JOURNAL
OF HEPATOLOGY

Normothermic regional perfusion – What is the benefit?

To the Editor:

We read with great interest the recent article by Hessheimer *et al.* on normothermic regional perfusion (NRP) in controlled donation after circulatory death (DCD) donors in Spain.[1] In this innovative national analysis, the authors compare NRP against super rapid retrieval in terms of relevant outcome parameters after liver transplantation. The results appear impressive, as they show a significant reduction of biliary complications by NRP (overall: 8 *vs.* 31%, ischemic cholangiopathy: 2 *vs.* 13%). This is also important from an economic perspective, as NRP is currently one of the cheapest machine perfusion techniques available.[1] We have however, several comments, which we would like to add.

First, although the study cohort is the largest available on effects of NRP in DCD livers Maastricht Type III, the overall risk classified by donor age, donor warm ischemia, cold ischemia, recipient age, and previous transplantation appears low.[2] For example, the median functional donor warm ischemia is very short, *e.g.* 12 and 15 min (NRP *vs.* super rapid cold flush and retrieval), and cold ischemia is less than 6 hrs in both groups.[1] Although we agree, that donors in this study (median donor age: 57 years, IQR: 45–65) are older compared to some previous reports,[3] the rate of biliary complications in the control group (super rapid retrieval) appears relatively high, compared with results from other centers, who frequently accept DCD livers of similar donor age with longer donor warm ischemia and cold storage.[4] We would therefore emphasize that outcomes in DCD liver transplants have been excellent despite super rapid retrieval and subsequent cold storage without any machine perfusion approach, when overall donor and recipient risks are low.[2]

Second, the discard rate of liver grafts in this report is substantial (34% NRP and 38% super rapid retrieval), and nearly unaffected by the NRP approach. The authors argue that similar discard rates have been reported in controlled DCD liver transplants in other countries.[2,5] However, it remains unclear which criteria were used for the decision to reject a DCD liver in this Spanish cohort, as very unspecific arguments, *e.g.* poor macroscopic appearance, were cited as the main reason.[1] We would furthermore emphasize that significantly lower discard rates despite higher risk grafts have been achieved by *ex situ* and end-ischemic machine liver perfusion techniques, such as hypothermic or normothermic oxygenated perfusion (Table 1).[6,7] Based on this, it is currently unclear if NRP can be expected to increase utilization of more livers grafts, which is one of the main targets of machine liver perfusion approaches.[8,9] Additionally, the number of declined livers prior to donor withdrawal of treatment and perfusion and, at what risk, is frequently underreported in recent available cohort studies.[1,6,7,9] For a more transparent comparison, all future studies on machine liver perfusion should therefore include a detailed report of parameters on graft quality, utilization rate and graft loss after transplantation (Table 1).[8]

Third, the authors provide no information on the assessment of liver quality during NRP, which is of the utmost importance, when higher risk grafts are perfused. Currently available markers in use include liver enzymes and lactate or bile production, which were recently shown not to be sufficient to exclude liver graft failure in the recipient.[9] In addition, viability assessment is also possible during both *ex situ* normothermic or hypothermic perfusion.

In this context, we would clearly state that all machine perfusion techniques which use oxygenated perfusates induce a certain degree of reperfusion injury, triggered by the release of reactive oxygen species.[10] The underlying protective mechanism of NRP and all other perfusion techniques is therefore dependent on the amount of injury and on the concurrent response mechanisms during machine liver perfusion.[8] This discovery should lead in the future to concepts assessing and predicting graft quality during machine perfusion.[8,9]

Fourth, the authors describe the period of postmortem NRP as economically favorable. However, no data exist to date supporting this statement. Additional staff including a perfusionist and experienced retrieval surgeons are often required to go to peripheral donor hospitals with an extra vehicle to transport sophisticated equipment for any DCD withdrawal, with a potentially slow or not proceeding donor, where livers are at risk of eventually being declined.[5] Such scenarios have a significant impact on the health economics in any country. Moreover, the retrieval process takes longer when NRP is used, due to the additional *in vivo* perfusion duration of 2 -4 hrs (or even 6 hrs), with subsequent organ removal, compared to the super rapid cannulation, where the operating theatre is required only for about one hour.

Finally, based on the good results of this low-risk cohort, the authors suggest a uniform application of NRP as procurement technique for all DCD donors in any other country. Although we believe NRP may be a valuable technique, we would, at this stage suggest instead, that the transplant community should currently avoid favoring any machine perfusion technique before results from randomized trials are available, comparing different approaches with a uniform risk assessment and convincing endpoints.[8]

Table 1. Risk parameter, utilization rate and outcomes of recent studies on DCD liver transplantations with different *in situ* and *ex situ* perfusion techniques.

Parameters of risk and outcome	Normothermic regional perfusion[1]	Endischemic normothermic perfusion[9]	Endischemic normothermic perfusion (Vittal)[7]	Endischemic hypothermic oxygenated perfusion[6]
Authors, year	Hessheimer A *et al.* 2018	Watson C *et al.* 2018	Mergental H *et al.* 2019	Muller X *et al.* 2019
Overall donors offered	?	? (declined by all centres)	185 in 15 months (declined by all centres)	23[§]
Donors with withdrawal of treatment	342 (190 for cold flush)		n.a.	23
No. of overall donors/livers perfused	152	47	31 (marginal DBD & DCD)[*]	23
No. of perfused DCD livers (n/%)	152	35	14	23
Utilization rate of DCD livers for transplantation in %	**95 (62.5%)**	**16 (45.7%)**	**22 (71%) entire cohort (DBD and DCD)**	**21 (91.3%)**
Main reason for declining the liver for transplantation	Macroscopic appearance (32/152 = 21.1%) Parameter during NRP (4/152 = 2.6%)	Lactate clearance <2.5/2h (n = 5), pH regulation (n = 2) Bile pH	Lactate clearance, pH regulation, perfusion quality, glucose utilization	FMN release >10,000 within first 30 min of HOPE (n = 2)
Percentage of livers would have been used with standard cold storage alone	?	0	? (% declined for logistics n.a.)	0
Donor age (years)	57 (45–65)	56 (46–65)	57 (30–84)	62 (53–69)
Donor BMI (kg/m^2)	n.a.	n.a.	29 (20–42)	27.2 (26.2–28.4)
Total donor warm ischemia time (min)	18 (13–23)	31 (24–36.8)	n.a.	38 (36–40)
Functional donor warm ischemia (min)	12 (9–16)	n.a.	>30 min (inclusion criteria)	36 (31–37)
Asystolic donor warm ischemia (min)	n.a.	12 (10–14)	n.a.	19 (17–21)
Cold storage (h)	5.3 (4.4–6.1)	6.4 (5.51–7.05)	7.33 (5.17–14.5)	3.5 (2.5–4.8)
Perfusion duration (min or h)	120 min (79–136)	120–240 min	10.2 h (6.04–10.8)	124.8 min (102–154.8)
Recipient age (yr)	56 (52–61)	n.a.	n.a.	62 (55–66)
Recipient lab MELD (points)	15 (11–19)	n.a.	n.a.	12 (10–14)
Rate of PNF (n/%)	2 (2%)	1 (6.3%)	0 (0)	0 (0)
Overall biliary complications (n/%)	8 (8.4%)	n.a.	n.a.	7 (33.3%)
Non–anastomotic strictures (n/%)	2 (2.1%)	4 (25%)	n.a.	1 (4.8%)
Non–tumour related graft loss (n/%)	11/95 (12%) (3 yr)	4/16 (25%) (602 d)	4/22 (18%) (90 d)	1/21 (4.8%) (3 yr)

All continuous variables are presented as median and interquartile range; Categorical variables are presented as total number and %. BMI, body mass index; DCD, donation after circulatory death; FMN, flavin mononucleotide; HOPE, hypothermic oxygenated perfusion; MELD, model for end-stage liver disease; n.a., not applicable, no information in the manuscript; NRP, normothermic regional perfusion; PNF, primary non-function.

[*] Out of 185 retrieved livers in the 15-month study period, 59 were discarded due to cancer, previous perfusion, fibrosis or severe damage; 25 because Vittal trial donor inclusion criteria were not met; 21 because the grafts were offered when the machine used for normothermic machine perfusion was already in use; 41 because there were no suitable recipients.

[§] All offered donor livers, which were considered during study period were classified as futile according to the UK-DCD-Risk-Score (2). Templates marked with ? could not be completed, due to missing information in the reference.

Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

AS, PM & PD wrote the manuscript and revised the text.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2019.03.019.

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Author names in bold designate shared co-first authorship

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Reply to: "Normothermic regional perfusion – What is the benefit?"

To the Editor:

We thank Drs. Schlegel, Muiesan, and Dutkowski for their interest in our manuscript[1] and are delighted to provide clearer and updated information regarding the use of normothermic regional perfusion (NRP) in controlled donation after circulatory death (cDCD) liver transplantation.

Our manuscript describes the Spanish experience with cDCD liver transplantation from national application in 2012 through 2016, comparing outcomes of transplants performed with NRP versus those performed with super rapid recovery (SRR).[2] Transplants were included from 20 centers, only 3 (15%) with previous experience performing uncontrolled donation after circulatory death. The results that we present can be achieved by not just perfusion and DCD "experts" but by virtually any liver transplant team. That said, the results we achieved with SRR are the same as those described by experienced centers using cDCD livers of a comparable profile,[3,4] and improvements achieved with NRP are strikingly similar to those recently reported by 2 UK centers describing 43 cDCD liver transplants performed with NRP.[5]

The Letter's authors claim the "risk" of the cDCD grafts we used was low based on a scoring system they developed.[6] The UK DCD Risk Score has not been independently validated but has found to be ineffective at predicting 1-year cDCD liver survival (its aim) in our recipients[7] and other British cohorts.[8] The authors do correctly describe our median functional donor warm ischemia times: 12 and 15 minutes when NRP and SRR were used, respectively. Femoral cannulae were placed prior to withdrawal of ventilatory support in 87% of cases using NRP, and warm ischemia times were shorter when NRP was employed. That said, the implication that the authors consistently experience longer warm ischemia times than even those for livers recovered with SRR is surprising. Only 11 of 342 cDCD donors considered for liver donation during the study period