



Normothermic Machine Perfusion Enabling Transplantation of a Declined Marginal Donor Liver: A Narrative Review of Organ Utilisation and Viability Assessment

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Abstract

The shortage of transplantable livers is partly a shortage of confidence. Organs are declined because nobody can tell whether they will work, and a liver on ice gives no information while it deteriorates. Perfusing it at body temperature does the opposite: it preserves function and lets that function be measured.

Objectives: To review the published evidence on normothermic machine perfusion in liver transplantation: what it changes in graft injury, organ utilisation and preservation time, what it does not change, and how viability assessment alters the decision to accept a marginal organ.

Material and Methods: Narrative review of randomised trials, viability assessment series, registry analyses and consensus guidance indexed in PubMed and the major transplantation and general medical journals. No new patient data were generated; every estimate quoted is one published by the original investigators.

Results: In a randomised trial of 220 liver transplantations across seven European centres, normothermic perfusion was associated with a 50 per cent lower level of graft injury measured by hepatocellular enzyme release, despite a 50 per cent lower rate of organ discard and a 54 per cent longer mean preservation time (11 hours 54 minutes against 7 hours 45). Early allograft dysfunction and post-reperfusion syndrome were reduced. There was no significant difference in bile duct complications, graft survival or patient survival, and median intensive care and hospital stays were similar.

Conclusion: The mechanism of benefit is best understood as information rather than preservation alone: perfusion allows a liver to be tested before it is committed, which is why discard fell while injury also fell. Survival benefit has not been demonstrated, and claiming it overstates what the trials show.

Abbreviations: AST – Aspartate Transaminase, DBD – Donation after Brainstem Death, DCD – Donation after Circulatory Death, EAD – Early Allograft Dysfunction, NMP – Normothermic Machine Perfusion, SCS – Static Cold Storage.

Keywords: Liver Transplantation; Normothermic Machine Perfusion; Marginal Donor Organs; Viability Assessment; Organ Utilisation

Introduction

Liver transplantation is highly effective and severely rationed by the supply of organs. Many potential donor livers are never used, because suboptimal organs tolerate conventional cold storage poorly and because there has been no reliable way to assess an organ's viability before implanting it [1,2].

Static cold storage works by slowing metabolism. It is simple, cheap and effective for a good organ, but it provides no functional information and the injury it permits accumulates with time, disproportionately in organs already marginal from steatosis, donor age or circulatory-death retrieval [3,4,5].

Normothermic machine perfusion maintains the liver at body temperature with oxygenated blood-based perfusate, avoiding cooling and allowing the organ both to recover and to be functionally tested outside the body [1,6,7]. Preclinical work established that cooling itself is the injurious step in marginal organs [27,28], and mechanistic reviews describe how perfusion mitigates ischaemia-reperfusion injury [34,35]. This review sets out what randomised comparison has shown and what it has not.

Material and Methods

Search strategy: PubMed and the archives of the major transplantation, hepatology and general medical journals were searched for studies of machine perfusion in liver transplantation. Search terms combined liver transplantation with normothermic machine perfusion, hypothermic oxygenated perfusion, viability assessment, organ discard, early allograft dysfunction and marginal donor. Reference lists of consensus guidance [8,9] were screened by hand for primary sources.

Eligibility: Studies were included if they compared a perfusion technique with static cold storage or with another perfusion modality in human liver transplantation, reported viability assessment criteria, or analysed organ utilisation. Preclinical and porcine studies are cited only where they establish a mechanism and are identified as such.

Data extraction and handling: Design, sample size, donor type, comparator, the primary endpoint and the reported result were extracted as published. The primary endpoint is reported alongside every result, because trials in this field use biochemical injury markers and early allograft dysfunction rather than survival, and the distinction determines what can be claimed. No pooling or re-analysis was performed. Figures 1 to 4 and Tables 1 and 2 reproduce published values only. This is a narrative synthesis and was not registered as a systematic review.

Results

The randomised European trial: Two hundred and twenty donor livers, from both brainstem-death and circulatory-death donors, were randomised to normothermic perfusion or static cold storage across seven centres in the United Kingdom, Spain, Germany and Belgium. The primary outcome was peak aspartate transaminase within seven days of transplantation, an accepted marker of hepatocellular injury [10,11].

The principal result: Normothermic perfusion was associated with a 50 per cent lower level of graft injury measured by hepatocellular enzyme release. It achieved this despite a 50 per cent lower rate of organ discard and a 54 per cent longer mean preservation time (Figure 1) [10]. Those three findings pull against each other, which is what makes the result interesting: the perfused arm used organs the cold-storage arm would have thrown away, kept them longer, and still injured them less.

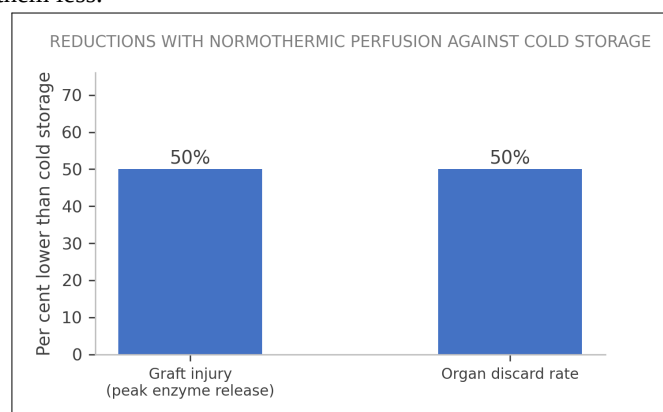


Figure 1: Reductions in graft injury and organ discard with normothermic perfusion against static cold storage [10]

Preservation time: Mean preservation time was 11 hours 54 minutes with perfusion against 7 hours 45 with cold storage (Figure 2) [10,12]. An adaptation of surgical practice occurred during the trial, with teams electing to perfuse for longer and implant at a more convenient hour. Longer preservation with less injury inverts the central constraint of cold storage, in which every additional hour costs the organ something.

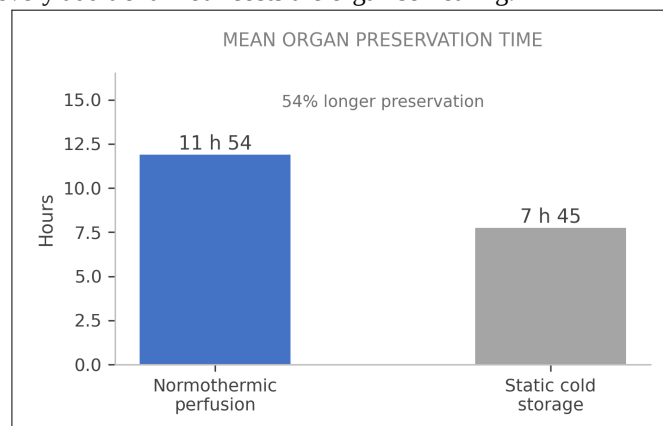


Figure 2: Mean organ preservation time under each modality [10,12]

Related evidence: Early allograft dysfunction rates were lower with perfusion, and post-reperfusion syndrome, itself associated with worse short-term outcome [26], was reduced by approximately 20 per cent [10,12]. A matched comparison from an earlier series reported median peak AST within seven days of 417 IU/L with perfusion against 902 with cold storage, with early allograft dysfunction in 15 against 22.5 per cent (Figure 3) [13]. A separate multicentre randomised trial using a portable normothermic device in 20 United States programmes was designed to test non-inferiority and then superiority for early allograft dysfunction, and reported a reduction [14,15].

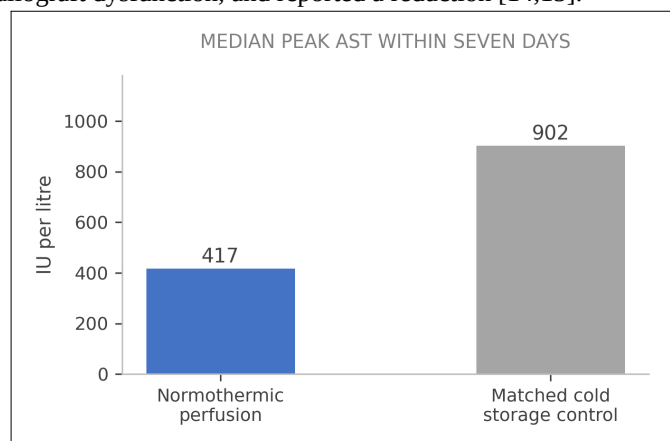


Figure 3: Median peak aspartate transaminase within seven days in a matched comparison [13]

What did not change: There was no significant difference in bile duct complications, in graft survival or in patient survival, and median intensive care and in-hospital stays were similar between groups (Figure 4) [10,12]. Rates of biliary stricture and primary non-function were low in both arms. One organ was discarded because of a device malfunction causing hypoperfusion [12].

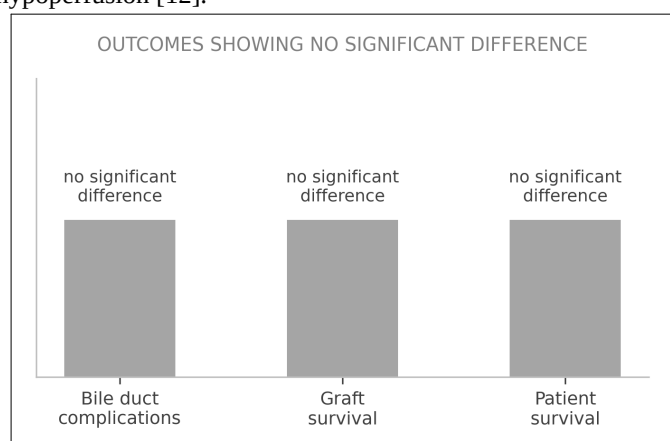


Figure 4: Outcomes showing no significant difference between perfusion and cold storage [10,12]

Study	Design and cohort	Principal reported finding
Nasralla et al. 2018 [10]	RCT, 220 transplants, 7 European centres	50% less graft injury, 50% lower discard, 54% longer preservation
Nasralla et al. 2018 [10]	Same trial, secondary outcomes	Lower early allograft dysfunction; no survival difference
Markmann et al. 2022 [14]	RCT, portable device, 20 US programmes	Reduced early allograft dysfunction against cold storage
Friend et al. [13]	Matched comparison series	Median peak AST 417 vs 902 IU/L; EAD 15% vs 22.5%
Mergental et al. 2020 [16]	Viability assessment of declined livers	Transplanted organs previously declined by all centres
van Rijn et al. 2021 [17]	RCT, hypothermic oxygenated perfusion, DCD	Reduced non-anastomotic biliary strictures
Dutkowski et al. 2019 [7]	Review of evolving perfusion strategies	Compares normothermic and hypothermic approaches

Table 1: Principal studies reviewed, with the finding as reported by the original investigators

Viability assessment: The clinically distinctive capability is testing. During perfusion, lactate clearance, bile production, perfusate pH, glucose metabolism and vascular flow can be measured in an organ that is metabolically active [6,16,18]. Series applying defined viability criteria have transplanted livers that had been declined by every centre offered them, with acceptable outcomes [16,19]. This is a different proposition from preservation: it converts an irreversible judgement made from donor history and appearance into a measurement made on the organ itself.

Alternatives and combinations: Hypothermic oxygenated perfusion is a simpler and cheaper modality that has randomised evidence of its own, including reduced non-anastomotic biliary strictures after circulatory-death donation [17,20]. It does not permit functional testing at physiological temperature, so the two approaches answer different questions [7,21]. Sequential and end-ischaemic protocols have been described, and no randomised comparison establishes a hierarchy between modalities [9,22,23]. Single-centre and pilot randomised experience with normothermic perfusion has been reported from Canada and Italy [30,31], and declined organs have been transplanted after perfusion in North American series [32]. Extended perfusion for up to a week has been demonstrated experimentally [33].

Outcome	What the randomised trial showed	Interpretation
Graft injury (peak AST)	50% lower with perfusion	Primary endpoint; biochemical, not clinical [10]
Organ discard	50% lower with perfusion	Viability testing changes the accept decision [10,16]
Preservation time	54% longer with perfusion	Constraint of cold storage inverted [10,12]
Early allograft dysfunction	Reduced	Reproduced in a separate randomised trial [10,14]
Biliary complications	No significant difference	Low event rates in both arms [10,12]
Graft and patient survival	No significant difference	Trial not powered for survival [10]

Table 2: Outcomes in the randomised comparison and what each supports

Discussion

The most instructive feature of the principal trial is the combination of its findings rather than any one of them. A 50 per cent reduction in enzyme release would be a reasonable result on its own. Achieving it while also discarding half as many organs and preserving them for half as long again is a different claim, because both of those should have made the injury figures worse [10].

The explanation is that perfusion supplies information. Under cold storage, a marginal liver is accepted or declined on donor age, steatosis, warm ischaemic time and the surgeon's judgement of its appearance. Under perfusion, it can be watched working: lactate cleared, bile produced, flows maintained [6,16,18]. Some organs that look poor perform well and are transplanted; some that look acceptable fail testing and are declined. Discard falls not because standards drop but because the decision improves.

What has not been shown deserves equal prominence. There was no significant difference in graft survival, patient survival or biliary complications [10]. This is frequently elided in summaries of the technology. The trial was not powered for survival, and absence of a demonstrated difference is not demonstration of absence, but a clinician or commissioner reading that perfusion improves survival is reading something the evidence does not say. What it does say is that more patients can be transplanted from the same donor pool, which is a benefit at the level of the waiting list rather than the individual recipient.

For the specific situation of a declined marginal organ, the implication is reasonably clear. A liver refused by other centres on appearance and donor history is exactly the organ for which a functional test carries most information, and series applying defined criteria have transplanted such organs successfully [16,19]. The caution is that viability thresholds differ between groups and have not been prospectively validated against each other, so what counts as a passing organ remains partly local [18,22,29].

Study limitations

The limitations belong to the underlying literature. The principal trial used a biochemical primary endpoint rather than a clinical one, and was not powered for survival or for biliary complications [10]. Blinding is impossible. Surgical practice adapted during the trial, lengthening preservation in the perfusion arm and confounding the comparison of preservation intervals [12]. Discard decisions were made by unblinded clinicians who knew which arm the organ was in, which is the mechanism of the discard finding and also a source of bias in it [10]. Viability criteria differ between series and have not been prospectively validated [16,18]. Comparison between normothermic and hypothermic modalities is indirect [7,17]. Cost-effectiveness in routine practice is not established [24], and the field has been urged to evaluate innovation systematically rather than adopt it informally [25]. And the trials were conducted in high-volume European and North American programmes whose baseline discard rates may not generalise [10,14].

Conclusion

Normothermic machine perfusion halves the biochemical injury a donor liver sustains, while allowing half as many organs to be discarded and preservation to run half as long again. The mechanism is not simply better preservation but better information: an organ that can be tested can be accepted or refused on evidence rather than on appearance, which is why a liver declined elsewhere may still be transplantable. What the randomised evidence does not show is any difference in graft survival, patient survival or biliary complications, and that should be stated whenever the technology is described. The benefit demonstrated so far accrues to the waiting list rather than to the individual recipient, and that is worth a great deal without being what it is often said to be.

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Conflict of Interest

The authors declare no competing interests.

Ethics Statement

This article reviews previously published studies only. No new patient data were collected and no participants were recruited, so ethical approval was not required.

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