Could you outline your professional background and the objective of your research on human liver grafts?

I started my surgical career in 1993 in Germany, and in 1995 moved to Wisconsin, USA, to the famous lab of Folkert Belzer and Jim Southard. During this visit, I became fascinated with the idea of machine perfusion for livers as an alternative to cold storage. Returning to Germany, I established my own lab and started research in the field of machine liver perfusion, alongside my surgical education. In 2004, I moved to Zurich, Switzerland, to join the group of Pierre-Alain Clavien, and continue work on machine liver perfusion and transplantation. Currently, I lead the abdominal transplant programme in Zurich, which recently succeeded in translating its research findings into human liver transplantation. The aim of applying machine perfusion in human livers is to improve graft quality and rescue extended criteria grafts for safer use in liver transplantation.

What are the issues associated with liver grafts donated after cardiac death (DCD)? How does your study seek to improve transplantation of these high-risk grafts?

The greatest issue associated with the use of DCD liver grafts is the development of an intrahepatic cholangiopathy, which frequently leads to graft failure and retransplantation. Our machine perfusion technique aims to reduce the risk of intrahepatic biliary complications.

Why did you choose to focus your research on hypothermic oxygenated perfusion (HOPE) to protect DCD liver grafts? How does this novel technique work?

Our HOPE technique is practical and simple, as there is no need to transport perfusion equipment to the place of organ procurement. In addition, the time of perfusion is short and there is no delay in the transplant procedure itself as HOPE can be applied during recipient hepatectomy. Furthermore, we perfuse exclusively through the portal vein, making any cannulation of arterial branches unnecessary. Thus, our approach is straightforward and inexpensive in contrast to other perfusion strategies, which must be started at the site of procurement and require continuous pumping and extensive technical effort.

You recently delivered the first report on the transplantation of human liver grafts obtained after cardiac arrest and treated with cold machine perfusion. Can you summarise your findings?

We showed that HOPE can be applied clinically in human DCD liver grafts without any apparent increase of adverse outcome. We thus indicated the feasibility and safety of such an approach. We also confirmed that reperfusion injury was low in machine-perfused DCD livers, despite prolonged donor warm ischaemia times. Most importantly, we documented excellent early and long-term outcomes. In particular, there was no intrahepatic cholangiopathy in the machine perfused DCD liver grafts.

Have you come across any challenges during your research?

In the past 15 years, we have encountered many challenges. Transplantation in rats and pigs is time consuming and difficult, and it took many years for us to move from simple isolated perfusion studies to transplant preservation.
models and to discover the potential mechanisms of protection.

Broadly speaking, how have the success rates of liver transplants increased over recent years? What are the priority areas for action at present?

Liver transplantation has become a highly successful treatment for non-malignant and malignant liver diseases. More than 70 per cent of recipients survive for at least five years at most centres, compared with only 20 per cent in the mid-1980s. However, there is a worldwide shortage of organs, and many patients deteriorate or die on waiting lists. Important research areas therefore include optimising marginal liver grafts, strategies to best match donors and recipients, liver transplantation for hepatic cancers and partial liver transplants as an alternative option.

**HOPE for liver transplant patients**

A team at the University Hospital Zurich in Switzerland has developed a practical and simple new perfusion technique. By better preserving the quality of organs and making borderline organs safe for use, the method will increase the number available for transplants.

DUE TO SHORTAGES in the availability of transplant organs worldwide, many patients die while waiting for lifesaving surgery. A serious cause for concern in the medical community, the gap between the supply and demand of organs continues to increase, leading to The Declaration of Istanbul calling for a new era of self-sufficiency, in which each country would provide enough organs for recipients from its own population.

Another way to lessen the discrepancy is using expanded criteria donors (ECDs), also called marginal organs. A major branch of ECDs are donation after cardiac death (DCD) organs that have been retrieved postmortem following the withdrawal of life support. These donors have generally suffered irreversible brain injury but do not meet the formal brain death criteria. Due to the period of oxygen deprivation after the heart stops beating, which can be lengthy due to ethical legislation in most countries, DCD organs often have ischaemic damage. Furthermore, they cannot be effectively preserved for long periods of time. While high-quality grafts can withstand storage times of up to 12 hours, grafts derived from ECDs are at a much higher risk of damage.

As the creation of new organs cannot be easily achieved, those available must be used effectively. Static cold storage is the gold standard for organ preservation worldwide, despite the fact that it can induce injury and damage the graft. DCD donors are an important source of organs; there is therefore a pressing need to improve preservation methods to maintain their viability from donation until transplantation to prevent graft failure.

**PERFECT PERFUSION**

Machine perfusion is one such alternative to static cold storage. Based on natural perfusion (the delivery of blood into tissue), this approach was first suggested as a means to preserve organs over 100 years ago. However, this dynamic method has since been cast off due to its complexity and the development of convenient cold storage methods. Now, returning to first thought, many have published promising results using the technique.

Professor Dr Philipp Dutkowski, Head of Visceral Organ Transplantation at the University Hospital Zurich, has taken a keen interest in these developments. Indeed, for the past 15 years he and his team have been developing a new machine perfusion approach for the liver. Their method, hypothermic oxygenated perfusion (HOPE), relies on cold oxygenation and can be applied via the portal vein after organ removal.

HOPE is associated with less reperfusion injury – the damage caused by the rapid re-entrance of blood into an organ – which is common in transplantation. A major improvement for the field, HOPE’s optimal time of action is just one-to-two hours. In addition, it can be performed in a transplant centre, while the recipient’s liver is being removed.

**MECHANISM OF PROTECTION**

Though machine perfusion is known to optimise livers prior to transplantation, the means behind this method has remained somewhat elusive. Shedding new light on the matter, Dutkowski’s team revealed the basis for the benefits of HOPE in a recent study.

Firstly, oxygenation delivered under hypothermic conditions (low temperature) protects the mitochondria and nucleus from injury. “Oxygenation appears decisive during hypothermic liver perfusion, as it induces a slowdown in the mitochondrial respiration rate before reperfusion,” Dutkowski explains. In fact, after just one hour of perfusion, the mitochondrial respiration rate is significantly reduced, which in turn helps reduce the risk of metabolic damage to the organ. Secondly, the use of cold perfusion, under low pressure, prevents damage to the cells lining the blood vessels, another cause of graft loss of function.

**IMMEDIATE IMPACT**

Over the years, HOPE has been tested in several rat and pig models, and more recently in human liver grafts. Indeed, in 2013 the team evaluated the ability of HOPE to recover high-risk organs. They proved the approach on eight patients with end-stage liver diseases, all of whom received DCD human livers.
INTELLIGENCE

HOPE

HYPOTHERMIC OXYGENATED PERFUSION OF HUMAN LIVER GRAFTS TRIAL

OBJECTIVE

To improve organ preservation internationally through a novel technique involving the perfusion of human liver grafts as opposed to the standard cold storage method.

KEY COLLABORATORS

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PROFESSOR DR PHILIPP DUTKOWSKI

started his surgical career in Germany at the University of Mainz, where he completed his board certification for Surgery in 1999 and Visceral Surgery in 2002. In parallel, Dutkowski obtained his Habilitation in 2001 after establishing a research group in the field of machine liver perfusion. In 2004, he joined the group of Professor Dr Pierre-Alain Clavien in Zurich, and succeeded to translate basic research into clinical application during human liver transplantation. Since 2009, Dutkowski has led the abdominal transplant programme at the Department of Surgery and Transplantation.

All the machine-perfused liver grafts showed excellent early function after transplantation. Furthermore, the release of liver enzymes (a marker of reperfusion injury), kidney function and hospital stays were either comparable or superior to matched liver grafts from brain death donors. There was no evidence of damage to the bile ducts (the biliary system), which is common in DCD organs.

This, the first report on cold machine perfusion of human liver grafts obtained after cardiac arrest, showed HOPE to be well tolerated, easy to use and protective against both early and later injuries. As a result, the team is undertaking a randomised, multicentre trial to analyse the effects of HOPE against the current static cold storage standard in brain dead donors.

HUMAN TRIAL

The trial, ‘HOPE of human liver grafts before transplantation’, aims to test the outcomes of machine liver perfusion compared to cold storage methods. The randomised trial will demonstrate – for the first time – the effect of this highly simplified perfusion technique in human liver grafts.

The study comprises patients undergoing liver transplantation at several European institutions, randomised into two groups – perfusion and control. After standard liver procurement at the site of donation, the cold stored organs will be transported to the transplant centre. After preparation of the liver, HOPE will be performed, while the control group will undergo continued cold storage. The livers will be implanted at the same time.

On completion, the team will measure major postoperative complications as the primary endpoint, but graft dysfunction, biliary injury, duration of hospital stay and cost will also be assessed. In addition, liver graft biopsies will be taken at the end of transplantation in order to identify markers of inflammatory response and reperfusion injury.

A WELCOME CHANGE

Able not only to preserve but also repair damage to marginal organs, unlike cold storage, HOPE offers a multitude of benefits for patients; providing more organs of better quality and promoting more rapid recovery after transplantation. Moreover, for those conducting the procedure, the technique also has many advantages over traditional cold storage techniques. It can be applied with ease worldwide, and will likely be very popular among transplant surgeons. “If our perfusion strategy proves to be effective in the planned randomised trial, we envision a high acceptance rate among transplant surgeons and a change in current preservation techniques,” Dutkowski concludes.