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Short Report

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Short Report

Outcomes of livers from donation after circulatory death donors with extended agonal phase and the adjunct of normothermic regional perfusion

James A. Richards[1,2,3,4,5,*], Rohit Gaurav[1,4], Sara S. Upponi[1,4,6], Lisa Swift[1], Corrina Fear[1], Gwilym J. Webb[1,7], Michael E. D. Allison[1,4,7], Christopher J. E. Watson[1,2,3,4] and Andrew J. Butler[1,2,3,4]

[1]Roy Calne Transplant Unit, Cambridge University Hospitals NHS Foundation Trust, Addenbrooke's Hospital, Cambridge, UK
[2]University of Cambridge Department of Surgery, Addenbrooke's Hospital, Cambridge, UK
[3]NIHR Blood and Transplant Research Unit (BTRU) at the University of Cambridge in collaboration with Newcastle University and in partnership with NHS Blood and Transplant (NHSBT), Cambridge, UK
[4]National Institute for Health and Care Research (NIHR) Cambridge Biomedical Research Centre, Cambridge, UK
[5]HPB and Liver Transplant Surgery, Royal Free Hospital, London, UK
[6]Department of Radiology, Cambridge University Hospitals NHS Foundation Trust, Addenbrooke's Hospital, Cambridge, UK
[7]Department of Medicine, Cambridge University Hospitals, Addenbrooke's Hospital, Cambridge, UK

*Correspondence to: James A. Richards, University of Cambridge Department of Surgery, Box 202, Level E9, Cambridge Biomedical Campus, Hills Road, Cambridge CB2 0QQ, UK (e-mail: jamesrichards@doctors.net.uk)

Introduction

In liver transplantation, graft donation after circulatory death (DCD) has emerged as an important source of liver grafts, but with considerable variation in use. Historically, liver transplantation using DCD grafts had inferior short- and long-term outcomes compared with donation after brainstem death (DBD), with higher rates of primary non-function and ischaemic cholangiopathy[1–3]. Early outcomes from DCD liver transplantation have improved recently[4], largely as a result of cautious donor selection[5].

In situ normothermic regional perfusion (NRP) leads to improved liver outcomes compared with traditional *in situ* cold perfusion[6–9]. NRP uses an extracorporeal circuit to warm, oxygenate, and circulate blood back into the abdominal organs after circulatory arrest. Reduced rates of early allograft dysfunction (EAD) and ischaemic cholangiopathy are seen after NRP compared with conventional procurement[6–9]. Other organs may also benefit from NRP in the donor, with reduction in the rate of delayed graft function noted in transplanted kidneys[10,11], although no benefit has been seen so far in transplanted pancreas[11].

DCD liver transplantation currently accounts for about one-quarter of deceased donor liver transplants in the UK[12]. The UK National Organ Retrieval Service teams wait a minimum of 3 h from withdrawal of life-supporting treatment before abandoning retrieval; liver donation is often only pursued for the first hour, with some recipient centres standing down after 30 min[5]. Only 30.5 per cent of retrieved DCD livers are subsequently transplanted, compared with 80.2 per cent of DBD livers[12]. If centres were prepared to pursue DCD donation for longerthan 30–60 minutes after withdrawal of life supporting treatment and if the rate of transplantation of retrieved DCD livers more closelymatched those from DBD donors, then there is huge potential to improve organ utilisation. One such solution is use of NRP and this study explored the outcomes of grafts transplanted after a withdrawal phase lasting more than 1 h.

Methods

This was a retrospective analysis of prospectively collected data on consecutive patients undergoing adult liver transplantation, at Addenbrooke's Hospital between 31 December 2010 and 15 January 2022, from Maastricht category 3 or 4 donors undergoing NRP according to previously published methodology, definitions, and target parameters[8,13–15]. Full methodology is provided in detail in *Supplementary materials*.

Results

During the study interval, 181 abdominal NRP retrievals were performed, and 130 of 181 livers (71.8 per cent) were transplanted. Of these, 7 were transplanted in other centres, and 22 underwent NRP followed by normothermic *ex situ* liver perfusion and were therefore excluded from further analysis.

In Cambridge, 101 livers were transplanted without additional *ex situ* perfusion and included in the analysis. The overall 12-month patient survival rate was 93.9 per cent and the death-censored graft survival rate was 98.0 per cent. Donor and recipient demographics are summarized in *Table S1*; there were no significant differences between cohorts. Asystolic times, duration of NRP, and cold ischaemia times were similar between groups (*Table S1*). Overall, 49 of 101 transplants (48.5 per cent) were scored as high risk or futile according to the UK DCD risk score[16], with no difference between cohorts (*Table S1*).

Among the 51 livers (28.2 per cent) that were not transplanted, the median agonal time was 12 (range 1–297) min and median

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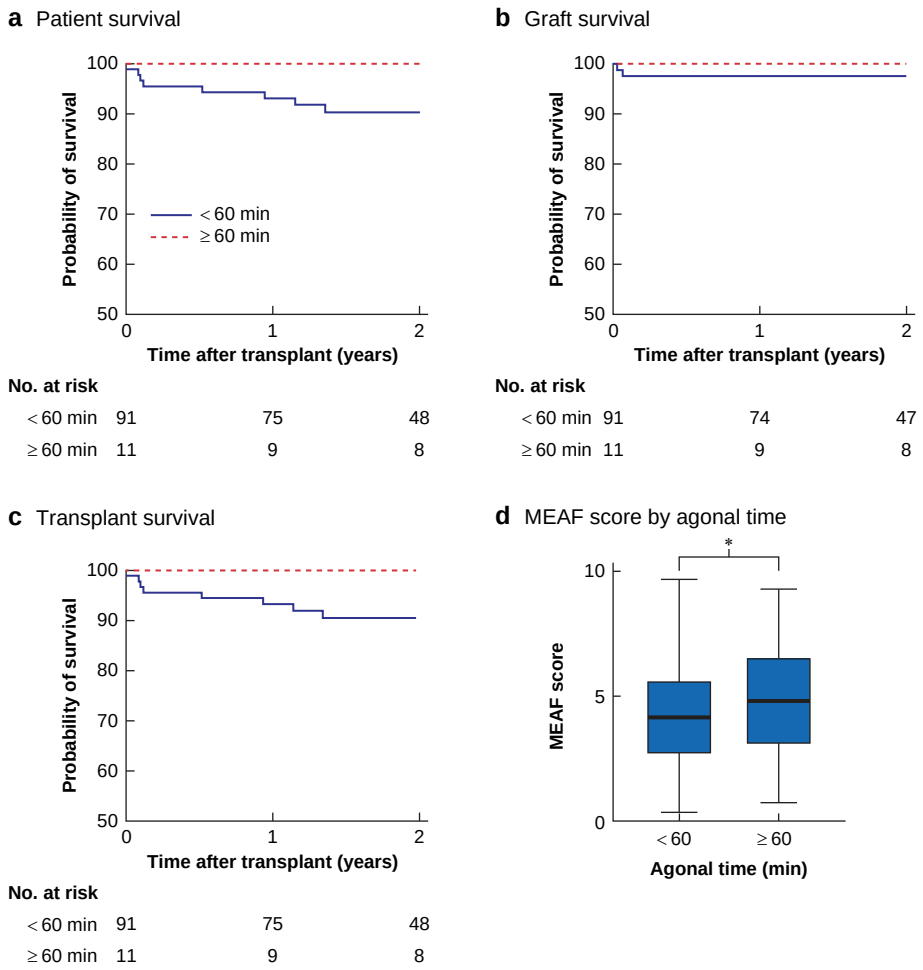

Fig. 1 Outcomes compared by agonal time

a–c Kaplan–Meier plots showing **a** patient, **b** graft, and **c** transplant survival; **a** $P = 0.929$, **b** $P = 0.256$, **c** $P = 0.929$ (Mantel–Cox analysis). **d** Box-and-whisker graph showing Model for Early Allograft Function (MEAF) scores. Median (bold line), i.q.r. (box), and range (whiskers) are shown; *$P = 0.871$ (Mann–Whitney *U* test).

asystolic time 17 (11–22) min; this was not statistically different from times for the cohort of transplanted livers that were utilized (agonal: $P = 0.946$, asystolic: $P = 0.695$; Mann–Whitney *U* test).

Impact of prolonged agonal time on outcome and early allograft dysfunction

The median agonal time was 13 (range 2–56) min for those in the control cohort (less than 60 min) and 108 (68–194) min in the prolonged agonal group. There was no difference in patient survival between groups, with 1-year rates of 93.1 and 100 per cent respectively ($P = 0.929$, Mantel–Cox analysis) (*Fig. 1a*). Death-censored graft survival at 1-year patient survival was 97.8 per cent for the group with an agonal time below 60 min and 100 per cent for the prolonged agonal group; there was no statistical difference between cohorts ($P = 0.256$) (*Fig. 1b*). Transplant survival (graft survival not censored for death) was not significantly different between cohorts ($P = 0.929$) (*Fig. 1c*).

There was no evidence of increased EAD in grafts from donors with a prolonged agonal phase compared with controls, either in terms of an increased Model for Early Allograft Function (MEAF) score (*Fig. 1d*) or according to the Olthoff definition (*Table S1*). There was no significant correlation between MEAF score and agonal time ($r_S = 0.003$, $P = 0.589$).

Overall, 39 of 101 patients (38.6 per cent) had significant acute kidney injury (AKI), but there was no significant difference between cohorts ($P = 0.413$, Pearson's χ^2 test) (*Table S1*).

Impact of asystolic time on survival

To determine whether asystolic time was the significant driver of poorer outcomes, outcomes of liver transplant recipients receiving organs from donors with a short (less than 15 min) or prolonged (15 min or longer) asystolic time were considered (*Fig. S1*); there was no significant difference in patient, graft or transplant survival ($P = 0.636$, $P = 0.178$, and $P = 0.487$ respectively).

There was no significant correlation between MEAF score and asystolic time ($r_S = 0.036$, $P = 0.458$), nor was there a significant difference in MEAF score between cohorts with a short or prolonged asystolic time ($P = 0.726$) (*Fig. S1*). The rate of EAD according to the Olthoff criteria was not significantly different between those with a short (3 of 34, 9 per cent) or a prolonged (11 of 67, 16.4 per cent) asystolic time ($P = 0.297$).

Discussion

The present study has shown that livers recovered using NRP from DCD donors with a prolonged agonal time or asystolic time can be

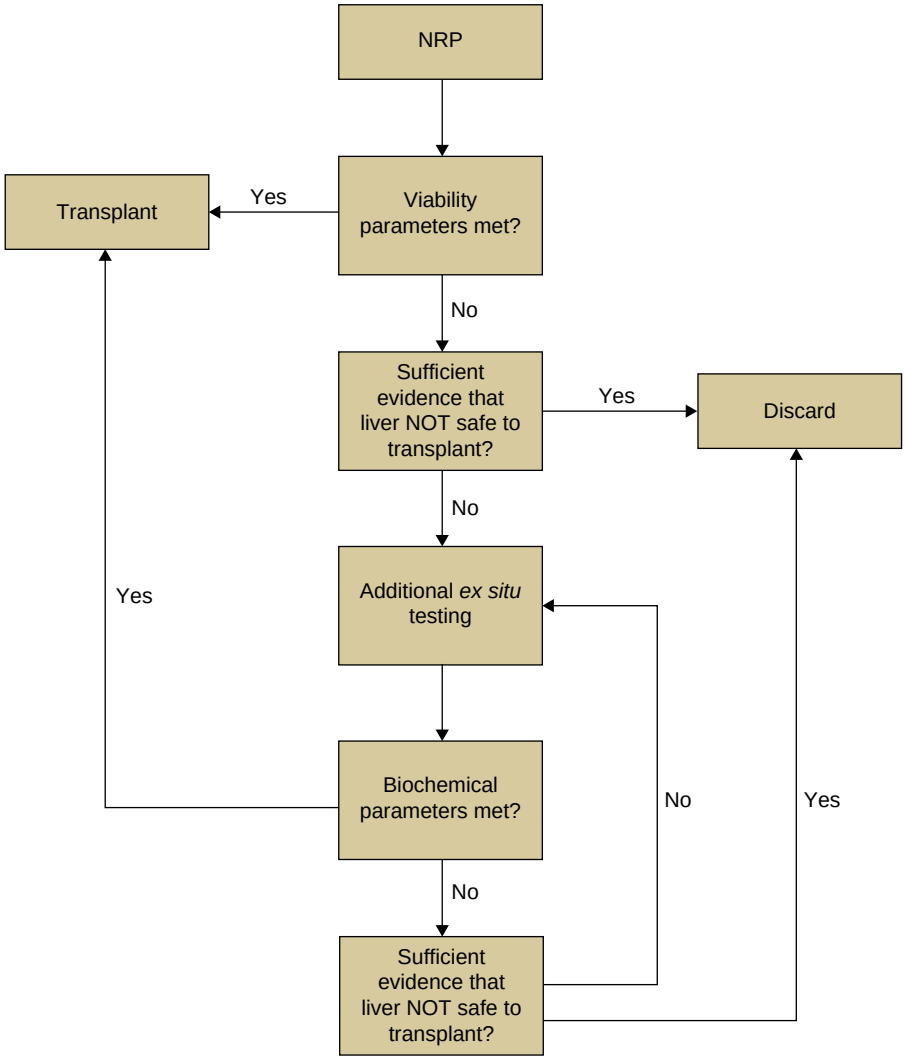

Fig. 2 *In situ* **normothermic regional perfusion decision-making algorithm**
NRP, *in situ* normothermic regional perfusion.

transplanted safely with excellent patient and graft outcomes (*Fig. 1* and *Fig. S1*) when viability parameters are favourable[17,18]. This was not at the expense of increased EAD, AKI or increased incidence of biliary complications (*Fig. 1* and *Table S1*).

In this series, 48.5 per cent of transplants were scored as high risk or futile according to the UK DCD risk score[16], but were utilized safely after NRP (*Fig. 1* and *Fig. S1*). The ability to utilize livers previously considered marginal, such as those with long withdrawal times, has allowed the authors' centre to have one of the shortest waiting times to transplant in the UK, with results that are among the best in the country[12]. Wider utilization of DCD livers recovered using NRP should remove concerns about inferior short- and long-term outcomes[1–3], which has hitherto limited their use[5].

The authors no longer restrict their use of DCD livers by arbitrary time cut-offs from the point of withdrawal; this study has demonstrated safe utilization of livers with prolonged agonal times (up to 194 min) as long as the liver demonstrates biochemical viability[17,18]. A decision-making algorithm[19] was proposed previously that evaluates each stage if there are sufficient data to suggest that an organ can be safely implanted or reasonably discarded. A similar approach is now advocated during NRP (*Fig. 2*). If the liver has not demonstrated suitably robust biochemical data to suggest viability within the 2-h time frame[17,18], but has not overtly declared itself as unsuitable for transplantation, a period of additional *ex situ* normothermic machine perfusion is considered to allow further evaluation (*Fig. 2*). It is suggested that livers from donors with prolonged withdrawal and asystolic phases can be transplanted safely after NRP if their biochemical viability parameters are favourable. More widespread adoption of this approach would allow an increase in donor liver utilization.

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Author contributions

James Richards (Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Software, Validation, Writing—original draft, Writing—review & editing), Rohit Gaurav (Data curation, Investigation, Methodology, Writing—review & editing), Sara Upponi (Conceptualization, Data curation, Methodology, Resources, Software, Writing—review & editing), Lisa Swift (Data curation, Investigation, Methodology, Writing—review & editing), Corrina Fear (Conceptualization, Data curation, Investigation, Methodology, Project administration, Writing—review & editing), Gwilym J Webb (Conceptualization, Methodology, Supervision, Writing—review & editing), Michael Allison (Conceptualization, Methodology, Supervision, Writing—review & editing), Christopher Watson (Conceptualization, Data curation, Investigation, Methodology, Project administration, Writing—review & editing), and Andrew Butler (Conceptualization, Data curation, Investigation, Methodology, Supervision, Writing—review & editing).

Disclosure

The authors declare no conflict of interest.

Supplementary material

Supplementary material is available at *BJS* online.

Data availability

Data included in this paper are available in principle, but any requests would have to be accompanied by the appropriate ethical board approval.

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