2 (3,9%)	3 (1,8%)
Neoplasia	0 (0%)	1 (0,6%)

cDCD controlled donation after circulatory death. DBD, donation after brain death.

Table 6. Complications at 12 months post transplantation

	cDCD N= 51	DBD N= 170
Infection	4 (7,8%)	21 (13,7%)
Immunosuppression induced	3 (5,9%)	23 (13,7%)
Surgical	3 (5,9%)	25 (14,9%)
Recurrence of liver disease	0 (0%)	3 (1,8%)
Neoplasia	0 (0%)	6 (3,6%)

cDCD controlled donation after circulatory death. DBD, donation after brain death.

3.6 Impact of post reperfusion syndrome on perioperative outcomes

In our study, the occurrence of post reperfusion syndrome was not statistically significantly associated with an increase of the following outcomes (Table 7), except for the AST peak, which was significantly lower in patients without SPR (SPR: AST=1557 UI/L [862;3755]; no SPR: AST=721 UI/L [468;1438], p <0,001), as well as the ALT peak (SPR: ALT= 1022 UI/L [862;3755]; no SPR: ALT= 545 UI/L [311;966], p= 0,01). The 1-year mortality didn't differ significantly whether PRS occurred (14% vs 6%, p=0,06). Overall survival at one year is shown in the Figure 6.

Early allograft dysfunction did not differ whether PRS occurred. 79 patients had a portocaval anastomosis. In these patients, 13 had a postreperfusion syndrome (16,5%), 66 didn't (86%).

Table 7. Effect of PRS on perioperative outcomes

	PRS (n=44)	No PRS (n=176)	*unadjusted*		*adjusted* [1]	
			OR/HR[2] [IC95%]	P	OR/HR[2] [IC95%]	P
1-year mortality	6 (14%)	10 (5,7%)	2,6 [0,95;7,15]	0,06	-	-
Retransplantation	2 (4,5%)	8 (4,5%)	1 (0,21;4,88]	1	-	-
Primary non function[3]	2 (4,5%)	2 (1,1%)	-	-	-	-
Acute graft rejection	3 (7%)	15 (8,5%)	0,81 [0,22;2,92]	0,74	-	-
Early allograft dysfunction	17 (39,5%)	45 (25,7%)	1,89 [0,94;3,8]	0,07	-	-
Biliary complication	10 (23,3%)	27 (15,5%)	1,64 [0,79;3,40]	0,18	-	-
Vascular complication	11 (25%)	38 (21,8%)	1,14 [0,57;2,28]	0,72	-	-
AST peak	1557 [862;3755]	721 [468;1438]	-	<0,001	-	<0,001
ALT peak	1022 [483;1782]	545 [311;966]	-	0,001	-	0,01
Time to AST/ALT peak	1 [0;1]	0 [0;1]	-	-	-	-
Acute kidney injury	23 (54,8%)	89 (50,6%)	1,18 [0,60;2,33]	0,62	-	-
Renal replacement therapy	4 (11,8%)	17 (12%)	0,98 [0,31;3,13]	0,97	-	-
Glomerular filtration rate at discharge	91 [65;103]	93 [68;107]	-	0,49	-	-
Anastomosis integrity at 7 days	9 (20,9%)	27 (15,5%)	1,44 [0,62;3,34]	0,39	-	-
Surgical revision	14 (31,8%)	44 (25,3%)	1,41 [0,77;2,56]	0,27	-	-
Endoscopic procedure[3]	1 (2,3%)	5 (2,9%)	-	-	-	-
Radiologic procedure	5 (11,4%)	9 (5,2%)	2,34 [0,74;7,36]	0,15	-	-
Medical complication	31 (70,5%)	118 (67%)	1,17 [0,57;2,41]	0,67	-	-
Clavien Dindo score	2 [2;3b]	2 [2;3b]	-	0,49	-	-

6-month readmission	14 (32,6%)	49 (28,5%)	1,21 [0,6;2,49]	0,60	-	-
Total length of hospitalization	19.0 ± 13.4	20.2 ± 18.2	-	0,67	-	-
Stay in critical care unit	1.3 ± 4.7	2.1 ± 12.1	-	0,67	-	-
Stay in postoperative intensive care	12.0 ± 6.4	11.7 ± 5.2	-	0,73	-	-
Stay in gastroenterology intensive care	1.8 ± 8.1	1.7 ± 5.9	-	0,15	-	-
Stay in medicine	4.0 ± 5.6	4.9 ± 8.0	-	0,92	-	-
3-months follow up						
Complications	14 (35%)	71 (41,3%)	0,77 [0,37;1,57]	0,47	-	-
Graft loss[3]	3 (7,3%)				-	-
Graft rejection	1 (2,5%)	2 (1,2%)	-	0,24	-	-
		14 (8,1%)	0,29 [0,04;2,27]			
12-months follow up						
Complications	16 (40%)	54 (31,6%)	1,44 [0,71;2,94]	0,31	-	-
Graft loss[3]	3 (7,5%)		-	-	-	-
Graft rejection	2 (5%)	5 (2,9%)	0,36 [0,08;1,59]	1,18	-	-
		22 (13%)				

cDCD controlled donation after circulatory death. DBD, donation after brain death.

[1] Adjusted for: age, portocaval anastomosis and MELD score. Adjustment was performed for factors found to be significant at a threshold of p <0,05.

[2] Odds ratio, except for 1-year mortality, surgical revision, biliary and vascular complications, for which Hazard ratios were realized.

[3] As primary non function, graft loss and necessity for an endoscopic procedure were rare events, no statistical analysis was possible.

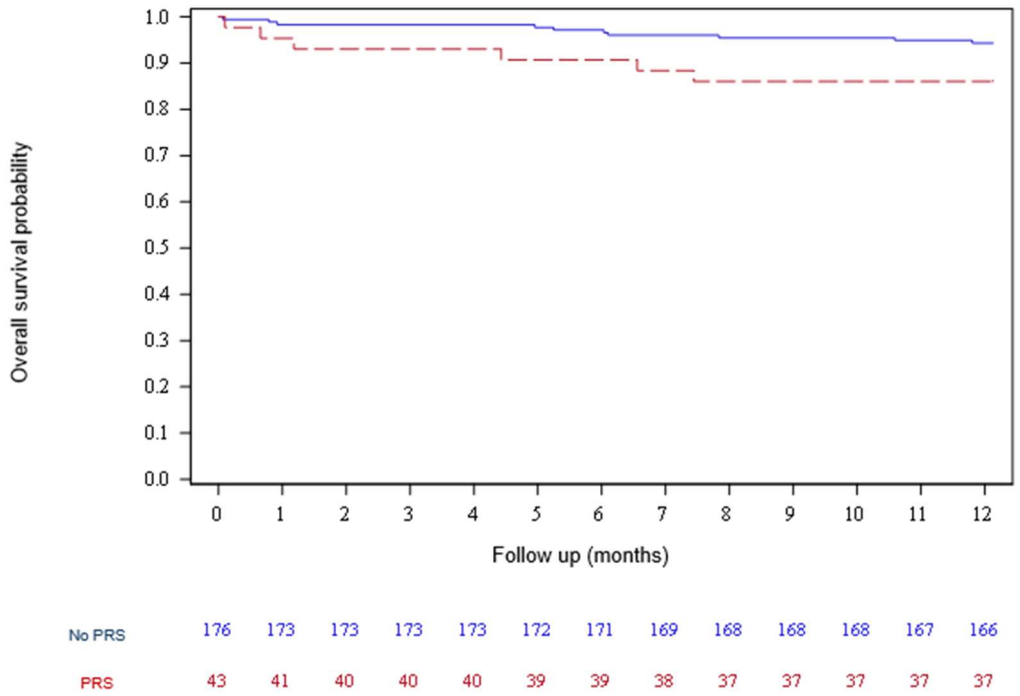

Figure 3. One-year survival. *p*=0,06. PRS, Post-reperfusion syndrome. cDCD, controlled donation after circulatory arrest. DBD, donation after brain death.

4 Discussion

To our knowledge, our cohort is one of the largest series comparing cDCD LT with NRP and DBD LT. We aimed to assess whether there was a difference in the incidence of PRS according to graft type. In our study, PRS onset was similar between cDCD LT with NRP and DBD LT.

Our patients were representative of the general population awaiting liver transplantation. Patients were mostly men, aged around 55 years old. In our center, alcohol-induced cirrhosis represents the main indication for liver transplantation. However, in the cDCD group, patients were mainly transplanted for CHC, which is also the case at national level. Mean MELD score at the inclusion was 14. Baseline characteristics were similar between groups.

Post-reperfusion syndrome occurred in 20% of patients, which is consistent with literature [25]. PRS is classically described as more frequent in cDCD LT [30]. We therefore assume that NRP is a protective factor against the onset of PRS. Moreover, as mentioned earlier, PRS usually appears to be a risk factor for a higher mortality, acute kidney failure, primary nonfunction, graft loss and retransplantation, early allograft dysfunction, higher transaminase release [22–29]. In our study, we found

higher mortality and EAD rates, although not statistically significant. Transaminase release was significantly higher in the PRS group, which indicates graft injury; however, we didn't find any difference on the onset of retransplantation, nor acute kidney failure. Clinical outcomes were therefore better than what's been described when PRS occurs. To explain this lower complication rate, we hypothesize that PRS in our population weren't severe types. Indeed, Hilmi et al [37] distinguished mild from severe forms of PRS according to the hypotension duration and the need for continuous infusion of vasopressor agents. As expected, severe PRS had worst outcomes: a higher rate of retransplantation, required more transfusions, and remained in the ICU longer.

Cold ischemia time has been described as a risk factor for PRS [22,26,28]. Cold ischemia time was statistically shorter in our cDCD group. However, the fact that we didn't find a higher rate of PRS in the cDCD group is consistent with the results of Hilmi et al, who found a shorter CIT in their severe PRS group compared to the mild or no PRS group. The role of CIT in post reperfusion syndrome can thus be discussed.

As described above, cDCD LT are typically associated with biliary complications and ischemic cholangiopathy. In our study, the incidence of biliary complications did not differ between groups. We can therefore assume that NRP reduces the risk of these outcomes. This result is in line with a very recent meta-analysis (August 2024) by Mastrovangelis et al. comparing the results of transplants from donors who died after cardiac arrest with NRP versus without NRP, and also comparing the outcomes of cDCD transplants with NRP versus BDB. When comparing non-NRP cDCD and NRP cDCD, their analysis showed that NRP reduced the risk of ischemic cholangiopathy, primary non-function, and recipient death. This strong result supports our finding that NRP significantly outweighs the disadvantages of cDCD transplantation. Whatsmore, in their analysis, NRP cDCD livers had similar outcomes to DBD grafts [40]. These findings are also consistent with those of Savier et al. [41] who found that transaminase release was lower in cDCD LT compared to DBD, and that EAD, AKI, 90-days graft loss and arterial and biliary complications were similar between groups.

In our study, we even found better outcomes in the cDCD group. Indeed, patients receiving this type of graft seemed to have less acute kidney failure, less medical complications, and the transaminase release was lower. This finding seems to reflect

a protective effect of NRP on the graft preservation. As graft quality is maintained, this protective effect appears to be sustained in the long term, with a lower one-year complication rate. These complications are divided into five categories: infections, immunosuppression-related adverse events, surgery-relative outcomes, relapses of liver disease, and neoplasia. The benefit mainly seems to lie in fewer infections and fewer immunosuppressive-related side-effects.

Patients in the cDCD group had a shorter length of stay, especially in ICU. That finding is interesting, given that length of stay is associated with complications, such as nosocomial infections, thromboembolic events, malnutrition. Whatsmore, shorter length of stay would mean lower cost of care.

Our study has limitations. Firstly, we did not have enough patients in the cDCD group to match patients according to their transplant type. However, we identified the potential cofounding variables after listing the risk factors for PRS in the literature. Secondly, we had multiple endpoints, which may limit the power of our work to detect a statistically significant difference. Finally, as portal vein unclamping is not always correctly identified in our anesthesia software, we had to modify the definition proposed by Hilmi et al [20]. We chose the infusion of bicarbonate as an objective reference. Bicarbonate administration is systematically given in our center in the minutes before unclamping. We therefore had to extend the delay to ten minutes instead of five. By extending this period, we run the risk of smoothing out any hemodynamic instability and thus underestimating the onset of ischemia-reperfusion syndrome.

Overall, this study showed that perioperative outcomes in the cDCD group were at least as good as in the DBD group, which is the standard method.

According to the ABM guidelines, recipients selected for a Maastricht 3 transplant are pre-screened to ensure that they meet few criterias for severity of illness. For example, hemodynamically unstable patients are excluded, as are patients registered for super-emergency treatment. Based on the assumption that there is an increased risk of graft tissue damage in the event of circulatory arrest, these conditions have been established to enhance the chances of a successful liver transplantation. These results are reassuring in terms of the safety of this type of transplant. As our groups are similar on their baseline characteristics, we avoid the risk of underestimating complications in the DCD group.

To go a step further, we could question the validity of considering a brain dead donation as being less at risk of damage to the transplanted organ. Indeed, in brain-dead donors, the transition to brain death causes a reduction in the major pituitary and hypothalamic hormone secretions. These changes lead to hemodynamic instability and blood volume fluctuations induced by diabetes insipidus. At the microcirculatory level, a cytokine release and a catecholaminergic storm are induced. Endothelial activation [44], complement activation and influx of inflammatory cells [45–47] are responsible for tissue damage to the graft. Hence, avoiding this hormone storm might protect the organs from tissue damage.

In conclusion, our study shows that, compared with DBD LT, cDCD LT using postmortem NRP doesn't increase the risk of post-reperfusion syndrome, and is safe in terms of 1-year survival, biliary complications and early allograft dysfunction. It could reduce the rate of medical complications, the duration of hospital stay, and decrease the risk of complications one year after the transplantation.

We therefore suggest that it might be possible to extend the indication of transplantation using organs from controlled circulatory dead donors, under the protection of normothermic regional perfusion, to a wider population of recipients, including unstable patients.

Conclusion

En conclusion, notre étude semble indiquer que la transplantation hépatique à partir de donneurs en mort circulatoire contrôlée utilisant une circulation régionale normothermique, comparativement aux donneurs en mort cérébrale, n'augmente pas le risque de syndrome d'ischémie-reperfusion, et n'accroît pas la mortalité à un an, ni le taux de complications biliaires ou de dysfonction précoce de greffon, comme ce qui était suggéré dans la littérature. Ce type de greffe pourrait même réduire le risque de complication médicale, d'insuffisance rénale aigue, de complications à un an, et la durée du séjour. L'amélioration de la morbidité de cette procédure pourrait s'expliquer par la mise en place d'une CRN, qui n'était pas utilisée dans les premières études s'intéressant aux résultats de ce type de greffon, et réduit significativement la durée d'ischémie froide.

Il serait intéressant d'étudier les résultats de ce type de greffon dans une population de receveurs ayant une pathologie décompensée, afin d'envisager pouvoir à terme en élargir les indications.

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Annexe

Appendix 1: Immunosuppression induction protocol

- Corticoids:
  - Methylprednisolone 500 mg IV on day 0
  - 250mg IV on day 1
  - Prednisone 20mg/d PO until discharge
- Mycophenolate mofetil :
  - > 80kg : 500mg 4x/d IV, then PO 1000mg 2x/d
  - 80kg : 500mg 3x/J IV, then PO 750mg 2x/d
- Tacrolimus :
  - Started at 0,1mg/kg/J in 2 takes
    - No renal failure : on day 0
    - Risk of renal failure (age > 60 years old ; high blood pressure, diabetes, heart disease, glomerular filtration rate < 60 mL/min, BMI > 25 kg/m², peroperative complication): on day 3 (first take in the evening)
  - Residual target rate ≈ 8-12 µg/L.
- Basiliximab : patient at risk of renal failure
  - 20mg IV on day 0 and day 4.

Appendix 2: Complications at 3 and 12-months follow up

These complications are described as follow:

- Infectious events: refers to any systemic infection, affecting urinary tract, biliary, digestive systems, as well as pneumonia, meningoencephalitis…
- Surgery related complications: adverse events related to graft anastomosis (strictures, thrombosis, false aneurysms), abdominal wall (infections, collections, ventrations).
- Complications due to immunosuppression: refers to viral reactivation, adverse immunosuppressive-drugs events, kidney injury induced by anticalcineurins.

- Neoplasia: refers to either primary neoplasia or metastasis. These complications were considered relative to transplantation, as immunosuppression induces a risk for neoplasia, and as liver cancers could relapse.
- Liver disease relapse: recurrence of primary liver disease that initially led to transplantation

AUTEUR : Nom : PLATTEEUW **Prénom :** Hélène
Date de Soutenance : 09/01/2025
Titre de la Thèse : Comparaison de l'incidence des syndromes d'ischémie reperfusion et des complications postopératoires précoces en transplantation hépatique entre 2 groupes de receveurs : greffons issus de donneurs en mort circulatoire contrôlée (Maastricht 3) versus greffons issus de donneurs en état de mort encéphalique. Etude rétrospective monocentrique.
Thèse - Médecine - Lille 2025
Cadre de classement : Médecine
DES + FST ou option : Anesthésie-Réanimation
Mots-clés : ischemie-reperfusion – transplantation – Maastricht 3

Résumé :

Contexte : Pour pallier la pénurie de greffons hépatiques, se sont développées les greffes à partir de Donneurs Décédés d'un Arrêt Cardiaque (DDAC). Ce type de greffe est associé à un surrisque de complications pouvant être liées au Syndrome d'Ischémie Reperfusion (SIR). L'utilisation d'une Circulation Régionale Normothermique (CRN) pourrait limiter ces risques. A travers cette étude, nous évaluons s'il existe une différence d'incidence du SIR selon le type de greffon : issus de DDAC ou de donneurs en Etat de Mort Encéphalique (EME). Nous évaluons également l'impact du type de greffon et de la survenue du SIR sur les complications périopératoires.

Patients et Méthodes : Etude observationnelle, rétrospective, au CHU de Lille, incluant les patients greffés hépatiques de janvier 2018 à juin 2022. Les caractéristiques avant, pendant et jusqu'à un an après la Transplantation Hépatique (TH) ont été recueillies. Le critère de jugement principal était la survenue du SIR, défini comme une chute de la PAM > 30% ou un arrêt circulatoire, ou l'administration d'adrénaline dans les 10 minutes suivant le déclampage portal. Les critères de jugements secondaires étaient la survie à un an, la survenue de complications périopératoires et l'étude des durées de séjour.

Résultats : Parmi les 390 patients greffés sur cette période, 221 étaient inclus. On ne retrouve pas de différence d'incidence du SIR (OR = 0,435 [0,17;1,12]). La survie était similaire dans les deux groupes (HR 0,21 [0,03;1,61] p=0,085). Les patients du groupe DDAC ont présenté un pic cytolytique plus faible, moins d'insuffisance rénale aigue, moins de complications médicales (OR 0,41 [0,21;0,84]), moins de complications à un an de la TH (OR 0,25 [0,11;0,60]). La durée totale d'hospitalisation était plus courte (12 [10;17] jours versus 15 [12,23], p=0,002), ainsi que la durée de séjour en réanimation (0,2 ± 1.3 jour versus 2,4 ± 12.4, p= 0,04). Le SIR était associé à un pic d'ASAT et d'ALAT plus faible (respectivement p<0,001 et p=0,01).

Conclusion : La TH à partir de DDAC utilisant une CRN n'augmente pas le risque de SIR, et semble protectrice par rapport au pic cytolytique, à la survenue d'insuffisance rénale aigue, de complications médicales périopératoires, et de complications à un an.

Composition du Jury :

Président :	Monsieur le Professeur Gilles LEBUFFE
Assesseurs :	Monsieur le Professeur Emmanuel BOLESLAWSKI
	Monsieur le Professeur Sébastien DHARANCY
Directeur :	Monsieur le Docteur Damien ROUSSELEAU