

End-ischemic Normothermic Oxygenated versus sequential Hypothermic and Normothermic Oxygenated Machine Perfusion for Rescue-allocated, Major Extended criteria Donors in Liver transplantation: A multicenter, randomized controlled trial – WARM-UP

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Background

The widening gap between donor liver supply and increasing transplantation indications has led to broader use of extended criteria donor (ECD) grafts, which carry an increased risk of primary non-function and perioperative complications. Normothermic machine perfusion (NMP) enables functional assessment under near-physiological conditions, improving the safe utilization of ECD livers. However, marginal grafts remain highly susceptible to ischemia-reperfusion injury (IRI). Hypothermic oxygenated perfusion (HOPE) mitigates IRI by restoring mitochondrial function prior to reperfusion. Sequential application of HOPE followed by NMP after controlled oxygenated rewarming (COR-NMP) combines mitochondrial recovery with functional assessment, representing a promising strategy for marginal grafts. While observational clinical data are promising, prospective evaluation against established NMP protocols is still needed.

Study Design

WARM-UP is a multicenter, open-label, randomized controlled trial evaluating sequential dual HOPE followed by dual NMP (D-HOPE/D-NMP) versus standard end-ischemic D-NMP in adult recipients of ECD livers allocated via Eurotransplant rescue allocation. Intervention grafts undergo 1–2 hours of D-HOPE, followed by controlled oxygenated rewarming and ≥4 hours of D-NMP. Control grafts receive ≥6 hours of D-NMP alone.

Objectives & Endpoints

Primary objective

To test the superiority of either sequential HOPE/NOPE or NOPE alone in an end-ischemic back to base setting with respect to the successful utilization of ECD livers.

Primary Endpoint

Utility & Efficacy (Composite endpoint = successful graft utilization [meeting VC at the end of perfusion] + no graft loss by 6 month + no death by 6 month + no post-transplant NAS cholangiopathy by 6 months)

Secondary objectives

To test the superiority of either sequential HOPE/NOPE or NOPE alone in reaching hard and surrogate markers of mid- and long-term outcomes after liver transplantation with ECD donor livers.

Secondary endpoints

- Discard rate (Discarded organs after HOPE/NOPE/All Organs on HOPE/NOPE)
- Primary Non Function [PNF] (= liver failure leading to death or the need for re-transplantation within 30 days of the primary operation)
- Retransplant rate within index stay
- Model of Early Allograft Function score (MEAF score). [Time Frame: During the first 3 postoperative days.] The MEAF score includes bilirubin, ALT max and INR max at postoperative day 3. Range 0 (better outcome) to 10 (worse outcome)
- Early Allograft Dysfunction Olthoff criteria on POD7 (= one of the following: Serum bilirubin ≥ 10 mg/dl, INR ≥ 1.6 , AST/ALT >2000 U/l during the first 7 days)
- Peak AST/ALT until POD7
- Post-transplant cholangiopathy (= one of the following: non anastomotic stricture [NAS]/ischemic bile duct lesion [ITBL] and cast formation to full thickness; bile duct necrosis in the presence of a patent hepatic artery) at 6 and 12 months [diagnosed by MRI or ERCP]
- Incidence of bile-duct anastomotic complications (=stenosis/leakage with 90 days requiring surgical, endoscopic or radiological intervention)
- In-hospital mortality and postoperative length of stay (discharge date-index stay [first]transplant date) competing risk analysis
- Incidence of early Biopsy proven rejection within the first 3 month
- Incidence of early (new) donor-specific antibodies within the first 3 months
- Patient survival at 6 and 12 months
- Graft survival at 6 and 12 months

Eligibility

Donor – Inclusion:

Major ECD Brain-dead or depending on national legislation DCD donor

Major ECD:

- Organ is allocated via the ET rescue allocation procedure and fulfills at least one of major ECD criteria:
- DCD (when appropriate depending on national legislation)
- Donor age >65
- Liver steatosis on biopsy $\geq 40\%$
- AST and/or ALT > 1000 IU/L at any time
- Latest Serum Bilirubin >3 mg/dl and/or γ -GT >100 U/l
- CIT ≥ 12 h

Donor – Exclusion:

The donor may be declined at the discretion of the transplant surgeon.

Recipient – Inclusion:

- Written informed consent prior to the performance of any study-specific procedure
- Affiliated to the national social security system
- Recipient age ≥ 18 years
- Patient undergoing primary liver transplantation
- labMELD ≤ 25
- Candidate for a first elective liver transplantation, whatever the indication

Recipient – Exclusion:

- Retransplantation
- Fulminant hepatic failure
- Split liver transplantation, Domino transplantation, Combined liver transplant, Living donor liver transplantation
- Unexpected medical contraindication to liver transplantation
- Patient under legal protection
- Patient deprived of liberty by a judicial or administrative decision
- Patient refusing to participate in the study
- Pregnant or lactating women
- Inability to understand information concerning the protocol

Criteria for discontinuing or modifying allocated interventions

Patients will terminate the study prematurely if:

- Technical problem preventing any use of the perfusion machine
- Non-transplantable patients (e.g., peritoneal carcinosis)
- Donor graft not meeting predefined viability criteria

Predefined viability criteria

For a liver to be considered viable, it must demonstrate homogeneous perfusion and metabolize perfusate lactate to levels ≤ 2.5 mmol/L within 3-6 hours of initiation of perfusion, and meet at least 2 of the following additional criteria

- Evidence of bile production
- Metabolism of glucose
- Maintenance of stable arterial and portal blood flows (≥ 150 and ≥ 500 mL/min, respectively)

Duration

- Duration of the inclusion and randomization period: 24 months.
- Duration of follow-up by patient: 12 months (± 30 days) after transplantation (36 months maximum).
- Total duration of the study: 36 months (± 30 days).
- Start of inclusions: January 2026

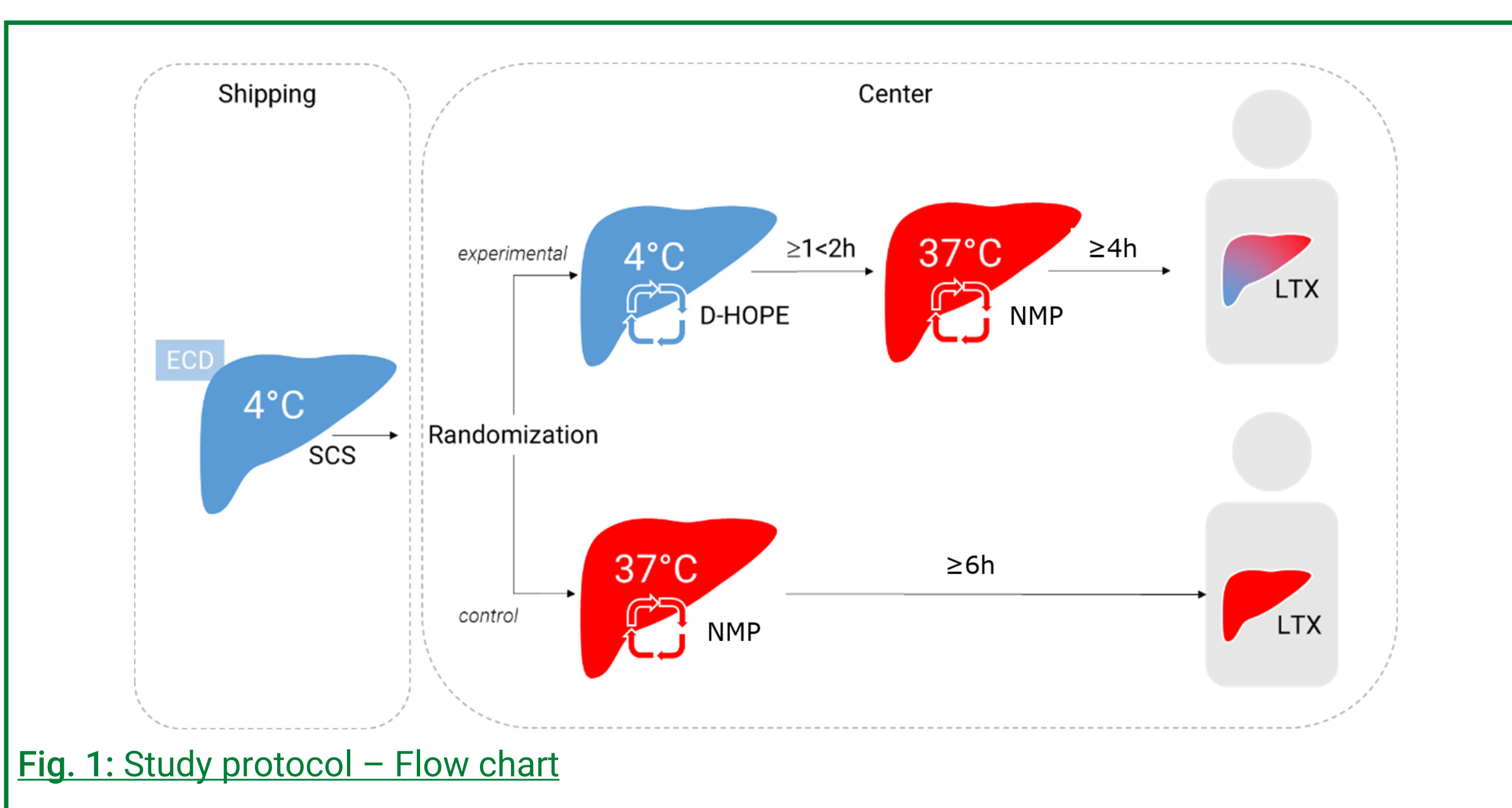


Fig. 1: Study protocol – Flow chart

Perfusion machines and perfusion fluids

- Any perfusion machine approved for HOPE or NOPE can be used
- Study sites may use their locally established standard.
- During NMP the use of RBCs as oxygen carriers is mandatory.
- Perfusion fluids should be kept consistent throughout the study.

Conclusion

The WARM-UP trial prospectively evaluates whether sequential D-HOPE/D-NMP improves post-transplant outcomes in ECD liver grafts compared to NMP alone. By combining mitochondrial reconditioning and viability assessment, this approach may enhance transplant safety and expand the donor pool. The trial aims to establish an evidence-based end-ischemic perfusion protocol for optimizing ECD liver transplantation.