XVIVO

XVIVO Whitepaper

HOPE – for improved organ preservation

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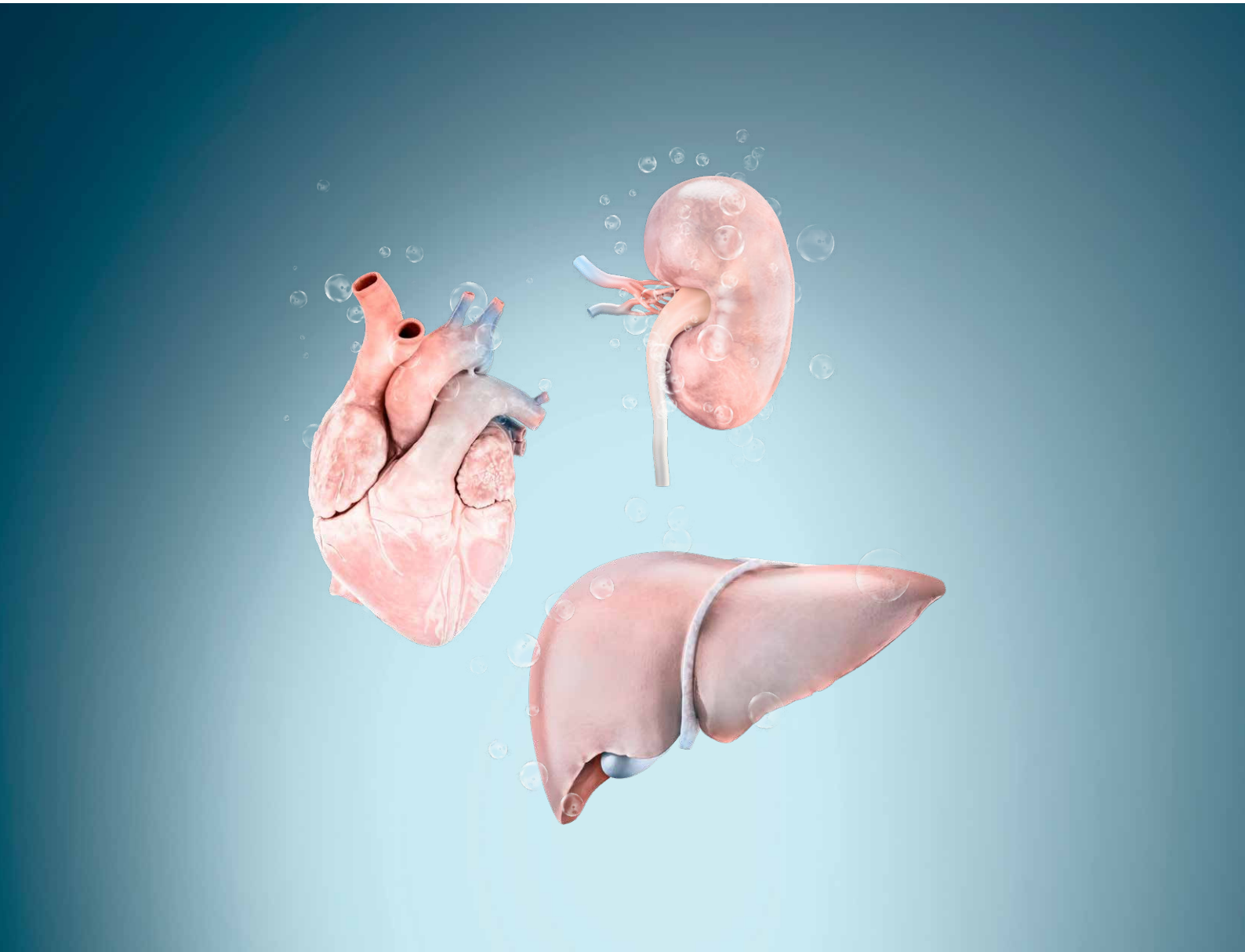

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Introduction to HOPE

Hypothermic Oxygenated Perfusion (HOPE) is an advanced organ preservation technique that has shown significant promise in improving outcomes for both standard and marginal organs from donation after brain death (DBD) and donation after circulatory death (DCD). Contrary to conventional organ preservation, where the donor organ is maintained in an ischemic state without perfusion (static cold storage, SCS), XVIVO's machine perfusion devices utilize HOPE combining cold preservation with continuous perfusion. By providing a controlled, nutrient-containing, and oxygenated environment during the cold preservation phase, HOPE addresses many of the challenges associated with traditional cold storage methods, especially in cases where the organs have been exposed to extended warm and/or cold ischemia or originate from a donor with a high-risk profile.

Challenges in organ preservation

Transplantation is a life-saving procedure that relies on organ donation. An inevitable part of transplantation is organ ischemia which involves the disruption of blood flow to the organ upon circulatory arrest. Ischemia results in the lack of oxygen and nutrient delivery and waste product accumulation which, in turn, triggers a cascade of physiological and biochemical insults that can compromise graft viability and function. While reperfusion of the ischemic tissue is essential for graft survival, re-introduction of oxygen and blood at the time of transplantation exacerbates the negative effects of ischemia. This may lead to extensive cell death, endothelial inflammation and early organ dysfunction. The process, known as ischemia-reperfusion injury (IRI), is a major challenge in transplantation medicine, as its effects constitute a significant source of morbidity and mortality following solid organ transplantation (1-3).

Research during the past decade has paved the way for improving organ preservation by increasing our understanding of the many interconnected molecular pathways that contribute to IRI (4).

Ischemia-reperfusion injury

Under normal conditions, oxygen is transported via the bloodstream to cells where it is used to create energy, adenosine triphosphate (ATP) , in a process called oxidative phosphorylation. During ischemia, the lack of oxygen causes cells to switch from aerobic (with oxygen) to anaerobic (without oxygen) metabolism, which results in a decrease in ATP production and intracellular acidosis.

A biproduct of oxidative phosphorylation is reactive oxygen species (ROS). Small amounts of ROS play important house-keeping functions in the cells during normal conditions, but high levels result in injury to cell membranes and cellular organelles, leading to cell death.

Other mechanisms that contribute to IRI are results of processes in the innate immune system, in complement activation as well as effects of cellular immune responses and coagulation. The attempt to restore the injured tissue results in a viscous cycle of exacerbated events further deteriorating the tissue. The pathophysiology of IRI and its interrelated processes are illustrated in Figure 1.

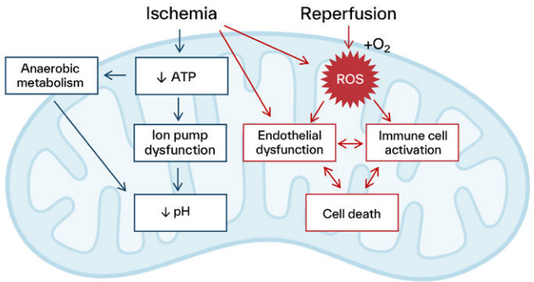


Figure 1. The pathophysiology of IRI. **Ischemia**: The lack of oxygen causes reduced adenosine triphosphate (ATP) production, leading to ion pump dysfunction and anaerobic metabolism. Ion pump dysfunction causes an imbalance in cellular osmolarity resulting in cell swelling (edema). The retention of hydrogen decreases cellular pH. Anaerobic metabolism causes accumulation of lactic acid which also decreases pH and may lead to metabolic acidosis. **Reperfusion:** The sudden reintroduction of oxygen upon reperfusion in the recipient causes a surge in reactive oxygen species (ROS), leading to an inflammatory response and immune cell activation. This can in turn trigger endothelial dysfunction and cell death (2, 5, 6).

Mitochondrial dysfunction and IRI

Mitochondria[1] are regarded as the primary trigger of ischemia-reperfusion injury and therefore play an important role in organ preservation (1).

Mitochondria are often referred to as the powerhouses of the cell, creating more than 90% of the energy (ATP) needed to sustain life and support a myriad of cellular processes (7). ATP is synthesized by mitochondria during oxidative phosphorylation, which is facilitated by a series of protein complexes, the electron transport chain (ETC), embedded in the inner membrane of mitochondria.

Oxidative phosphorylation is initiated by Succinate and NADH, produced during glycolysis and fatty-acid metabolism, entering the ETC and acting as initial electron donors. As electrons (e-) are passed from one complex to another, protons (H+) are pumped out of the matrix, forming a membrane gradient, which eventually drives the synthesis of ATP (Figure 2). Under normal conditions (i.e., when oxygen is available) oxygen functions as the final electron-acceptor of the ETC. When oxygen is not available the ETC is halted; however, as glycolysis and fatty-acid metabolism does not require oxygen, succinate and NADH continue to be produced. This leads to the accumulation of succinate and NADH that cannot be further metabolized to NAD+ and fumarate, respectively, as the following steps in the ETC is oxygen dependent. Upon reperfusion succinate is rapidly re-oxidized leading to a surge of reactive oxygen species (ROS) (Figure 2).

1. A cell contains between 1000-2500 mitochondria [REF: Pizzorno (2014) 'Mitochondria-Fundamental to Life and Health']

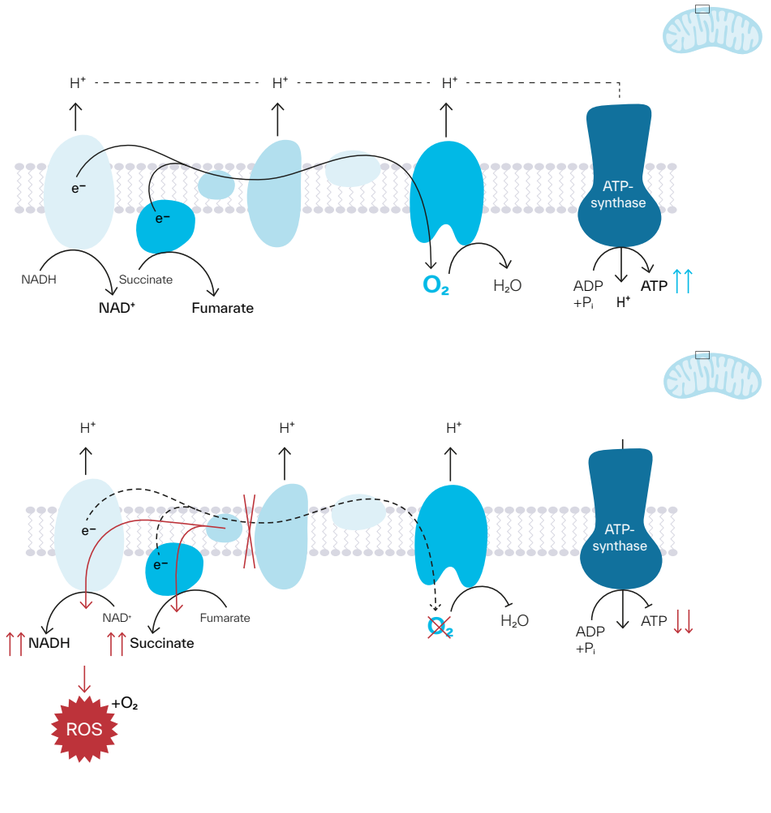


Figure 2. Function of the mitochondrial electron transport chain (ETC) under normoxic (with oxygen; Top) and ischemic (without oxygen) conditions (see text for details).

The accumulation of mitochondrial succinate during ischemia has been identified as one of the main drivers of ROS production upon reperfusion, and the longer the CIT lasts, the more succinate will accumulate.

Studies in mice show similar accumulation of succinate during ischemia for heart, liver and kidney tissues indicating that the mechanisms behind IRI are conserved across all solid organs studied (2) (Figure 3).

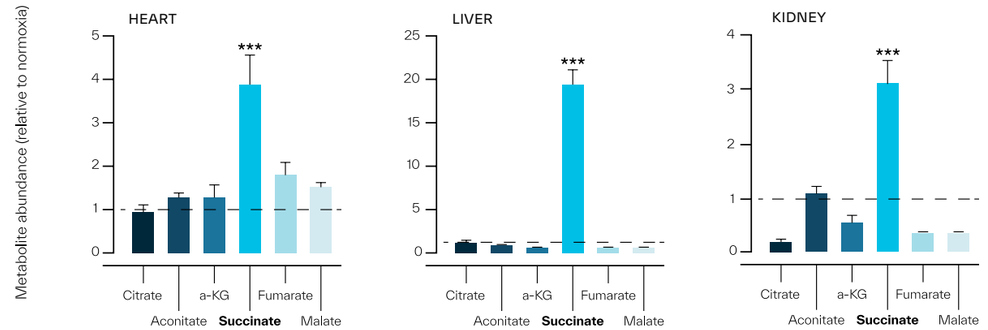


Figure 3. Ischemia leads to the accumulation of mitochondrial succinate, which upon reperfusion is the main source of ROS-production. This mechanism is universal and occurs, albeit at different levels, in all solid organs studied.***p<0.001. Adapted from Chouchani et al 2014 [2].

Innate immune system and IRI

The innate immune system plays an important role in IRI (5) (Figure 4). The release of ROS upon reperfusion leads to massive cell death, which in turn, result in the release of damage associated molecular patterns (DAMPs). Sensing of DAMPs by the innate immune system causes an increase in pro-inflammatory cytokines and activation of circulating immune cells (5, 8). Next to the release of DAMPs or inflammatory mediators, molecular alterations in the donor organ following IRI can also result in the activation of innate immunity via the complement system. Activation of the complement system can lead to the formation of the membrane attack complex (MAC). Assembly of the MAC leads to pores that disrupt the cell membrane of target cells, leading to endothelial dysfunction and cell death. (5)

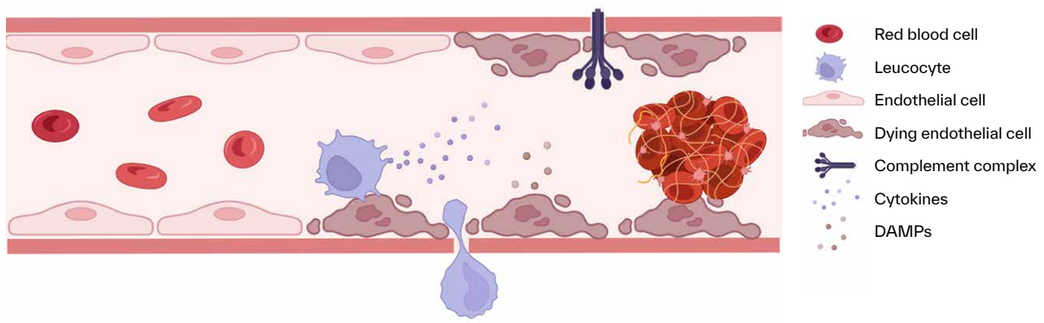


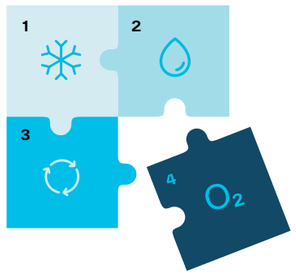
Figure 4. The role of IRI in the activation of the innate immune system and endothelial injury.

Endothelial dysfunction and IRI

Under normal physiological conditions, the vascular endothelium is constantly exposed to the flow of blood which stimulates the production of several factors that regulate vascular tone[1] and anti-inflammatory processes (5, 9). The vascular flow creates necessary shear-stress on the endothelial cells, which maintains an antithrombotic, antiproliferative and anti-immunogenic state. During ischemia, the lack of blood flow and biomechanical stimuli leads to acute endothelial dysfunction, vasoconstriction, and endothelial cell death (9, 10). IRI induced endothelial injury also plays a major role in inflammation with leukocyte adhesion and infiltration of immune cells (8) (Figure 4).

1. The contractile activity of vascular smooth muscle cells in the walls of small arteries and arterioles, is the major determinant of the resistance to blood flow through the circulation.

Key features of HOPE



1. Hypothermic preservation to reduce cellular metabolism
2. Dedicated perfusion solution to protect against edema and IRI
3. Perfusion of the vasculature to maintain vascular tone
4. Active oxygenation to support residual metabolic activity

Key feature 1:
Hypothermic preservation

The principles of organ preservation have traditionally relied on hypothermia to depress cellular metabolism and enzymatic activity using cold static storage. In 1959, Levy et al., (11) demonstrated that hypothermia significantly reduces metabolic rate in a reversible manner. Lowering the organ's temperature decreases its demand for oxygen and nutrients, thereby delaying the harmful effects of ischemia, which otherwise leads to cellular damage and loss of viability. Generally, the metabolic rate for most biological and chemical reactions decreases by about 50% for every 10°C reduction in temperature (12-16) (Figure 5).

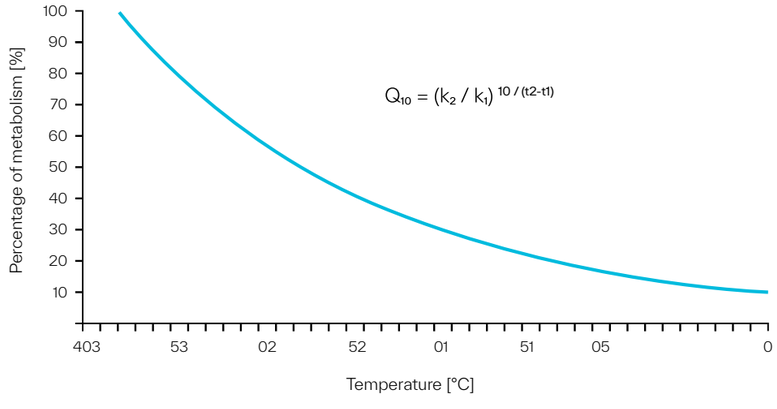


Figure 5. The relationship between temperature and metabolic activity. The Q10 temperature coefficient is a measure of the rate of change of a biological or chemical system by decreasing the temperature by 10 °C.

The simplest way to achieve a reduced metabolic state is through static cold storage (SCS), where the donor organ is placed in a sterile bag filled with cold preservation solution and transported on ice to the recipient hospital. The development of specialized cold storage solutions, designed to protect against edema and ischemia-reperfusion injury (12), has enhanced the effectiveness of SCS. This straightforward technique has been instrumental in enabling solid organ transplantation and remains the most widely used method for preserving deceased donor organs.

Despite efforts to optimize cold storage conditions, SCS fails to support residual metabolism. Consequently, ischemic processes—such as oxygen deprivation and the accumulation of metabolic waste products—are merely delayed, leading to a gradual decline in cellular viability. This limitation restricts the time an organ can remain viable during SCS.

Prolonged cold ischemia time (CIT) adversely affects both early and late post-transplant outcomes, particularly with organs donated after circulatory death (DCD) or extended criteria donation (e.g. older donors or donors with comorbidities) after brain death (ECD-DBD) (17).

Tolerability for cold ischemia varies significantly across different organs. For hearts, cold ischemia exceeding 3-4 hours is associated with increased morbidity and one-year mortality rates (18, 19). In contrast, liver and kidney grafts are more resilient, withstanding up to 6 and 12 hours of cold ischemia, respectively (20, 21).

Key feature 2:

The perfusion solution

The compositions of organ perfusion solutions are based on different physical and chemical properties that work together to optimize the perfusion and preservation of the organ.

Viscosity

Generally speaking, the more viscous a solution is, the higher pressure must be applied to achieve the same flow through a vessel. However, solutions containing red blood cells behave differently; viscosity decreases once flow is achived (22). It is important to have a balanced viscosity in a perfusion solution allowing for sufficient distribution throughout the organ and providing necessary shear stress to the endothelium to maintain the anti-inflammatory, antithrombotic and antiproliferative properties, without inducing shear stress injury to the endothelium (23).

Electrolyte composition

Organ perfusion solutions can be classified as either intracellular or extracellular, depending on the potassium and sodium concentrations; high potassium, low sodium intracellularly and low potassium, high sodium composition extracellularly (24). In vivo these electrolyte gradients are maintained by sodium-potassium ion pumps that are dependent on energy from ATP to function. If ATP is not available as during ischemic insult, the pumps can no longer function, and the ion gradients cannot be maintained. This leads to an influx of sodium into the cells and efflux of potassium into the extracellular space. If not counteracted, water moves across the cell membranes together with ions and cellular edema occurs.

Oncotic pressure

The oncotic pressure of a perfusion solution counteracts the build-up of both intracellular and interstitial oedema. The oncotic properties are obtained by including large molecules, that do not easily pass through the endothelial gap junctions. While electrolytes are small enough to freely pass through the gaps and quickly reach equilibrium between the intravascular and extravascular compartments, oncotic molecules continue to provide a force moving water from the extravascular to the intravascular compartment, counteracting edema formation (Figure 6). During perfusion, the hydrostatic pressure forces water from the vasculature into the extracellular compartment making it imparative to recover water to the perfusate using oncotic molecules to avoid edema formation. Common molecules included in perfusion solutions based on their oncotic properties are human serum albumin (HSA), Dextran 40, polyethlylene glycol 35 (PEG 35) and hydroxiethyl starch (HES) (24).

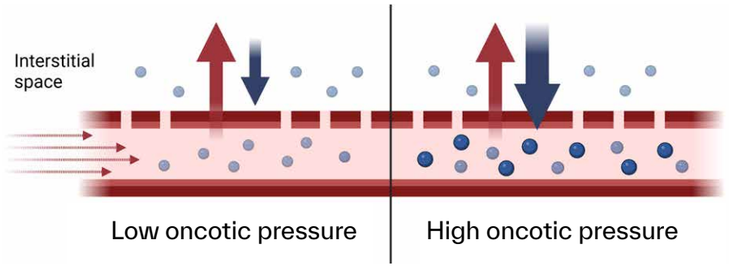


Figure 6. Oncotic molecules are included to generate oncotic pressure across the capillary walls to prevent loss of intravascular fluid into the extravascular space thereby preventing edema.

Direct endothelial interaction effects

A perfusion solution is in direct contact with the endothelium and affects the properties of the endothelial cells. Apart from the physical effects relating to shear stress and oncotic pressure, the molecular composition affects the cells. Dextran 40 and PEG 35 are both molecules that directly interact with the endothelium to preserve its structures (25). Dextran 40 also improves microcirculation and coats the endothelium to reduce excessive inflammatory and thrombogenic effect post-reperfusion (26, 27). HSA has the advantage of acting as a carrier of nutrients and hormones to the endothelium as well as facilitating removal of waste products.

Metabolic substrates

To support the residual metabolism during hypothermic organ perfusion, basic levels of metabolic substrates are required. In most cases, glucose is sufficient although, energy substrate precursers such as adenine or adenosine may be included to enhance ATP regenaration (24).

pH

Managing the pH of the perfusate is important to avoid inducing severe acidosis. However, a slightly acidic pH might provide a beneficial effect, particularly during oxygenated perfusion. Slight acidosis protects hypoxic tissue from ischemic injury, and it has been shown that in vivo oxygenated perfusion with physiological pH results in more severe tissue injury than initial reperfusion during slightly acidic conditions (28, 29).

Oxygen solubility

The properties of the solution are relevant for the solubility of oxygen, especially in a system not using any oxygen carriers. Oxygen solubility is increased during hypothermic conditions, whereas a high ionic content of the perfusate decreases the oxygen solubility.

Key feature 3:

Vascular perfusion

During HOPE, recirculating perfusate (either acellular or containing red blood cells) is continuously pumped through the organ. In addition to ensuring continuous delivery of nutrients and efficient cooling of the graft, the biomechanical stimuli exerted by the flow itself promotes the production of several factors (e.g. nitric oxide) that regulate vascular tone (i.e. the contraction / vasoconstriction and relaxation / vasodilatation of the blood vessels). Nitric oxide (NO) is an important vasodilator, allowing for sufficient blood flow through the organ. Besides regulating vascular tone, NO also has an anti-inflammatory effect by inhibiting leukocyte adherence to the endothelium (5).

Perfusion also flushes out potential cell debris and metabolic waste products. Even if metabolic substrates are added to the preservation solution during SCS, metabolic waste (e.g. lactate, CO2, urea, and ammonia) cannot be disposed of if the vasculature is not perfused. Accumulation of toxic wastes in tissue will eventually damage cells, causing irreversible organ malfunction after transplantation (30).

Just like in vivo, vascular flow (e.g. blood or perfusate) is directly related to perfusion pressure (e.g. blood pressure or pump pressure) and inversely related to vascular resistance. There is a critical balance between providing sufficient pressure to allow for complete perfusion of the organ, but not too high as to cause endothelial damage.

There are different types of perfusion systems used clinically, i.e., those that are pressure-controlled and others that are flow-controlled. In pressure-controlled systems, if vascular resistance increases, due to e.g. vasoconstriction or atherosclerosis / blockage, the pressure applied remains the same, limiting the risk of endothelial injury. Avoiding pressure induced stress on the endothelium is especially important in the hypothermic setting as the low temperature increases the vulnerability of endothelial cells to endothelial shear stress injury. This is in contrast to flow-controlled systems, where perfusion pressure increases with increasing vascular resistance, and therefore also the risk of over-perfusion and endothelial injury (31).

All XVIVO's HOPE systems are pressure-controlled.

Key feature 4:

Active oxygenation

During the past 20 years, multiple pre-clinical and clinical efforts have been dedicated to understanding the mechanisms behind the beneficial effects of HOPE in solid organ transplantation. Initially, it was thought that addition of oxygen was not necessary during hypothermic machine perfusion due to the level of reduced metabolism and might even increase detrimental ROS formation (32). This, however, was later shown to be untrue with experimental studies in kidney showing that high oxygen concentrations during HOPE actually leads to lower levels of oxidative stress. (33, 34)

Optimal preservation has been shown to rely on sufficient perfusate oxygenation under hypothermic conditions (32, 35). Active oxygenation of the nutrient-rich perfusate supports the residual cellular metabolic activity of the donor organ throughout the entire perfusion procedure by promoting ATP production and reducing oxidative stress at the time of reperfusion during transplantation.

During HOPE, an external oxygenator or gas exchange system is used to maintain a steady flow of oxygen to the perfusion solution. The oxygenator mimics the function of the lungs by actively and continuously enriching the solution with oxygen, ensuring that the oxygen content is replenished throughout the perfusion procedure and does not diminish over time.

Studies have shown that oxygenation during hypothermic preservation results in significantly higher ATP levels, a massive reduction in ROS formation, and significantly lower levels of organ damage when compared to non-oxygenated preservation (33, 34) (Figure 6).

All XVIVO's HOPE systems are actively oxygenated using an oxygenator.

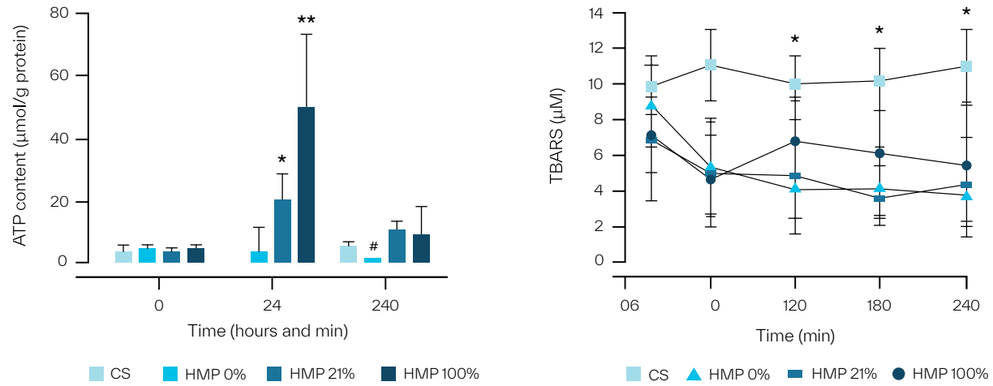


Figure 7. Effects of oxygen during hypothermic machine perfusion of porcine kidneys. Effects of oxygen during hypothermic machine perfusion of porcine kidneys. After 30 min of warm ischemia, porcine slaughterhouse kidneys were preserved for 24 h by means of: SCS (n=6); HMP (n=6); HMP + 21% O2 (n=6); HMP + 100% O2 (n=6). HMP was performed at 4°C with pulsatile pressure-controlled perfusion with a mean arterial pressure of 25 mmHg using Kidney Assist Transport (XVIVO). Left: before preservation was initiated, ATP was almost completely depleted in every group. After 24 h of preservation, HOPE led to a significant increase in ATP levels. Right: TBARS (an indicator of oxidative stress) were measured during reperfusion - with HOPE showing the lowest levels of oxidative stress. Image adapted from Venema et al (2019).

Organ-specific applications of HOPE

HOPE can be applied directly following organ recovery until transplantation (continuous perfusion) or after a period of SCS (end-ischemic perfusion). Although we do not yet fully understand which grafts benefit most from what perfusion protocol, we know that active oxygenation is vital, even during hypothermic conditions.

While many of the underlying mechanisms involved in IRI are on a cellular level and therefore conserved across organs, organs are not equally vulnerable to ischemic injury. In order to preserve each organ in the best possible way, organ-specific needs must therefore be met by tailoring the preservation. The following chapters describe in more detail how XVIVO's machine perfusion systems address these organ-specific needs using HOPE.

HOPE in liver preservation

Under normal physiological conditions the liver receives blood (i.e. is perfused) via both the hepatic artery (HA) and the portal vein (PV). The HA supplies the liver with oxygen-rich arterial blood under high pulsatile pressure (120/80 mmHg) and low flow (~500 ml/min) and the PV supplies the liver with nutrient-rich, venous blood from the small intestine under low-pressure (12 mmHg) and high flow (~1000 ml/min). While ~70% of the liver's blood supply enters through the PV, perfusion via the HA is important for maintaining vessel structure and integrity of bile ducts (36).

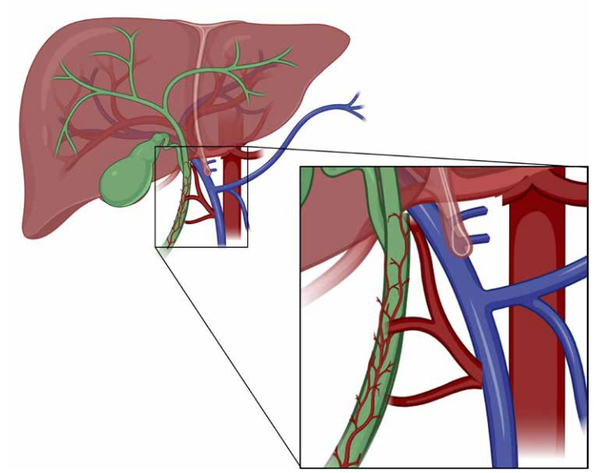


Figure 8. The peribiliary vascular plexus (PVP), including hepatic artery (HA) and bile duct. The HA drains into the PVP, which is the microvasculature that provides oxygen and nutrients to the bile ducts.

HOPE of the liver can be performed through both the PV and HA, or through the PV only. If both the PV and HA are perfused it is referred to as DHOPE (as in dual-HOPE). When to choose which protocol is still under debate, but it has been suggested that DHOPE may be particularly beneficial following donation after circulatory death (DCD) due to the increased susceptibility of the bile ducts to warm ischemic injury (37). This is thought to be a main cause of the higher incidence of bile duct injury / cholangiopathy in DCD liver transplantation (37). The additional perfusion via the HA during DHOPE might be particularly beneficial for the bile ducts and cholangiocytes (epithelial cells lining the bile ducts) as these are mainly perfused by the HA.

The clinical benefit of HOPE/DHOPE in liver transplantation is well documented, with numerous clinical studies and systematic reviews demonstrating significant improvements in graft survival and reduced rate of serious adverse events and biliary complications compared to SCS (38-41). HOPE/DHOPE has also been shown to extend liver graft preservation times up to 20 hours with maintained outcomes (42), and has been proven cost-effective (43, 44).

Description of Liver Assist™

Liver Assist™ is an ex vivo machine perfusion system for end-ischemic hypothermic and normothermic oxygenated perfusion of donor livers prior to transplantation into recipients. The system consists of two main components, the reusable Liver Assist device and single use Liver Assist Perfusion Set. The Liver Assist device includes two separate pump units, one for perfusion of the portal vein (PV) and the other for perfusion of the hepatic artery (HA), as well as a thermo-unit for temperature control of the perfusion solution. The pump- and thermo-units are mounted on a dedicated tabletop trolley to allow for in-hospital transport while also providing an accessible work surface with organ reservoir holder wherein the liver reservoir of the Liver Assist Perfusion set can be placed (Figure 9).

Figure 9. XVIVO's Liver Assist™ device.

The PV pump unit of Liver Assist operates in a continuous mode (i.e. non-pulsatile) with a pressure that can be set between 0 to 16 mmHg, and the HA pump unit operates in a pulsatile mode of 60 BPM to mimic physiological blood flow with a pressure that can be set between 0 to 90 mmHg[1].

The Liver Assist device is used together with a sterile, preassembled, single-use perfusion set. Each perfusion set includes a dual-lid reservoir and cannula(s) for the liver and two perfusion circuits. Each perfusion circuit contains an oxygenator with an integrated heat exchanger.

The perfusate used during HOPE / DHOPE with Liver Assist is the University of Wisconsin – Machine Perfusion Solution (UW-MPS)[2], an acellular perfusion solution used for both renal and hepatic hypothermic perfusion.

Compared to both the XVIVO Heart Assist Transport and Kidney Assist Transport systems, Liver Assist is not transportable. Instead of initiating HOPE directly following organ recovery, HOPE with Liver Assist is applied at the recipient hospital after a period of SCS (i.e., end-ischemic)[3]. In contrast to kidneys, where the timing of HOPE seems essential (45), a short period (1-2h) of pre-transplant end-ischemic HOPE / DHOPE is sufficient to restore hepatic ATP levels and mitigate the detrimental effects of IRI (35, 46, 47).

HOPE in kidney preservation

Compared to other major organs, renal oxygen consumption per gram of tissue is high, second only to that of the heart (2.7 vs. 4.3 mmol/kg/min for the heart) (48). Despite this, hypothermic machine perfusion (HMP) of kidneys has largely been performed without supplemental oxygen. Studies have shown that even without oxygen, HMP improves outcomes for kidney transplant recipients (45); however, as shown in the COMPARE study, the simple addition of oxygen during continuous HMP (i.e., HOPE) leads to added benefits in kidneys from older DCD donors (49), including further improvements in graft survival, improved kidney function up to 1-year after transplant, and reduced incidence of acute rejection.

Description of Kidney Assist Transport™

Kidney Assist Transport™ is a portable system for continuous hypothermic oxygenated perfusion of kidneys during transport from donor to recipient.

The system consists of two main components, the reusable Kidney Assist Transport device, and the single use Kidney Assist Transport Perfusion Set.

Figure 10. The XVIVO Kidney Assist Transport system™. Left: Kidney Assist Transport device (closed view); Right: Kidney Assist Transport device and Perfusion Set (exploded view).

1. Pressure settings for both pumps differ depending on temperature and protocol used.
2. UW-MPS is not manufactured by XVIVO
3. Also referred to as 'Back-to-base'

The Kidney Assist Transport device is a reusable thermo-insulated enclosure with dedicated ice reservoirs for passive cooling of both perfusate and kidney. A separate compartment holds the electronics, batteries and medical grade oxygen cylinder. The device has sufficient battery power and holds enough oxygen and ice for up to 24 hours of HOPE. When used stationery, the device can be connected to an external power supply. The system is pressure-controlled and perfuses the kidney in a pulsatile manner at 60 BPM to mimic physiological blood flow. While the perfusion pressure can be adjusted by the user (0 to 50 mmHg), the default setting is 30/20 mmHg (mean pressure of 25 mmHg).

The device is used together with a sterile, single-use Kidney Assist Transport Perfusion Set consisting of a preassembled perfusion circuit[1] with an oxygenator, as well as a kidney holder, lids, cannulas and syringes.

Just as with Liver Assist, the perfusate used with Kidney Assist Transport is UW-MPS.[2] This is a semi-intracellular solution based on HES as the oncotic molecule and glucose and adenine for metabolic activity.

During operation, perfusion parameters (flow, temperature and vascular resistance) are monitored and displayed continuously. Vascular resistance is continuously calculated by dividing the mean pressure in mmHg by the flow in ml/min.

HOPE in heart preservation

Of all solid organs, the heart is most vulnerable to ischemic injury due to its high metabolic demand. Cardioplegic arrest significantly reduces the metabolic activity of a heart and by also inducing hypothermia the myocardium is further protected. At 8 °C about 15 % of the oxygen consumption remains compared to a warm arrested heart (50). There's a strong association between prolonged cold ischemic time and increased post-transplant morbidity and mortality. Even with shorter ischemic times, poor postoperative heart function is frequently observed. Primary graft dysfunction (PGD) is a well described phenomenon and the main driver of early mortality. PGD is reported to affect up to 28% of patients receiving a donor heart transported on static cold storage. (51).

In the 'NIHP 2019' randomized controlled trial (52), the observed incidence of severe PGD was 5 events (5%) in the HOPE group versus 21 events (20%) in the SCS group, corresponding to a risk reduction of 76% (RR, 0.24; 95% CI, 0.10- 0.62). Further, the reduction in severe PGD was reflected in an increased 1-year survival in the HOPE group.

In conclusion, clinical investigations have shown that HOPE with the XVIVO Heart Assist Transport™ System safely extends preservation time to 8 hours and beyond, reduces incidence of primary graft dysfunction, severe transplant complications, and improves 1-year survival when compared to static cold storage. (52-54)

Description of the XVIVO Heart Assist Transport™ System

XVIVO Heart Assist Transport™ consists of an insulated transportation box with integrated cooler unit, a pressure-controlled perfusion system, a gas exchange system, and an integrated battery.

The perfusion pressure is by default set to 20 mmHg, generating a corresponding flow depending on the size and vascular resistance of the perfused heart, typically 75 – 300 ml/min. The temperature of the perfusate is set to the fixed value of +8 °C. The carbogen gas flow is set to 100 ml/min.

XVIVO Heart Assist Transport Perfusion Set includes a reservoir where the heart is contained and a cannula on which the heart is attached. The reservoir contains tubing for the perfusion set, an oxygenator for gas exchange, and pressure and temperature sensors.

1. The perfusion circuit also includes a reservoir, pump head, pressure sensor, filling line, oxygen line, sample port, a sterile drape and compatible tubing.
2. UW-MPS is not manufactured by XVIVO

XVIVO Heart Solution is a hyper-oncotic colloid perfusion solution containing human serum albumin (HSA), dextran, glucose and triiodothyronine (T3). The XVIVO Heart Solution Supplement contains hydrocortisone, epinephrine, norepinephrine and cocaine hydrochloride. The XVIVO Heart Solution Supplement is added to the XVIVO Heart Solution before use. In addition, compatible, packed red blood cells from the blood bank and sodium bicarbonate, potassium chloride, insulin, heparin and antibiotics are added when preparing the perfusion solution.

During use, the heart is submerged in the cold oxygenated perfusion solution, kept in a non-beating state, and the perfusion parameters are controlled by the device during transport.

Figure 11. The XVIVO Heart Assist Transport System; Left: XVIVO Heart Assist Transport, with XVIVO Heart Assist Transport Perfusion Set; Right: XVIVO Heart Solution (XHS) and XVIVO Heart Solution Supplement (XHSS)

Tailor-made perfusion solution

The composition of the supplemented XVIVO Heart Solution is optimized for hypothermic oxygenated perfusion. It ensures efficient vascular distribution, protects the endothelium and supports residual metabolism. It mimics the electrolyte composition of plasma to maintain a normal electrolyte environment for the endothelium, but with increased potassium and magnesium concentrations to safely keep the heart in an arrested state. Human Serum Albumin (HSA) is used as a colloid to prevent edema formation during perfusion. Dextran 40 coats the endothelium upon reperfusion preventing pathologic interaction with leucocytes. Glucose and Triiodothyronine (T3) are included in sufficient amounts to support the residual metabolism.

Red blood cells (RBC) are added to the perfusate aiming at a hematocrit of 10 %. A perfusate containing RBC has a significantly greater oxygen carrying capacity through binding to hemoglobin, compared to the oxygen dissolved in the crystalloid compartment (55). This provides an additional layer of safety; in the unlikely event of interruption of perfusion or gas supply, the oxygen content (reserve) is much higher in the coronary arteries with RBCs present. RBCs also act as a buffer balancing the pH in the tissue and facilitate the microcirculation by direct and indirect effects on the capillary endothelium (56).

Concluding remarks

HOPE represents a significant advancement in organ preservation, offering well documented improvements over traditional static cold storage. By combining cold preservation with continuous perfusion and active oxygenation, HOPE mitigates the detrimental effects of ischemia-reperfusion injury.

As research continues to unravel the mechanisms and pathophysiology of ischemia-reperfusion injury, we now understand that optimal preservation of donor organs requires oxygen and maintenance of residual metabolism, even during hypothermic conditions.

The benefits of HOPE in solid organ transplantation have been extensively proven for liver and kidney. A patient receiving a donor organ preserved with HOPE has better chances of long-time graft survival and lower risk of transplant related morbidity. With our latest technology conferring the benefits of HOPE also to hearts, XVIVO's ongoing commitment to research and innovation allows leading clinicians and researchers to continue pushing the boundaries of organ transplantation.

For further reading about the current clinical evidence with HOPE, please refer to our rgan-specific Clinical Evidence Summaries, available on XVIVO's webpage: https://www.xvivogroup.com/scientific-summaries/

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