XVIVO

XVIVO heart technology

# Clinical evidence summary

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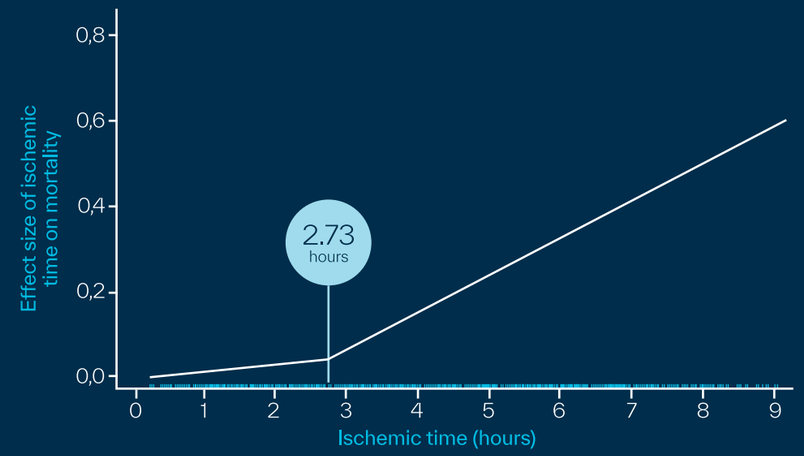
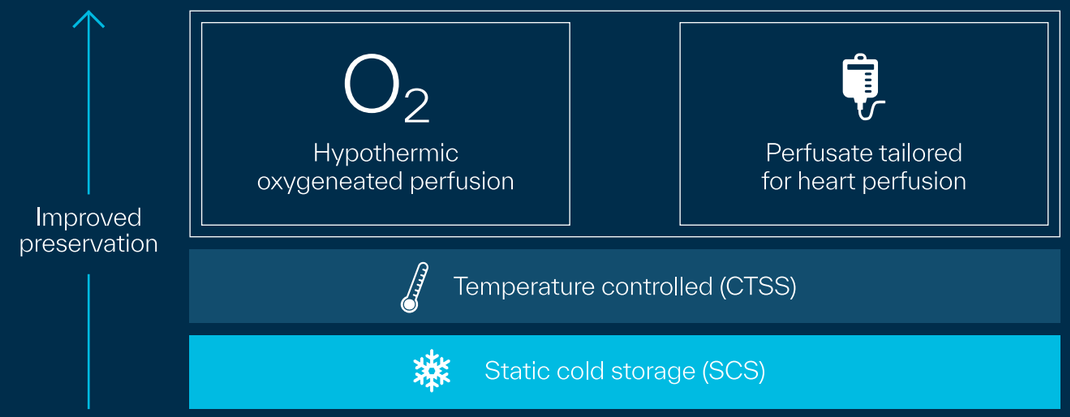
The vast majority of hearts transplanted worldwide are still preserved using static cold storage (SCS), but the challenges associated with the duration of ischemic time are well-known.

Optimal donor heart ischemic time is <3 hours with optimal donor heart ischemic time is < 3 hours with SCS.




Adapted from: Tang et al., (2022), Determining optimal donor heart ischemic times in adult cardiac transplantation

But now there is new HOPE: hypothermic oxygenated perfusion.

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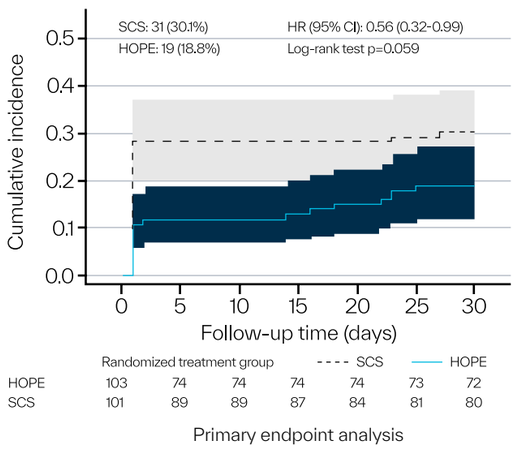
# First ever randomized controlled study comparing hypothermic oxygenated perfusion (HOPE) with static cold storage (SCS)

## Hypothermic oxygenated perfusion of the donor heart in heart transplantation: the short-term outcome from a randomised, controlled, open-label, multicentre clinical trial

F. Rega, G. Lebreton, M. Para, S. Michel, R. Schramm, E. Begot, K. Vandendriessche, C. Kamla, G. Gerosa, M. Berman, U. Boeken, S. Clark, A. Ranasinghe, F. Ius, A. Forteza, A. Pivodic, F. Hennig, S. Guenther, A. Zuckermann, C. Knosalla, G. Dellgren, A. Wallinder.

The Lancet / 2024 / doi.org/10.1016/S0140-6736(24)01078-X

A total of 229 patients were enrolled across 15 investigational sites in 8 European countries between November 2019 and May 2023. The primary analysis population included 204 transplanted patients. All donor hearts preserved with HOPE were deemed transplantable after perfusion.




Primary endpoint analysis

The primary outcome was time-to-first-event of a composite measure, including cardiac-related death, moderate or severe PGD of the left ventricle, PGD of the right ventricle, acute cellular rejection of at least grade 2R, or graft failure within 30 days after transplantation.

The cumulative incidence of primary endpoint events was 19 (19%) in the HOPE group and 31 (30%) in the SCS group, corresponding to a risk reduction of 44%, (HR, 0.56; 95% CI, 0.32 to 0.99; log-rank, p=0.059). After adjustment for trial site effects the risk reduction was 49% (HR, 0.51, 95% CI, 0.28 – 0.91; log-rank, p=0.022).

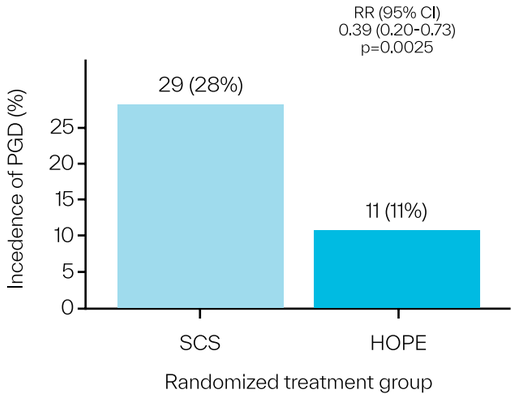
**44%** Risk for severe transplant complications reduced by 44% in the HOPE group

Following a prespecified sensitivity analysis, the primary endpoint was divided into PGD, which can only occur in the first 24 h after transplantation according to ISHLT definitions, and the other components of the primary endpoint analyzed for 30 days of follow-up.

There were significantly fewer PGD events in the HOPE group (11%, n = 11) compared to the SCS group (29%, n = 29), (RR 0.39; 95% CI, 0.20 to 0.73) corresponding to a risk reduction of 61%. No significant differences were observed for the remaining components of the primary endpoint, (HR, 1.04; 95% CI, 0.41 to 2.62).

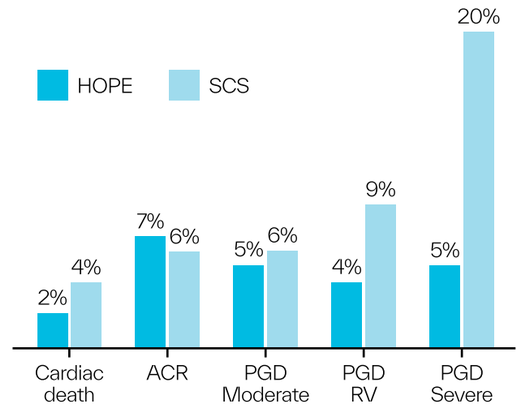
The components of the primary endpoint were analyzed separately as secondary endpoints. The largest difference between the groups was observed in the incidence of severe PGD; 5 (5%) in the HOPE group versus 21 (20%) in the SCS group, corresponding to a risk reduction of 76% (RR, 0.24; 95% CI, 0.10- 0.62).

**61%** Risk for PGD reduced by 61%




PGD components of the primary endpoint (time-to-first-event).

**76%** Risk for severe PGD reduced by 76%




Secondary endpoint analysis: Components of the primary endpoint

Serious adverse events (SAEs) were analysed in the safety population which consisted of all patients who received a transplant (97 HOPE and 125 SCS). SAEs occurred in 65% of the recipients in the HOPE group (in total 158 events) and in 70% in the SCS group (222 events).

Major adverse cardiac transplant events were reported in 18 (18%) and 33 (32%) patients in the HOPE and SCS group corresponding to risk reduction of 44%.

ECMO was used in 19 (19%) patients in the HOPE group and 28 (27%) patients in the SCS group, corresponding to 31% risk reduction.

The 44% risk reduction in the primary endpoint associated with HOPE indicates a clinically meaningful benefit. Post-transplant complications, measured as major adverse cardiac transplant events, were also significantly reduced. Analysis of secondary outcomes confirms that HOPE was beneficial in reducing primary graft dysfunction.

> "..ischemia-reperfusion injury caused by SCS can be mitigated and transplant outcome improved if donor hearts are preserved using HOPE."
>
> Rega et al, 2024

# Investigator initiated clinical research investigating hypothermic oxygenated perfusion (HOPE) with XVIVO heart technology

EUROPE

## Successful clinical transplantation of hearts donated after circulatory death using direct procurement followed by hypothermic oxygenated perfusion: A report of the first 3 cases

J. Brouckaert, K. Vandendriessche, K. Degezelle, K. Van De Voorde, F. De Burghgraeve, L. Desmet, D. Vlasselaers, C. Ingels, D. Dauwe, E. De Troy, L. Ceulemans, D. Van Raemdonck, D. Monbaliu, B. Meyns, R. Van den Eynde, S. Rex, J. Van Cleemput, and F. Rega.

J Heart Lung Transplant / 2024 / doi.org/10.1016/j.healun.2024.07.018

This publication is a report of the first three clinical cases of transplantation of hearts donated after circulatory death (DCD) using direct procurement followed by hypothermic oxygenated perfusion (DP-HOPE).

The donors were Maastricht category III, of ages 40-52 years, and the functional warm ischemic times were 15-21 minutes. All donor hearts perfused on the XVIVO Heart Assist Transport had stable aortic flows during a total out-of-body-time of 4-6 hours. All three recipients were easily weaned off cardiopulmonary bypass in sinus rhythm and were extubated in the operating room. Perioperative transesophageal echocardiography showed good biventricular function without any relevant inotropic support. None of the patients experienced Primary Graft Dysfunction (PGD) and none received mechanical circulatory support. All three patients are at home and in good health at respectively 110, 90, and 55 days posttransplant.

> "[HOPE] is a promising strategy to improve and simplify DCD heart procurement and preservation."
>
> Brouckaert et al, 2024





## Successful heart transplant after 12 h preservation aboard a commercial flight

G. Lebreton, P. Leprince.

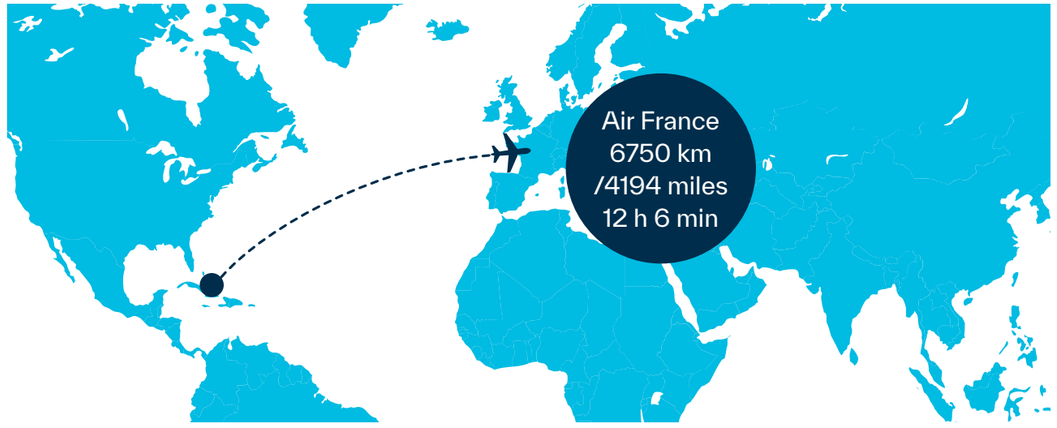
The Lancet/ 2024 / doi:10.1016/S0140-6736(24)00258-7

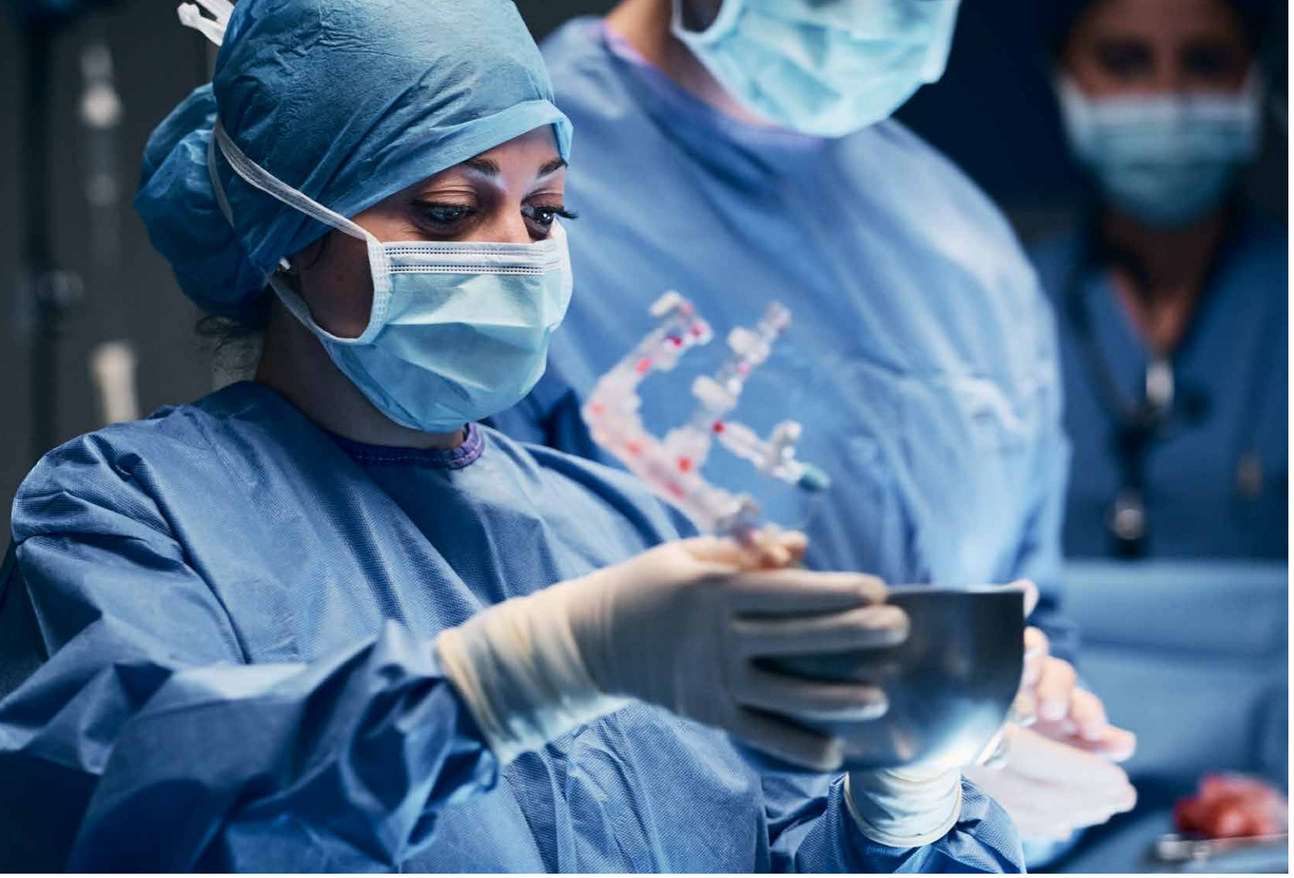
For the first time, a heart transplant has been successfully performed after transport of a donor heart across the Atlantic Ocean. The donor was a 48-year-old male, located in the French West Indies. The heart was transported to Paris in the cabin on a commercial flight. Preservation (12 h 6 min) and perfusion (10 h 32 min) was uneventful, despite severe turbulence. The recipient was a 70-year-old man with terminal ischaemic cardiomyopathy and chronic renal insufficiency. After transplantation, the heart immediately had normal biventricular function without any graft dysfunction. The cardiac index was 3·4 L/min per $m^2$ with only a low dose of inotropic support. The patient was extubated 10 h after the surgery, had 2 days of continuous renal replacement therapy, and was weaned off inotropic support on day 5. The recipient was discharged 30 days after surgery.

> "For the first time, a heart transplant has been successfully performed after transport of a donor heart across the Atlantic Ocean, marking a substantial advancement in the realm of organ transplantation."
>
> Lebreton and Leprince, 2024

> "This transplant marks the first instance of a donated heart being flown across the Atlantic, covering a distance of 6750 km from the French West Indies to Paris, a feat previously unimaginable in organ transplantation."
>
> Lebreton and Leprince, 2024

The first-ever transplantation with a donor heart transported across the Atlantic Ocean.





Alexandra Moroianu,
Heart recipient, Australia

AUSTRALIA/NEW ZEALAND

In Australia and New Zealand, where long distances have limited utilization of donor hearts, safe extension of the preservation time is crucial. Not only is HOPE enabling long distance procurement, it is also allowing implanting teams to select recipients whose operative complexity may require prolonged time beyond the current limitations of traditional static cold storage.

## Hypothermic oxygenated perfusion (HOPE) safely and effectively extends acceptable donor heart preservation times – results of the Australian and New Zealand trial

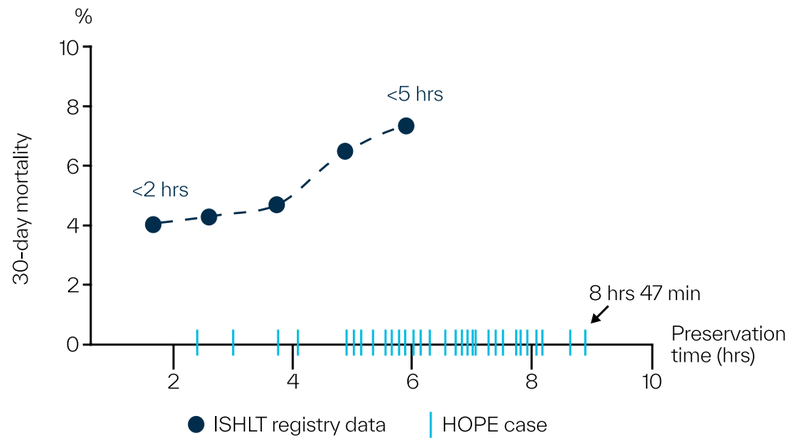
D. McGiffin, C. Kure, P. Macdonald, P. Jansz, S. Emmanuel, S. Marasco, A. Doi, C. Merry, R. Larbalestier, A.Shah, A. Geldenhuys, A. Sibal, C. Wasywich, J. Mathew, E. Paul, C. Cheshire, A. Leet, J. Hare, S. Graham, J. Fraser, D. Kaye.

J. Heart Lung Transplant / 2023 / doi: 10.1016/j.healun.2023.10.020

In this nonrandomized, single arm, multicenter trial a total of 36 patients were transplanted with donor hearts preserved using HOPE with the XVIVO Heart Assist Transport. Each center completed one or two standard preservation time cases, followed by long preservation time cases. The mean preservation time in the long preservation time group was 414 minutes, the longest being 8 hours and 47 minutes. 26 hearts were transported for a distance longer than 1000 km, and four of them longer than 3000 km. Thirty-day survival was 100%. One recipient in the long preservation group developed severe right ventricular PGD. Two recipients developed severe secondary PGD (one in each group). Thirty-day survival with HOPE was superior compared to historical data from the International Society of Heart and Lung Transplantation (ISHLT) Registry where a strong relationship between mortality and increasing ischemic time was affirmed.

**HOPE**

enabled excellent outcomes with low ECMO rates, even in complex recipients and after extended preservation times.

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# Australian outcomes from heart transplantation in the machine perfusion era

Y. Joshi, C. MacLean, S. Emmanuel, K. Wang, C. Soto, J. Villanueva, L. Gao, A. Doyle, S. Dutta, J. Wu, N. Vaidhya, E. Granger, A. Watson, M. Connellan, A. Iyer. P. Jansz, and P. Macdonald.

Ann Cardiothorac Surg / 2024 / doi: 10.21037/acs-2024-dcd-0069

This publication presents a retrospective analysis of heart transplants that occurred at St Vincent's Hospital, Sydney, from January 2021 to February 2024, with focus on different preservation strategies and recipient outcomes such as severe primary graft dysfunction (sPGD) and mortality.

Heart transplants were categorized into three groups:

(I) DCD-NMP (n=44): heart transplants from DCD donors, perfused utilizing normothermic machine perfusion (NMP) with Transmedics OCS Heart;

(II) DBD-HOPE (n=38): hearts transplanted from DBD donors and perfused utilizing hypothermic oxygenated perfusion (HOPE) with the XVIVO XHAT device. XHAT was used if the anticipated donor ischemic time exceeded 6 hours either due to donor location, transport time and/or recipient complexity;

(III) DBD-SCS (n=78): heart transplants from DBD donors preserved utilizing traditional static cold storage (SCS).

The donor preservation time in the DBD-HOPE group was 361+-89 minutes, which was significantly longer than in the other groups, P<0.001. Not only is this indicative of utilization of HOPE for long distance procurement, it is also a by-product of implanting teams being able to select more complex recipients. DBD-HOPE group had significantly more recipients requiring a re-do sternotomy at the time of transplant compared to the other two groups, as well as significantly longer cardiopulmonary bypass and cross clamp times, reflecting the increased complexity of the recipients.

Despite the increased recipient complexity and mean preservation time exceeding 6 hours in the DBD-HOPE group, there was no significant difference between all groups in: survival, rates of sPGD, length of hospital stay or incidence of permanent stroke.

The rates of sPGD requiring extracorporeal membrane oxygenation (ECMO) in the DCD-NMP, DBD-HOPE and DBD-SCS groups were 7%, 5% and 5% respectively, P=0.9.

For the groups DCD-NMP, DBD-HOPE and DBD-SCS respectively: 30-day survival was 100%, 97% and 100%; 1-year survival was: 94%, 90% and 94%; and 2-year survival was: 90%, 90% and 89% (P=0.9).

> "For BD donors, [HOPE] allows for donor hearts to be preserved significantly longer than SCS with no differences in survival or sPGD."
>
> Joshi et al, 2024





# Initial australian experience with the XVIVO non-ischaemic hypothermic perfusion device for heart preservation

S. Emmanuel, K.Muthiah, D. Tardo, P. MacDonald, C. Hayward, D. McGiffin, D. Kaye, J. Fraser, P. Jansz.

J. Heart Lung Transplant / 2023 / doi:10.1016. j.healun.2023.02.133

This abstract highlights outcomes from the first 13 patients who received a donor heart preserved with the XVIVO Heart Preservation System at St Vincent's Hospital, Sydney, Australia. Patient selection was part of the Australia-New Zealand Trial. The median donor ischaemic time was 404 minutes (range 296-527). 12 patients were successfully weaned from cardiopulmonary bypass post-transplant, 1 patient required VA-ECMO due to secondary graft dysfunction for a duration of 2 days. Median length of stay at intensive care unit (ICU) was 4 days (range 2-37). Median intubation time was 19 hours (13-316). Median post-operative length of stay was 32 days (11-119). There was no post-operative mortality.

# Favorable impact of hypothermic machine perfusion (HMP) on early renal outcomes in patients undergoing heart transplantation using prolonged (6-8 hour) donor hearts

D. Kaye, J. Fraser, P. Jansz, P. MacDonald, S. Marasco, A. Doi, C. Merry, S. Emmanuel, R. Larbalestier, A. Shah, A. Geldenhuys, A. Sibal, C. Wasywich, C. Kure, D. McGiffin.

J. Heart Lung Transplant / 2023 / doi: 10.1016/j.healun.2023.02.1702

In this study, renal function and need for dialysis in participants (n=32) of the Australia and New Zealand Trial of HOPE to a cohort of conventional single center heart transplantation patients (C-HTx, n=62) were compared at 24, 48 and 72 hours. Despite the prolonged ischemic time (377±15 vs 185±15 mins, p<0.001) in HOPE patients, the use of renal replacement therapy (RRT) at 72 hours tended to be less than in C-HTx (22% vs 37%). The post-operative increase in creatinine in non-RRT was attenuated in HOPE vs C-HTx patients at 24 hrs (26±10 vs 49±7 umol/L, p=0.06), 48 hrs (23±12 vs 69±12 umol/L, p=0.008) and 72 hrs (14±13 vs 60±13 umol/L, p=0.03). Despite the use of donor hearts with prolonged ischemic times, renal outcomes in recipients of cardiac allografts preserved using HOPE were comparable or better than those in patients with shorter preservation times with static cold storage.

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# Pre-clinical research investigating hypothermic oxygenated perfusion (HOPE)

The following pages present summaries of investigator initiated pre-clinical studies looking into HOPE and the mechanisms behind the improved preservation.

## Safe orthotopic transplantation of hearts harvested 24 hours after brain death and preserved for 24 hours

S. Steen, A. Paskevicius, Q. Liao, T. Sjöberg.

Scand Cardiovasc J. / 2016 / doi: 10.3109/14017431.2016.1154598

Steen et al 2016 investigated HOPE in a porcine model, where the donor hearts (n=10) were perfused for 24 hours at 8°C in cycles of 15 min perfusion followed by 60 min without perfusion. The control group consisted of three donor hearts preserved with static cold storage for 24 hours. After preservation, the hearts were transplanted and followed during 24 hours. In the control group all recipient pigs died within 1 hour in spite of maximal inotropic support. Necropsy of the control group hearts showed minimal ventricular lumen due to massive edema. All transplanted pigs in the test group were weaned off extra corporeal circulation (ECC) shortly after reperfusion and had stable circulation with normal urinary output during the 24 h post transplantation observation period. An adrenaline stress test in the end of the follow up period showed that all transplanted hearts had the capacity to develop a dose-dependent increase in aortic pressure, indicating a well-functioning myocardium.





## Intact coronary and myocardial functions after 24 hours of non-ischemic heart preservation

G. Qin, B. Wohlfart, L. Zuo, J. Hu, T. Sjöberg and S. Steen.

Scand Cardiovasc J. / 2020/ doi: 10.1080/14017431.2019

24 hour preservation with HOPE was investigated by Qin et al 2020, studying endothelium-dependent relaxation of the coronary arteries and myocardial contractility. Porcine hearts were preserved for 24 h at 8°C in cycles of 15 minutes perfusion with a pressure of 20 mmHg, 40 minutes perfusion with a pressure of 10 mmHg and 5 minutes non-perfusion. Segments of the perfused coronary arteries were studied in organ baths and compared to fresh controls. There were no significant differences of myocardial water content, endothelium-dependent relaxation, endothelium-independent relaxation, peak force of myocardium contraction, time from stimulus to peak force, time from peak to half relaxation, potentiation, or calcium recirculation between the 24-hour perfusion group and a fresh control group..

## Donor heart ischemic time can be extended beyond 9 hours using hypothermic machine perfusion in sheep

L.E. See Hoe, G.L. Bassi, K. Wildi, M.R. Passmore, M. Bouquet, K. Sato, S. Heinsar, C. Ainola, N. Bartnikowski, E.S. Wilson, K. Hyslop, K. Skeggs, N.G. Obonyo, T. Shuker, L. Bradbury, C. Palmieri, S. Engkilde-Pedersen, C. McDonald, S.M. Colombo, M.A. Wells, J.D. Reid, H. O'Neill, S. Livingstone, G. Abbate, A. Haymet, J.-S. Jung, N. Sato, L. James, T. He, N. White, M.A. Redd, J.E. Millar, M.V. Malfertheiner, P. Molenaar, D. Platts, J. Chan, J.Y. Suen, D.C. McGiffin, and J.F. Fraser.

J. Heart Lung Transplant / 2023 / doi: 10.1016/j.healun.2023.03.020

In this study, three groups were compared following heart transplantation in a sheep model; 2 hours static cold storage (SCS) (n = 16), 2 hours hypothermic oxygenated perfusion (HOPE) (n = 12), and 8 hours HOPE (n = 14). During HOPE, the donor heart was intermittently perfused at 8°C in cycles of 15 min perfusion (using a perfusion pressure of 20-25 mm Hg) and 60 mins of non-perfusion. All HOPE recipients (n = 26) completed the study to 6 hours observation post-transplant, required less vasoactive support for hemodynamic stability and exhibited superior metabolic and fluid status and inflammatory profiles compared to SCS recipients. Contractile function and cardiac damage (troponin I release and histological assessment) were comparable between groups.

## Non-ischaemic heart preservation to improve donor heart quality

L. Wang, N. Chilvers, M. Huang, L. Bates, C.Y. Pang, G. Chelsea, M. Brown, M. Murphy, G. MacGowan, S. Ali, and J. Dark.

J. Heart Lung Transplant / 2023 / doi.org/10.1016/j.healun.2023.02.205

Human hearts declined for transplant were preserved with HOPE (n=8, 5 donation after brain death (DBD), 3 donation after circulatory death (DCD)) and static cold storage (SCS) (n= 5; DBD) to compare the differences in the left ventricular (LV) function. LV biopsies were taken at the end of preservation for immunofluorescence staining and measurement of succinate and adenosine diphosphate/adenosine triphosphate ratio (ATP/ADP). All hearts were then reperfused on a modified Langendorff system at 37°C for LV functional assessment. All HOPE hearts had significantly better contractility, relaxation and developed higher pressure after one hour of reperfusion than the SCS hearts. The authors concluded that this could be explained by less mitochondrial dysfunction, better energy profile, and fewer loss of cardiomyocytes through necroptosis after preservation.

## Ex-situ oxygenated hypothermic machine perfusion in donation after circulatory death heart transplantation following either direct procurement or in-situ normothermic regional perfusion

N. Moeslund, I.A Ertugrul, M.A Hu, F. Flyvholm Dalsgaard, L.B Ilkjaer, P. Ryhammer, M. Pedersen, M. E. Erasmus, H. Eiskjaer.

J. Heart Lung Transplant / 2023 / doi:10.1016/j.healun.2023.01.014

This study investigated primary graft function in donation after circulatory death (DCD) hearts preserved with HOPE following either direct procurement (DPP) or normothermic regional perfusion (NRP) with subsequent transplantation in a porcine model. After weaning from cardiopulmonary bypass, ventricular function was assessed by pressure-volume admittance and Swan-Ganz catheters. Left ventricular contractility was correlated to available HOPE parameters using Spearman's rank correlation. The authors suggest that coronary flow and oxygen extraction during HOPE may be important predictors of early post-transplantation graft contractile function from DCD donors.



# List of publications

### CLINICAL INVESTIGATIONS

**Brouckaert J**, et al. *Successful clinical transplantation of hearts donated after circulatory death using direct procurement followed by hypothermic oxygenated perfusion: A report of the first 3 cases*. J Heart Lung Transplant. 2024;43(11):1907-10.

**Emmanuel S**, et al. (117) *Initial Australian Experience with the Xvivo Non-Ischaemic Hypothermic Perfusion Device for Heart Preservation.* The Journal of Heart and Lung Transplantation. 2023;42(4):S61-S2.

**Joshi Y**, et al. *Australian outcomes from heart transplantation in the machine perfusion era*. Annals of Cardiothoracic Surgery. 2024.

**Kaye AD**. F*avorable Impact of Hypothermic Machine Perfusion (HMP) on Early Renal Outcomes in Patients Undergoing Heart Transplantation Using Prolonged (6-8 Hour) Donor Hearts*. The Journal of Heart and Lung Transplantation. 2023;42:188.

**Lebreton G**, et al. *Successful heart transplant after 12 h preservation aboard a commercial flight*. Lancet. 2024;403(10431):1019.

**McGiffin DC**, et al. *Hypothermic oxygenated perfusion (HOPE) safely and effectively extends acceptable donor heart preservation times: Results of the Australian and New Zealand trial.* J Heart Lung Transplant. 2023.

**Rega F**, et al. *Hypothermic oxygenated perfusion of the donor heart in heart transplantation: the short-term outcome from a randomised, controlled, open-label, multicentre clinical trial.* Lancet. 2024;404(10453):670-82.

**Tang PC**, et al. *Determining optimal donor heart ischemic times in adult cardiac transplantation.* J Card Surg. 2022;37(7):2042-50.

### PRE-CLINICAL RESEARCH

**Moeslund N**, et al. *Ex-situ oxygenated hypothermic machine perfusion in donation after circulatory death heart transplantation following either direct procurement or in-situ normothermic regional perfusion.* J Heart Lung Transplant. 2023;42(6):730-40.

**Qin G**, et al. *Intact coronary and myocardial functions after 24 hours of non-ischemic heart preservation.* Scand Cardiovasc J. 2020;54(1):59-65.

**See Hoe LE**, et al. *Donor heart ischemic time can be extended beyond 9 hours using hypothermic machine perfusion in sheep.* J Heart Lung Transplant. 2023;42(8):1015-29.

**Steen S**, et al. *Safe orthotopic transplantation of hearts harvested 24 hours after brain death and preserved for 24 hours.* Scand Cardiovasc J. 2016;50(3):193-200.

**Wang L**, et al. (189) *Non-Ischaemic Heart Preservation to Improve Donor Heart Quality.* The Journal of Heart and Lung Transplantation. 2023;42(4):S93-S4.

CAUTION: Investigational device. Limited by Federal (United States) law to investigational use. These claims have not been evaluated by the Food and Drug Administration. The XVIVO heart technology is not commercially available.

# Nobody should die waiting for a new organ

Founded in 1998, XVIVO is the only MedTech company dedicated to extending the life of all major organs – so transplant teams around the world can save more lives. Our solutions allow leading clinicians and researchers to push the boundaries of organ transplantation.

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