Conflict of interest

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

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Authors' contributions

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

Supplementary data

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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

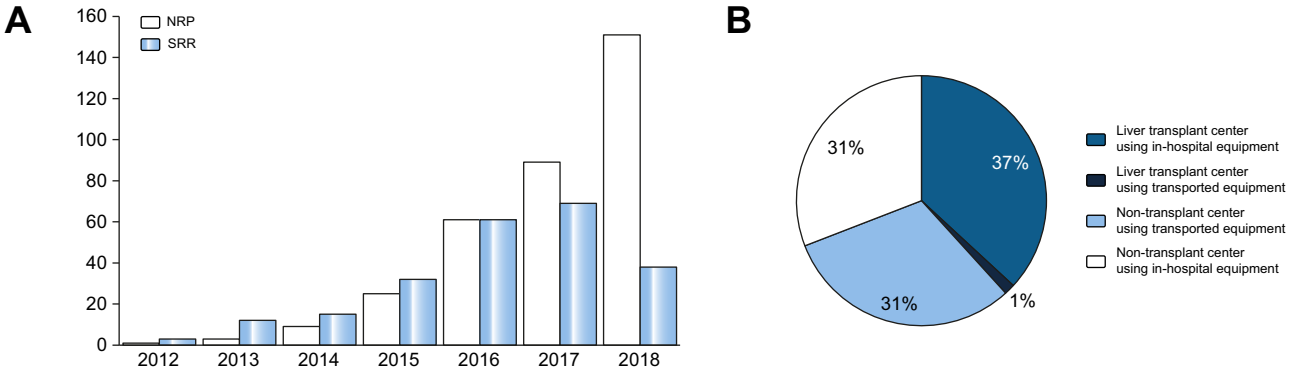

Fig. 1. Liver transplant approaches in Spain. (A) Year-to-year evolution of cDCD liver transplant activity in Spain, divided according to organ recovery method: NRP, super rapid cold perfusion and SRR. (B) In the past 2 years, NRP has become the recovery method of choice in cDCD liver transplantation in Spain. In 2018, it was applied 217 times at 62 different hospitals. In the majority of these cases (62%), NRP was performed at non-liver transplant centers using either in-hospital or transported equipment. *Source: Organización Nacional de Trasplantes (www.ont.es).* cDCD, controlled donation after circulatory death; NRP, normothermic regional perfusion; SRR, super rapid recovery.

were turned down due to prolonged warm ischemia (3%). The facts that i) indication for proceeding with cDCD in Spain is strict and predicated on likelihood of arrest within 60 minutes of withdrawal of care and ii) cDCD donors in Spain have been in intensive care 7–10 days prior to withdrawal (*vs.* 2–3 days in the UK)[3,5] may explain the consistently shorter warm ischemia times we experienced.

While we did not argue in our manuscript that our discard rates are similar to those in other countries, the authors are correct in pointing this out. Between 2012 and 2016, 38% of cDCD livers recovered with SRR and 34% recovered with NRP in Spain were ultimately discarded, similar to the 33% of retrieved cDCD livers declined in 2017/2018 in the UK.[9] Our figures are national averages, and individual centers have lower discard rates. Obviously, the "rate" depends on the denominator, and comparing national averages with rates described in smaller pilot studies, where pre-selection has been performed on grafts included, is misleading.[1]

As in donation after brain death (DBD) liver transplantation, cDCD liver evaluation is not exact, and visual assessment by the surgical team is still the ultimate measure of viability when *ex situ* perfusion is not employed. The majority of cDCD livers turned down in our study were observed to be moderately-to-severely steatotic, poorly perfused, fibrotic, or cirrhotic.[2] While hepatic aminotransferases in the perfusate were assessed as an indication of hepatic injury, they rose very little in most cases (only 4 livers were turned down due to rising aminotransferases), and liver viability assessment in the strictest sense was not performed. This does not mean that true viability assessment may not be performed during NRP, as bile is produced, and evaluation of bile production and biochemistry may serve as useful means to assess significant biliary injury.

When NRP is employed, the cost of the cDCD process increases €2,500–5,000 with respect to standard DBD or cDCD with SRR. This cost is lower than that required to perfuse a liver *ex situ*, where disposable components of the machine perfusion circuit alone are at the higher end of the aforementioned range. Considering costs, one also has to keep in mind that NRP is simultaneously used to recover cDCD kidneys, pancreata, and hearts, as well, and benefits of NRP in terms of post-transplantation outcomes extend to these organs.[10]

In their final comments, the Letter's authors call for a moratorium on widespread application of any perfusion technology in human liver transplantation pending results of randomized trials. This recommendation defies reality in countries such as Spain, France, and Italy. In Spain, the use of NRP in cDCD has risen exponentially since 2012 (Fig. 1A). In 2018, 189 cDCD livers were transplanted: 151 with NRP and 38 with SRR. NRP was applied in >200 cDCD donors at 62 hospitals, in a third of cases at non-transplant hospitals by local teams (Fig. 1B). The application of NRP is widely disseminated here and has allowed for implementation of cDCD at all levels. Given excellent post-transplant results,[2] it seems improbable if not unethical that centers currently using NRP would abandon it and risk increased biliary complications and graft loss pending a level 1 clinical trial.

While NRP increases upfront costs associated with cDCD transplantation compared with SRR, it may be used by both transplant and perfusion experts and less experienced professionals to treat and potentially assess the quality of multiple organs, not just the liver. At a time when healthcare systems are concerned with achieving the greatest benefit at the lowest cost, NRP appears to be the DCD perfusion strategy that best meets this need.

Conflict of interest

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

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Supplementary data

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