LTSI LIVER TRANSPLANTATION SOCIETY OF INDIA

LIVER REPORT

October 2022 Issue 4

LIVEREPORT 4

Editors' Note



Dear Friends,

Welcome to the fourth issue of LiveReport. In this issue, we look at a hot topic in current liver transplant literature - The role of machine perfusion in liver preservation.

In our Up Close & Personal section, we interview Professor Pierre Clavien who has published extensively in almost every aspect of surgery. Prof Clavien speaks about his team's latest invention the Wyss liver perfusion machine- which has been underdevelopment for over 5 years. He talks about his career pathway, the story behind the Clavien-Dindo score and his advice to young clinicians aspiring to a career in surgical research.

We learn about the history of machine perfusion in organ preservation and hear from a young Indian surgeon who worked in the original research behind the Organox machine. We have guest contributors who discuss how machine perfusion in liver transplantation is changing clinical practices in the USA and UK and finally how these studies are relevant to the India setting. In the Journal Club, we look at two recently published studies on the role of machine perfusion in adult and pediatric liver transplantation. Even the Jumble Puzzle in this issue is related to machine perfusion!!

We have our usual content including Tricks of the Trade where the CLBS team discusses their technique of reducing usage of expensive preservation fluids in LDLT, Transplant Vignettes which looks at the origin of the CTP score and Hot Stuff where Dr Magnus gives us the inside story behind the successful transplantation of a liver preserved for three days and expert commentary by Dr Shweta Singh on the applicability of ERAS protocols in LDLT in the India context.

*We hope you enjoy reading this issue and would love to hear **ANY** feedback from you to try and make it better and more relevant to the LTSI community.*

Your Editorial team,

N. Murugan
Sujoy Pal
Srinivas Reddy

Up Close & Personal

Professor Pierre-Alain Clavien- *Surgeon Scientist Extraordinaire*

Professor Pierre Alaine Clavien is the Professor & Chairman of Surgery at the University of Zurich.

In a career spanning three decades, he has changed the way we measure surgical outcomes while also leading cutting-edge research in liver regeneration & organ preservation. Despite his busy schedule, Prof Clavien agreed to speak to ***LiveReport*** *on the eve of his group's latest publication on long-term liver preservation. Here, we explore his career, his work, his tips on combining clinical work with research and his vision for the future of transplantation.*

Interviewed by

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Congratulations on your recent publication in Nature Biotechnology about the successful transplantation of a three-day preserved liver. Why did you choose normothermic perfusion as your preferred method for long-term preservation instead of techniques such as cryopreservation or stem cell repopulation which other groups are studying?

The interest in our group was always liver injury and regeneration. We know that the liver regenerates, but can it regenerate outside the body? The aim of our research and the grant application was to find out whether segments of the liver would regenerate outside of the body in a machine. Or, in a patient with cancer of the liver, can we regenerate the noncancerous portion of the liver outside the body and perform an auto-transplantation later on? From ALPPS, we know that the human liver can fully regenerate in one week. That was the vision behind designing a machine that can perfuse the liver for a week or more.

But this didn't happen in one day. We collaborated with engineers from across the road here at the Swiss Federal Institute of Technology. We got research funding from a Swiss philanthropist, Hansjoerg Wyss, and we developed this machine over a 5 years period, initially using pig livers and then human livers rejected for transplantation. We realized that not only could we preserve the organ but also evaluate its quality. We have a high mortality on the waiting list in Switzerland.

So we decided to offer this technology to a patient who had a large recurrent hepatocellular carcinoma and had little chance of getting an organ in time. We had the authorization to take a rejected organ by all centers, put in the machine and use it. The patient was transplanted on the fourth day of ex vivo graft preservation and is doing very well with now a one and a half year follow up.

Prof Clavien and his colleague Prof Philip Dutkowski performing a transplant procedure

Have you done any more transplants over the last year since this patient?
No, we did that a year ago and it is very difficult for ethical reasons to do such transplants right now. We are launching a trial in Switzerland for about 20 marginal livers. We plan to put these organs in the machine- evaluate, repair and then transplant.

What was the longest duration that you have preserved a liver on warm perfusion?
15 days for a human liver! We did an initial pre-clinical study on 21 rejected liver grafts by all centers. Half of them recovered disclosing normal functions, while the other half did not recover and even deteriorate. This enabled us to define criteria of viability for the livers preserved in the machine and thus identify those which we may safely use for transplantation.

How is this machine different from currently available normothermic preservation systems?
When we embarked on this project our goal was very clear, it was focused on long term preservation. The other machine(s) could preserve for 6-12 hours- but none have worked long term. From our previous experiments we knew that we needed at least 3 days of perfusion for the liver to disclose some repair processes. The idea was simple, it was to develop a machine where the liver doesn't realise that it is outside the body. It took 2 years to develop; it includes an artificial lung, artificial kidney and even an artificial diaphragm with inbuilt sensors to maintain homeostasis like adjusting glucose levels with real time injection of insulin or glucagon. With this, the liver believes that it is still in the body.

> *"The idea was simple, to develop a machine where the liver doesn't realise that it is outside the body"*

You have had a fascinating career in Surgery. So, let's start at the very beginning, what made you choose a career in medicine and then do surgery?
Some people say that they were born to be surgeons, it is not so in my case. I was probably the last one to sign up for medical school! I was not sure what to do and it was chosen more by excluding other options. Then I wanted to do pediatrics but after a month's training at the Hammersmith hospital in London with Dr Leslie Blumgart I decided it was surgery that I wanted. It has never something I planned years in advance.

You went to Toronto after your training in Switzerland. How did you end up there?

I did my training in surgery partly in Basel and in Geneva. But Switzerland is a very small country, a little bit smaller than India! We had a good medicine set up, but I felt like on an island- felt it's too small to learn enough. With help from one of my teachers in Basel, Professor M. Allgoewer, I did a tour of the US and Canada. At that time, I had absolutely no clue about HPB surgery and had barely seen a liver resection before.

In Toronto, I met the chairman, Dr Bernie Langer, who asked me what I wanted to do. Since I told him that I was not sure and open to any field of surgery, he was quite disappointed about such doubt in me! He however organized a tour of the campus, I met a lot of people in Toronto, particularly Dr Steven Strasberg, who had an active lab for organ preservation, and I had never seen a transplant before. But I was hooked, and I started working with him and converted to a PhD to look at the science behind this. This work was associated with a clinical fellowship and complete my time in Toronto by being trained in liver transplantation and HPB surgery.

"Some people say that they were born to be surgeons, it is not so in my case. I was probably the last one to sign up for medical school"

Why do you think there hasn't been much progress in organ preservation for so many years and suddenly we see a lot of work in this area in the last few years?

As a transplant surgeon, you probably know the reason already. My PhD was a few years after the UW solution was introduced. UW solution had 11 ingredients, but nobody knew what these ingredients were doing… but it worked. So, my job was basically to find out which ingredient was important, which till today we don't know for sure! It was a simple method of preservation and it was effective, the liver could be preserved for 12 hours or more which was enough. It served the purpose. Then 20 year later the machines came. Mind you, this was not a new idea- even Starzl and others were trying to do that before. But now we have the technology to refine this approach and there is more data on its benefit. There is certainly also some business interest contributing to its growth.

The Clavien grading of surgical complications- its elegant and simple with more that 30 000 citations on PubMed. Can you tell us about how this score was developed?

Thank you for this question. This again happened a little bit by chance, when I was working in the lab in Toronto with Steven Strasberg. When you do research in the lab, you get some free-time and may take such opportunities to some extra work. That was the time of the introduction of laparoscopic cholecystectomy, around 1992-1993. I assisted Prof Strasberg for the first lap cholecystectomy in Canada, which lasted 7 hours! At this time, the question was - Is the laparoscopic approach a good procedure or not? We realized that we don't know what to measure to answer this question, and this was the beginning of my interest in outcome research. We worked on a classification of complications using data compiled from Geneva, Switzerland and Toronto, Canada. We compared with open cholecystectomy to show the benefits of laparoscopy. We published this new classification of complications in the journal Surgery. But I became disappointed that it was not used very much, there were only a few citations over the subsequent 10 years or so.

When I moved to Zurich, Switzerland, I decided to take an honest look at what was wrong with it. A young resident in my department, Daniel Dindo joined me; we did some brainstorming and tried to make it more intuitive. For example, we omitted the length of stay which we felt was too subjective. We modified a few other aspects and submitted the inaugural paper to Annals of Surgery in 2004. Again, the proposal was ignored for the first year or two. Then suddenly, it happened. A few publications used it to compare outcomes and the citations increased and became accepted as a standard in many countries and fields of surgery. That's the way it is.

Your recent work has been on outcome benchmarks for complex surgeries. These studies have primarily enrolled high volume centers from the West. Do you think they would apply equally to low volume centers, or for centers from middle and low-income countries?

I think this new way of benchmarking might be useful for anybody who looks at delivering quality care. The problem with most outcome studies is that there are a lot of undetected variables in the background which may not be apparent in multivariate analyses, leading to biased results. The credibility of those studies with sophisticated statistical analyses are not always clear. We decided to minimise such bias, so instead of taking every case, we select only the optimal or good cases- we call them the benchmark cases. We go to the best center(s), high volume centers with experts in the area. We then look at outcomes for these ideal cases to come up with benchmark values, i.e., we can define the threshold limits for many endpoints such as mortality, complications, disease free survival etc. This information is available to every center for comparisons. If the centers' results are within these thresholds, then they are delivering care comparable to the "best" expert centers. If they are outside, they can introspect, explore what went wrong and what can be done to improve. This works whether you are a low-volume or high-volume center. This benchmark approach is now on the market and available to all. We will wait and see whether people find it useful.

Are you considering including centers from Asian countries in these benchmark studies, countries such as India- where large volumes are being done?

Absolutely, when we design the benchmark values, it must optimally come from 3 continents. For cadaveric liver transplant, we could not do this really, as Japanese data or data from many other countries in Asia could not be included because there was not many cadaveric organ data available. Now we are doing one with data from 7 high volume centers from India on living donor liver transplantation. We would select the good cases in these centers and then establish the benchmark values for many parameters such as hepatic artery thrombosis or long-term results. Let's say, if the best centers from 3 continents have hepatic artery thrombosis of 1%- that becomes the benchmark. If my center then has a 5% HAT rate, then I need to investigate the causes- is it due to difficult cases or do we have just more complications in simple cases?

Coming back to organ preservation, most studies are now being funded by companies which would eventually take over the intellectual property rights. Do you think there is a risk of organ preservation research going the way of pharmacological research, making it too expensive for standalone labs or research groups to carry out?

Very good question. The problem is this, it's a complicated and expensive technology which requires dedicated

experts- not everyone can do it. You can really hand-count the number of centers working on it. We were lucky to be funded by the Wyss research institute, which has nothing to do with the industry, as this is an academic translational center. Till today we have got around 7 million USD. On the other hand, in Oxford for example, they went rapidly with a company (Organox ®). That means the company owns everything. For our first case, we reported our result only one year after transplantation. We know that in liver transplantation, complications can occur even after 6 months. We waited for exactly a year before releasing the report. I did not want to be in the list of those who go on television and the next day, the patient is dead.

It is very rare for the first model of any car to succeed. It is the second or third model which is a success. We would like to come up with a machine which is mature enough, and that takes some time. We are not pushed by the funders to go into market. But ultimately, we will have to.

Anniversary celebration of the Wyss Zurich Team with the patient. From left to right: Matteo Müller, Prof. Mark Tibbitt, the patient, Prof. Pierre-Alain Clavien, Lucia Bautista Borrego, Max Hefti and Richard Sousa Da Silva.

I know you have previously said that even Professor Starzl would have problems doing transplants in the current bureaucratic environment. How difficult has it been for you to get approvals for such cutting-edge research?

Huge problems! Even with this case, where it was a compassionate use, there were endless ethical and paperwork issues, it was a nightmare. Innovation is a challenge these days because, when you want to do something new and somewhat risky, you only find people who will explain why it should not be done, why it is too dangerous. Even our hospital had concerns, thankfully we had the support of the Swiss organ distributing network in Switzerland (Swisstransplant), which has to manage a high mortality on the waiting list due to the lack of available organs. They know the relevance of such projects.

We wanted to do transplants in pigs and manage them during the post-operative period for at least a month before moving to humans. The ethical authorities refused this permission; we could not wake up the pigs after the transplants- they need to be sacrificed. So, we could not really analyse the function of the pig livers experimentally before we moved to the human transplant. So, to answer your question, it is a major challenge for all of us to work on innovation in medicine. In fact it's an even a bigger problem if you are known for innovations. Many may say that this individual is dangerous and can do too much. Better stop him now!!

"As scientist and surgeons, we are the people who probably better understand the problems our patients face"

Unlike in the past, it is very rare to find a surgeon nowadays with an active research profile like yours. You are one of the few who has bridged the gap between operating room and the lab. What do you think are the necessary characteristics of a surgeon scientist? Can every young surgeon aspire to be one?

This is indeed difficult. Research is less simple today, you need to train both in surgery and then in the lab with other experts, as technology is so advanced now. Many countries do not offer that, because it involves time and money. You need protected time, support of your institution and a mentor and get recognition in your institution for your achievements. These values are gone in many places and that's true even for high economy countries.

North America has been doing this the right way for many years, that's one of the reasons why I went there for my training. If you are working hard and succeed with research, you are valued. In my country and many others, it is less so. They would say if she/he is not going to operate, she/he may not be a competent surgeon and will not generate money. Even some patients may say, if you do not operate every day and are doing research, I do not want to be operated by you. This is exactly the opposite to the perception in the US where many feel that research makes doctors better.

We need to actively fight this trend. As scientist and surgeons, we are the people who probably better understand the problems our patients face. It is our responsibility to look for solutions and plan experiments with the help of other specialists to improve patient's care. In our department we try to support our junior colleagues, give them protected time for research, often to complete a PhD. There are many young surgeons who are doing a great job here.

Your research work has extended across multiple fields. Which achievement of yours do you value the most? Which aspect of your career would you highlight in your acceptance speech when they give you the Nobel!!

I don't know (laughs). If you have three kids and you ask which one you value the most, that is a bit difficult. We have lot of emotions attached to our research even for the work that didn't fly. If you look at medicine in general, I think the one with the most impact has been the one on outcomes, maybe it helped improve our practice. If you talk of science, then it is clearly the work on liver regeneration, organ preservation and the machine. I cannot choose between these two babies. As for the acceptance speech, you may have to wait a long time, but that's ok (laughs)!

"....find a good place for your training, believe in what you are doing, and be persistent- because no one is successful the first time"

Between your clinical, research, mentoring and organizational responsibilities, do you have any downtime?

Well, if you enjoy your work, then you never work! That's not exactly true, of course. As a transplant surgeon sometimes at 2AM in the morning, we would prefer to do something else. Things have changed, I don't know how it is in India, but here- quality of life has become very important for the young people! Previously in Basel, where I applied first, there used to be 100 applicants for 1 spot. Now we are happy if we can find applicants for all the spots. If

you are a good scientist, you might find 2 applicants for 1 spot. In the US, there are very few Americans who will do a transplant. It is rather people like you and me. But, yes, to answer your question. I ski – that's what we Swiss do (laughs), play tennis, even if we just lost Roger Federer, and a few other things. And yes, I do have a life outside of the lab.

Did you get a chance to visit India? What was your experience?
In Geneva, where I studied medicine, we get a long break after our exams. I visited India twice with almost no money during that time. Travelled by train from North to South, East to West- enjoyed the trip very much. Saw Calcutta, Madras, Kerala. I loved India and its many cultures. Got a bit sick though… if you eat at roadside shops you must face the consequences. I did! But I loved my trip, I loved your country, and I would like to come again.

Any message for young surgeons from India considering a career in liver transplantation?
Well, I would say, first find a good place for your training, believe in what you are doing, and be persistent- because no one is successful the first time. You mentioned Dr Starzl, but that was another time. He did it against everyone's opinions. People would have repeatedly bad outcome, but he never gave up. It is important to believe in yourself and the key message is "be persistent".
This is an exciting time to be a liver transplant surgeon. There are many research developments- organ preservation, regeneration, new indications - it is far from the end for liver transplant research, I think it is rather just the beginning of new areas like oncologic transplantation. I don't know if we will ever transplant pig livers, but there is a big future in transplanting artificial or extracorporeal manipulated grafts and it is all very exciting.

Solution to Jumble Puzzle (Puzzle on Page 36)

Viable
Static
Cannula
Pressure

When the only offer option available was a discarded organ, what the patient needed was a .....***LIVER ASSIST***

In Focus

Machine Perfusion of Liver Grafts

Machine perfusion of livers is back in the news!
After more than four decades of unrivalled supremacy, the era of static cold storage for deceased donor liver grafts is being challenged by the machines. And these machines are coming in all sorts and shapes- hypothermic, normothermic, sub-normothermic; with oxygen, without oxygen; single perfusion, double perfusion...the list is long and continues to get longer. These machines are clinically available outside clinical trials– in the UK, USA, Europe and now in India. But what is the actual situation on the ground? How has availability of this technology changed practice in the countries? And how does this change the way we perform deceased donor liver transplantation in India?
This issue of LiveReport looks at the origin story of machine perfusion, initial research of normothermic perfusion in liver preservation and how it is changing clinical practice across the world.

Machine perfusion- Back to the future?

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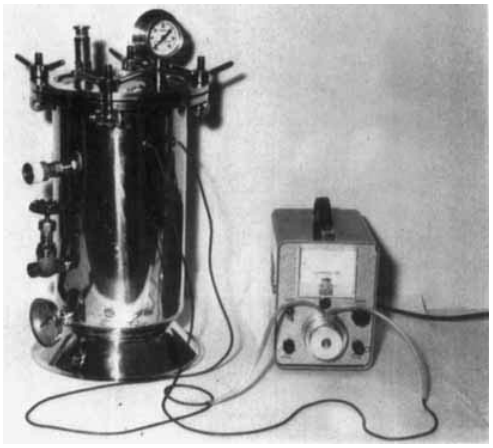
Machine perfusion of the deceased donor liver has come a full circle.
Research in organ preservation by machine perfusion was predated almost half a century before by the work of Nobel laureate Alexis Carrel and Philanthropist Charles Lindbergh. Together they developed the Carrel-Lindbergh apparatus which could preserve small organs like the thyroid for weeks using a sophisticated system of continuous perfusion of the organ's vascular system. While it remained a scientific curiosity at that time (a model is still exhibited at the

Alexis Carrel and Charles Lindbergh along with their perfusion apparatus featured on the cover of the Time magazine in 1935

Smithsonian's National Museum of American History, Washington DC) it became the basis for the heart lung machine and organ preservation by perfusion. Early transplantation practice was primarily a race against time-the donor and recipient operations happened side by side, the donor kidney was removed and rushed next door to be implanted in the recipient bed before the organ warmed up or the blood vessels clotted off. During the first successful kidney transplantation between identical twins performed by Dr Murray and team, the donor kidney endured a warm ischemia of 88 minutes, a life time by today's standards. That it worked smoothly and the era of clinical transplantation dawned is a miracle by itself!

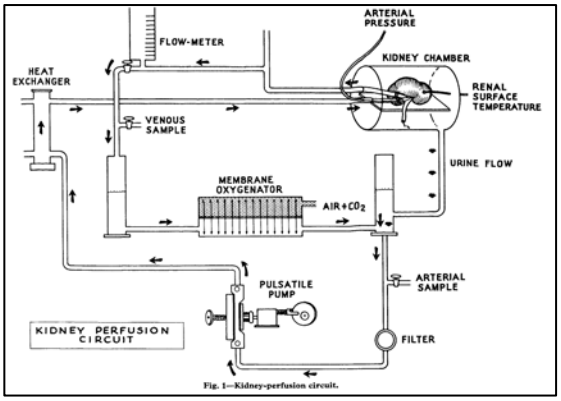
Once deceased donor transplantation was established as a treatment option, some means of preventing graft 'death' had to be developed. Scientists during the early 60s had already individually shown the importance of cooling of the organ, providing oxygen, shortening the duration of ischemia and preventing graft thrombosis using heparin in improving the success rate of kidney transplantation.

Thomas Starzl, then working in Denver, was the first to collate these dispersed bits of knowledge and establish a sequence of steps to ensure kidney graft viability- Expanding on the work of Ackermann and Barnard at Cape Town published a year before, Strazl started using a combination of donor hypothermia to 30°C, storage in a hyperbaric oxygen chamber and cold perfusion with diluted blood and to preserve kidneys. He used similar protocols while adding dual (portal & arterial) perfusion with diluted blood to preserve the livers in his early series of deceased donor liver transplantation. The way Starzl brought together already known facts and built on it reiterates his uncanny ability to see beyond the obvious.

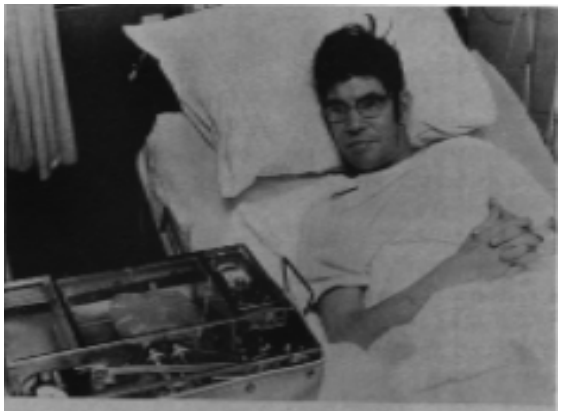


The hyperbaric chamber and perfusion. The perfusion tubing is slotted in the pump head and connected to the inflow and outflow nipples on the chamber wall. The pressure gauge, safety valve, quick-coupling Connector, exhaust valve, and thermometer are visible on the chamber. (From Ackermann et al BJS 1966)

Meanwhile in Boston, Folkert Belzer continued to work on cold perfusion of kidneys using plasma (later changed to cryoprecipitated plasma) to extend preservation of kidneys to 72 hours. The perfusion machine which needed a van for transport was gradually miniaturised into a portable kidney perfusion machine which transported a donor kidney from the US to Holland to be transplanted - the first recorded flight of a donor organ which was successfully transplanted. The race to develop the perfect machine to preserve organs was truly on!



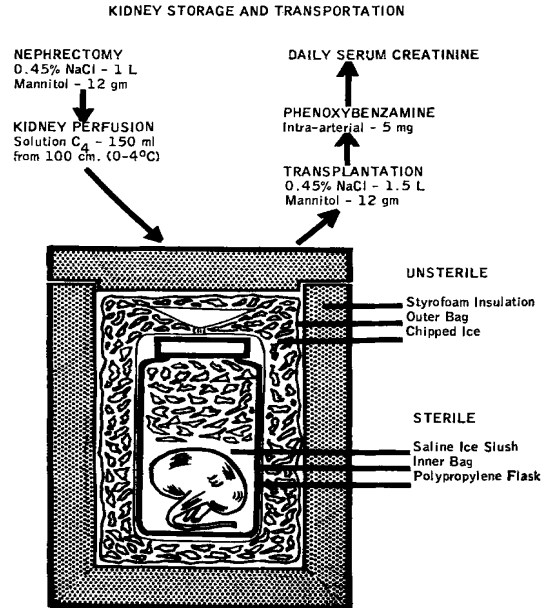
The perfusion circuit used by Belzer for machine perfusion of renal grafts. The current perfusion machines continue to have a broadly similar layout.



The portable version of the machine which was used to perfuse the kidney during its flight to Holland, along with the eventual Dutch recipient

Unfortunately, the party was crashed by Geoff Collins, a young surgeon working in Dr Terasaki's lab in Los Angeles. Using a simple cold flush with a solution mimicking intracellular fluid, Collins demonstrated that canine kidneys could be safely stored for

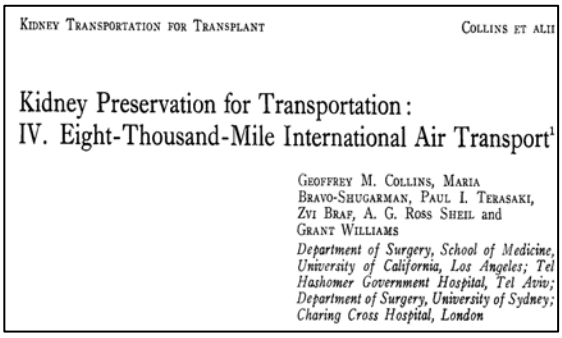
24 hours in a humble plastic box. To add insult to injury, Collins flew 11 canine kidneys preserved in his preservation solution (codenamed C4) from LA to destinations in London, Sydney and Tel Aviv - a distance of 8000 miles and which were then transplanted there with good results.



Schematic diagram showing static cold storage preservation using Collins solution (From Collins et al ANZSurg 1970)

Between 1970 and 1990, static cold storage had become the standard with the only research question being the way to improve the preservation fluid The era of complex machines to preserve organs for transplantation had effectively ended except in the labs of a few maverick researchers.

Things started to change in the late 1990s as the concept of non-heart beating donation of kidneys was rediscovered as a means to increase the number of transplantations.


KIDNEY TRANSPORTATION FOR TRANSPLANT — COLLINS ET ALII

Kidney Preservation for Transportation:
IV. Eight-Thousand-Mile International Air Transport[1]

GEOFFREY M. COLLINS, MARIA BRAVO-SHUGARMAN, PAUL I. TERASAKI, ZVI BRAF, A. G. ROSS SHEIL and GRANT WILLIAMS

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The eye-catching title head of article by Collins et al reflected the competitive spirit amongst proponents of various preservation techniques. This and subsequent clinical successes effectively established SCS as the standard method of prolonged kidney preservation. (From Collins et al ANZSurg 1970)

Increasing use of marginal and older organs also started to highlight the drawbacks of the ridiculously simple technique of dunking organs in cold fluid while waiting for implantation. Researchers started dusting out their old research work to get back into the race to improve organ preservation. Another key factor was that by the early 2000s organ transplantation was big business and companies were becoming aware of the size of the potential market for organ preservation technology.

Over the last 20 years, the focus has once again returned to machine perfusion. The change is nowhere more remarkable than in kidney preservation where the percentage of pumped kidneys has increased from less than 5% to over 50% in the US and most of Europe. However, its potential for improving outcomes of marginal liver grafts is more significant as the implications of allograft dysfunction or failure in liver transplantation is much more severe. A wide variety of technologies are now in the market or in development most based on pioneering research literally flushed out by Collins' simple kidney cold flush technique. Long live the machines!!

Pioneering research in normothermic machine perfusion of Liver- *The Indian Connection*

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Srikanth Reddy is the clinical lead for transplantation, surgical lead for intestinal transplantation and chair of HPB cancer MDT in Oxford. His research efforts led to development of first human experience of intestinal transplantation for pseudomyxoma and the current research focuses on using focused ultrasound therapy for ablation of pancreatic cancers and enhancing chemotherapy drug delivery into liver cancers.

After completing medical school and General Surgery training in JIPMER, Pondicherry, I moved to UK and joined the Oxford Transplant Centre in 2001 as a Junior Resident. The unit
was led by recently appointed Professor of Transplantation - Peter Friend. The UK Postgraduate surgical training was very competitive, and a period of research was mandatory for career progression. Professor Friend was kind enough to accommodate me in his fledgling research group. There had been very little work on normothermic machine perfusion (NMP) at that time, though there was considerable ongoing research on using cold machine perfusion for organ preservation. NMP was based on the hypothesis that preservation injury can be minimised by avoiding both cooling and hypoxia, thereby removing the

two major factors contributing to preservation injury. Schon et al. working with Professor Neuhaus in Berlin had successfully preserved deceased porcine donor livers using NMP for a short duration of upto 4 hours. However, extended duration of preservation had not been demonstrated. Using autoregulation for portal perfusion was thought to be a key in obtaining prolonged successful preservation of upto 72 hours. Prof Peter Friend had initiated NMP of livers in Cambridge as extracorporeal support for liver failure and the research moved to Oxford when he was recruited as chair of transplantation in Oxford.

I was tasked by Professor Friend with proving that NMP can be used to preserve porcine livers for transplantation. This was an exciting opportunity to undertake a dedicated period of research in a surgically oriented field. There were many challenges in the early days including limited resources, funding and personnel- even in a place like Oxford! We had to be resourceful such as starting experiments at 5 am before clinical activity, repair blood gas and diathermy machines ourselves to name a few.

The pig was chosen as a large animal model as commercially available paediatric cardiopulmonary bypass components could be used to support their livers. The pig liver had many anatomical and physiological similarities to humans, and we knew that the pig liver was more vulnerable to preservation injury than humans. We imagined that any technique shown to be successful in pigs was likely to be effective in a clinical setting. The initial challenge was developing a reliable model of pig liver transplantation. The transplants were complicated by excessive bowel congestion and splenic rupture which was solved by establishing a passive veno-

venous bypass from the splenic vein to external jugular vein using a non-thrombogenic cannula.

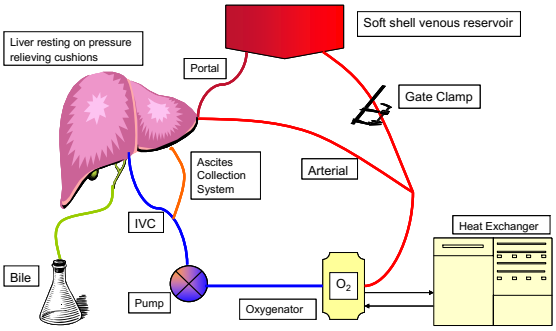
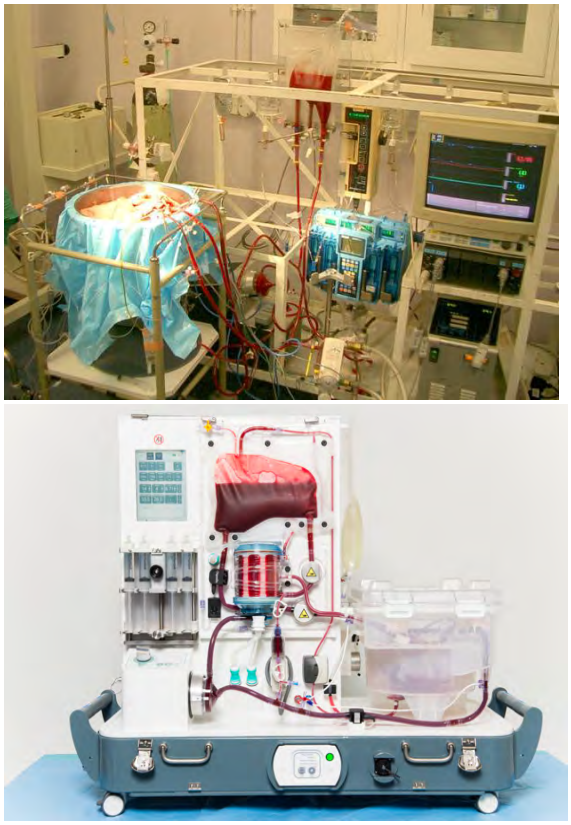


Figure: Schematic Diagram of Perfusion Circuit used in the experiments

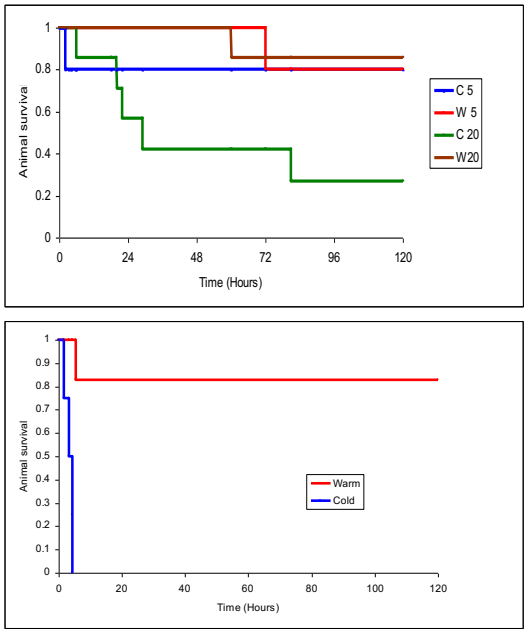
Jens Brockmann joined the group from Munster, Germany and brought considerable experience in performing pig liver transplants reducing technical failures. We were also fortunate to have an animal facility on the hospital campus allowing seamless transition between research and clinical work on a day-to-day basis and involvement of a highly skilled cardiac anaesthetist - David Pigott for transplant experiments.

NMP was performed by assembling several tubes and connectors incorporating an oxygenator, centrifugal pump, heat exchanger and reservoir before each experiment. All the equipment apart from the oxygenator were sterilised and reused to reduce costs. Over 40 pig liver transplants were performed over 2 years which demonstrated that 1. NMP was similar to Cold preservation (CP) for short duration of preservation of healthy DBD livers 2. NMP was superior to CP over extended preservation times and 3. NMP was superior to CP livers for marginal DCD livers. Survival at 5 days was chosen as the primary end point and a 5 day time point was chosen as it enabled effects of preservation - ischaemia and reperfusion injury to be seen but would be too soon for major immunological reactions. Also, for logistic and cost reasons it was not possible to keep the animals surviving indefinitely.



A) Photograph of a liver undergoing normothermic perfusion using the experimental setup in the lab and B) The OrganOx machine in action

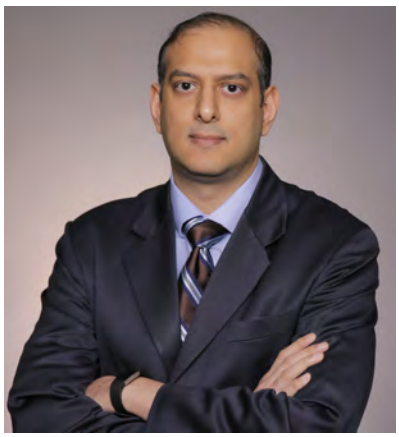
This challenging and rewarding work was possible under Professor Friend's unending supervision and contribution of many research members including Jens Brockmann, Nikolai Maniakin, Dino Guireirro, Miguel Zilvetti, Xia Feng, Shantanu Bhattacharjya and David Piggott. These results conclusively proved the superiority of NMP over CP and Peter Friend in collaboration with a biomedical engineer- Constantin Coussios developed a commercial NMP device through University of Oxford spin out company OrganOx.



A) Survival of pigs that underwent DBD liver transplants. Preservation was time dependent in the cold group with survival being lower after 20 hours preservation compared to 5 hours preservation. However, it was time independent in the NMP group with survival similar after 5 and 20 hours of preservation.
B)Survival of pigs that underwent DCD liver transplants with 40 minutes warm ischaemia (P=0.001). All the animals in the cold group died within 4 hours of transplantation, whereas 5 of the 6 animals in the warm group survived 5 days.

I believe that a period of research is mandatory for any ambitious surgical trainee and I was fortunate to find an outstanding supervisor in a world leading University. This period of dedicated research broadened my horizons, led to 6 peer reviewed publications and facilitated a career in surgery in the UK. Most importantly, it was satisfying to see this preclinical work play an important role in the development of clinical practice changing technology.

Machine perfusion of livers in the USA- *Cautious optimism*



Dr Abhishek Mathur

Assistant professor surgery,
Center for liver disease and transplantation,
New York Presbyterian/ Columbia University, NY, USA

FDA approval for two NMP machines *(OrganOx and Transmedics OCS)* was granted less than 12 months ago and as such its clinical impact across the United States is in a process of evolution. Understanding the data on NMP use is critical to understanding its adoption in the United States. The rationale for benefit has been laid out in the two initial RCTs utilizing each of the FDA approved devices.[1,2] Both devices have clearly demonstrated a reduction in early allograft dysfunction and the RCT in the US showed a decrease in ICU and hospital LOS. Both Nasralla et al and Markmann et al have demonstrated reduction in the organ discard rates (24% to 11.7%) and increased utilization of DCD grafts (51% vs 26%) with NMP vs static cold storage.

Also important to NMP utilization is an understanding of its limitations. While both these studies are compelling, the

application of NMP to more significant extended criteria donors (ECD) is still unsettled. As an example, the DCD organs in Nasralla et al's RCT had a modest median warm-ischemia time of 21mins and Markamnn et al had an enrolment WIT cut off of 30mins for enrolment in their RCT. Utilization of NMP to more advanced ECD organs that are discarded was reviewed in the VITTAL clinical trial by the Birmingham group.[3] While they were able to utilize otherwise discarded organs the rate of ischemic cholangiopathy in the DCD group was close to 30%.

These benefits and limitations of NMP are likely to guide utilization variably across the United States. In the USA about 12,000-13,000 patients are added to the transplant list every year and there are about 8000 adult liver recipients transplanted every year. The majority (95%) of adult transplants in the United States are through deceased donation. Over time the percentage of extended criteria organs used has increased. However, overall discard rates are still close to 10% and this is even more pronounced with DCD organs at close 25%. Furthermore, discard rates are highly variable among centers – with more aggressive/experienced centers utilizing ECD organs at a higher rate. Importantly even at high ECD use centers the organ has to be carefully matched to a recipient who is usually a low MELD patient who could tolerate the early allograft dysfunction and its potential detrimental impact on other organ systems.

Therefore, uptake of NMP will be variable across centers depending on their 'risk' profile. Centers with less experience with ECD organs may derive a greater benefit by developing "machine courage" with NMP use to assess ECD organs!

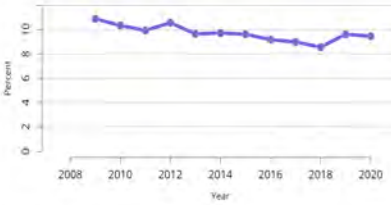


Figure LI 44. Overall percent of livers recovered for transplant and not transplanted. Percentages of livers not transplanted out of all livers recovered for transplant.

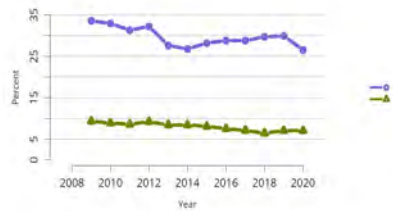


Figure LI 51. Percent of livers recovered for transplant and not transplanted by DCD status. Percentages of livers not transplanted out of all livers recovered for transplant. DBD, donation after brain death; DCD, donation after circulatory death.

Liver discard rates in the USA over the last 12 years. DCD liver discard rates are 5-6 times greater than DBD discard rates.

Centers who are already experienced with ECD organs will benefit from potentially having improved patient outcomes with reduced EAD and ICU stays. Furthermore, it may allow utilization of these organs even in a sicker cohort of patients with NMP's ability for a reduced reperfusion injury. We are already seeing these scenarios play out anecdotally -particularly in places like New York – where there are seven centers in a relatively small geographic area. 'Machine courage' in less experienced centers will increase their share of ECD transplants and may impact transplant numbers of centers which were traditionally more aggressive in accepting these organs.

As noted above NMP use in more advanced ECD organs is unsettled. This represents a fertile place for research. Transplant centers in academic organizations will therefore be further motivated to be early adopters to be at the forefront of this work which could eventually lead to greater organ utilization.

Figure 3 Increasing use of machine perfusion in the preservation of deceased donor organs (UNOS data). Liver perfusion had increased from 0.1% in 2016 to 1.4% by the end of 2018. This was much before perfusion technology had been FDA approved and available to all centers.

Each individual center has to weigh the benefits and limitation of NMP use with the substantial costs associated with the technology. If an organ is not utilized despite machine perfusion those charges may have to be written down by the center. These "dry runs" can add up quickly for centers with smaller resources. Furthermore, utilization of NMP and building resources around it requires buy in at multiple levels of each organization. This may lead to centers again showing varying degrees of utilization in how often and what scenarios they are willing to deploy NMP.

It is clear that NMP is here to stay and will be transforming the landscape of transplantation. The impact and level of utilization of NMP across the centers in the United States remains to be seen and is going to be based on a complex interplay of factors.

Machine perfusion of livers in the UK- *Increasing utilization*

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In the United Kingdom, the shortage of deceased donor livers and the increasing use of DCD and other marginal livers has driven the development of novel technologies for organ preservation and reconditioning. According to the latest NHS Blood and Transplant (NHSBT) report, up to 15% of people awaiting a liver transplant operation died or were removed from waiting list due to ill health. Ex-situ machine perfusion technologies such as Normothermic Machine Perfusion (NMP) and Hypothermic Machine Perfusion (HMP), and in-situ Normothermic Regional Perfusion (NRP) allows safe expansion of donor organs, enable objective assessment of their quality and viability, improve the quality of marginal livers, and extend the preservation time allowing logistics and challenging transplants.
The number of machine perfused livers are increasing steadily in the UK. 26% of all first adult liver transplants performed in the

UK between April 2021 and March 2022, were machine perfused livers, compared to 20% in the previous year. Also, donation after circulatory death (DCD) liver utilisation has increased from 17% in 2020-2021 to 26% in 2021-2022 due to increasing use of machine perfusion to assess these organs, reducing primary non-function rate, and reduced incidence of ischaemic cholangiopathy.

NMP (OrganOx metra®) is utilized for both donation after brain death (DBD) and DCD organs, with variations in functional assessment protocols across the UK centres and varied organ utilisation rates. The liver can be put on the NMP at retrieval centre (continuous mode) or a more pragmatic approach, at the transplant centre (back-to-base mode). The first report of a phase 1 trial (first-in-human) of OrganOx metra® was reported in 2016, which showed significantly lower peak AST in the first 7 days after transplantation. Led by the UK, a multicentre RCT by the Consortium for Organ Preservation in Europe (COPE) with 220 livers compared to standard cold storage (SCS) showed 50% lower level of graft injury, 50% lower rate of organ discard and a 54% longer mean preservation time, with no difference in bile duct complications, graft, or patient survival.

OrganOx metra in action at the Leeds Liver Unit (with Yashavanth Kumar and Jennifer Logue)

Over the last few years, NMP has allowed safe expansion of both extended criteria DBD and DCD organs to allow transplantation of discarded (declined) livers by all UK centres (VITTAL trial; Viability Testing and Transplantation of Marginal Livers), improve access for retransplant recipients (NAPLES initiative), allow longer preservation to allow logistics (challenging transplants, multiple transplants, avoiding overnight transplants, theatre/staffing logistics), ex-situ splitting on machine, etc. Two NIHR funded studies will hopefully throw more light into the utilisation aspects (PLUS; Perfused Liver Utilisation Study) and if it is possible to defat a steatotic liver (DeFat Study).

HOPE setup– VitaSmart™ (Bridge to Life)

HMP (or Hypothermic Oxygenated Perfusion; HOPE) reduced ischaemia reperfusion injury (IRI) of DCD livers and could be portal vein perfusion alone (HOPE) or via both the portal vein and hepatic artery (dual HOPE or dHOPE). Since the RCT published in NEJM in 2021, comparing HOPE with SCS, there has been increased use of HOPE for DCDs (i.e., the DCDs which doesn't need assessment prior to transplantation). The study showed significant reduction in nonanastomotic biliary strictures (NAS) in HOPE group compared to SCS group (6% vs. 18%; risk ratio 0.36, p=0.03). In UK, only a few centres use HOPE, as other centres rely on NRP for DCDs.

NRP allows assessment of DCD organs by creating an extracorporeal membrane

oxygenation (ECMO) on the controlled DCD (cDCD) donors. This can be a combined thoracic-abdominal or abdominal alone NRP. NRP increased the odds of liver being transplanted by 3-folds, with superior 1-year liver transplant survival with a 51% lower risk-adjusted hazard of transplant failure (HR=0.494), when compared to standard DCDs. Cambridge and Edinburgh have been the only two centres with large experience with NRP. A recent single centre report from Cambridge showed no clinically significant NAS in 69 NRP livers, when compared to 14% for 97 SCS and 11% for 67 NMP livers. For those NRP retrievals where the functionality assessment is not clear, the liver can be subsequently placed on NMP for further assessment before transplanting or discarding.

The current practice of MP in the seven UK LTx centers is variable. In Leeds, every DCD liver undergoes HOPE, and those with borderline function get assessed on NMP for viability; and some marginal DBD grafts undergo NMP for viability assessment. There is currently a need for a trial comparing all three technologies with SCS. Though the cost implications are significant they are probably offset by the gains - reduced discard rates, reduced reperfusion syndrome, reduced post-transplant acute kidney injury, shorter stay and overall improved graft survival. All perfusion technologies are available as lease from companies, with consumable kits funded by the NHS trust or charities [consumable kit price per liver – NMP - £ 4680 (approx. Rs. 4,25,000); HMP - £ 3360 (approx. Rs. 3,00,000); NRP - £ 3500 (approx. Rs. 3,20,000). There is ongoing work on national funding for NRP services through NHSBT and centralized Assessment and Recovery Centres (ARCs) which will perfuse the liver and transport to the centres for transplantation.

Machine Perfusion of livers in India- *Proceed with caution*

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Over the past 3 decades, dramatic improvements in organ preservation, comprehension of disease process, surgical techniques and importantly, introduction of innovative technology has resulted in liver transplantation (LT) becoming the standard of care for patients with end-stage liver disease. Due to its potential applicability in organ maintenance and expansion of the donor pool in LT, the machine perfusion device (MPD) is one such technological advance which has garnered tremendous interest. Globally, early enthusiasm regarding these devices has now been tempered with more sobering outcomes. Furthermore, with evolving evidence, the gamut of its application is being restricted to a more focussed group of patients/organs. It remains undisputed that these devices improve outcomes in a selected subset of organs, and are not mandatory to deceased donor programs.

Given its potential market in India, these devices were introduced with much hype. Intuitively, the media bought into the frenzy, purporting them as the next-big revolution in LT. Behind the glitz of this new technology, lay the granular underbelly, which needs taking into consideration. Most LT in India is privately funded and the economic burden of the expendables is borne by the patient. On one side there is a push towards curtailing these expenses to make LT more affordable, on the other, additional cost of up to 20% (expendables/case for MPD) make such devices prohibitively expensive.

The use of such devices does not guarantee a uniformly good outcome. Acquiring these devices may lead to unreasonable expectations. Healthcare providers may use it as a marketing tool, promoting this new technology as a panacea. Further issues may crop up when the devices are used in a few hospitals, and an organ fails in a hospital not using the device. There are likely to be accusations of suboptimal care on the second hospital's part, resulting in graft failure. These may have tremendous implications, and may even result in a defensive, universal, unindicated application of the device to avoid legal issues. Giving into this 'medical peer pressure' is likely to have further adverse ramifications, potentially breeding sensationalism within the media, leading to mistrust in the process of deceased donation. It is also crucial to appreciate that even a single untoward incident may derail the whole deceased donor program, and even set it back by many years.

Pioneering attempts at development of new technology are necessary to improve outcomes in surgery. It a team-effort between the doctor and the engineer, which facilitates the conception, introduction and practical application of newer enhanced technology. The use of such technologies in progressively sophisticated procedures must be carefully monitored and gradually implemented to ensure patient safety. It is innate human nature to use any new device as the proverbial 'Maslow's hammer'. Its practical, real-world application however, needs to be tempered against the realistic demand sensitive to cultural, social and economic regional considerations.

A typical road-map for introduction of a new technology in our part of the world would need to include evidence from an Indian/South-Asian cohort as a part of large, multicentre studies. Further, this introduction needs to be graduated, wherein the financial obligations are borne by the concerned companies, allowing for a fairer fulfilment of the tenets of utility, autonomy, and non-malfeasance. Such an initiation can be overseen and streamlined under the guidance of altruistic national bodies like the LTSI.

Hot stuff

Livers on the shelf?

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GI & Minimal Access Surgery
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In May 2021, the multidisciplinary research team in Zurich lead by Prof Pierre Clavien– a collaboration of University Hospital Zurich (USZ), ETH Zurich and the University of Zurich (UZH) –treated a rejected human liver in the machine for three days and then implanted it into a cancer patient with no chance of getting a standard liver graft in time. One year later, the patient is doing well.

Liver4Life: a Wyss Zurich project

The Liver4Life project was launched in 2015 under the umbrella of the Wyss Zurich Translational Center (Wyss Zurich). It brings together the highly specialized technical know-how and biomedical knowledge of around ten medical professionals, biologists and engineers. The project is being financed with donations from the initiator of Wyss Zurich, Dr. H.C. Mult. Hansjörg Wyss.

Philantropist Hansjörg Wyss

The liver graft

On 19 May 2021, the team were offered a liver graft from a 29-year-old female donor suffering from an invasive abdominal desmoid fibromatosis associated with chronic intra-abdominal abscesses and recurrent sepsis episodes due to multi-resistant bacteria. Additionally, there was a 4-cm tumor of unclear nature in segment 1 of the liver.

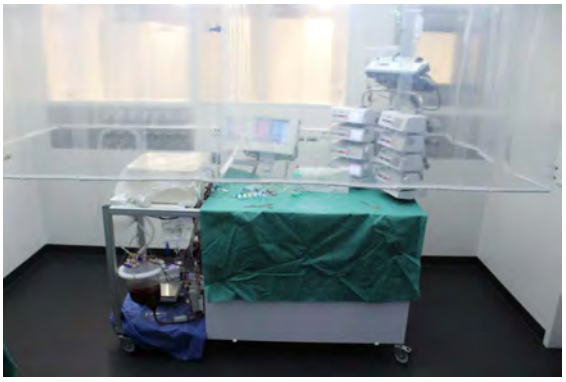
This potential liver graft (weight, 1.7 kg) was refused by all other centers, primarily because it required diagnostic work-up of the liver lesion, which was not immediately possible, and because of the ongoing sepsis in the donor with multi-resistant microorganisms. This liver graft was procured and was subsequently connected to the Wyss perfusion device.

The team connects the donor liver to the perfusion machine in the clean room.

The Wyss machine

The Wyss machine mimics the human body as accurately as possible to provide ideal conditions for the human liver. The

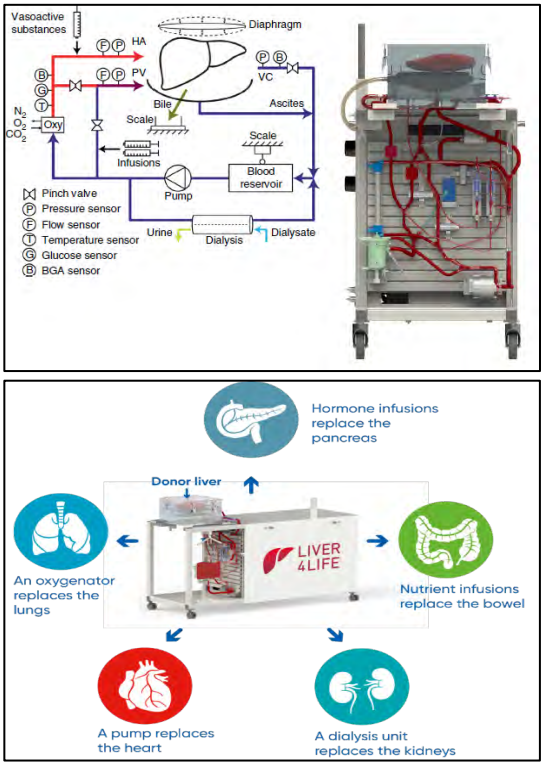
perfusion machine sort of acted as a second human body and allowed the liver specimen to survive externally for three days.



The perfusion machine in operation. The donor liver is kept in the white container on the left.

The liver was perfused through both the hepatic artery and portal vein. Oxygen-rich blood at elevated pressure (mean arterial pressure (MAP) ≥ 65 mmHg) in a pulsatile manner was pumped into the hepatic artery, whereas the portal vein receives blood at low pressure (around 5–10 mmHg) with a reduced oxygen content (venous blood, non-pulsatile). The system maintains oxygen saturation of 65% in the vena cava by continuously adjusting oxygen content in the portal vein. Hepatic artery hemodynamics are tightly controlled by automated infusion of vasoconstrictors and vasodilators into the hepatic artery line. The pressure in the vena cava is continuously kept at physiological levels close to 0 mmHg (0–2 mmHg) to prevent liver congestion.

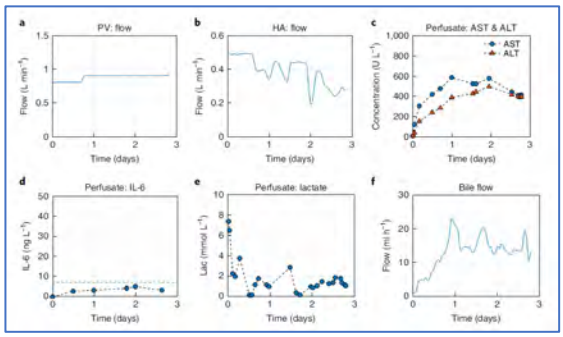
Parenteral nutrition and ursodeoxycholic acid are infused into the portal vein line. Automated insulin and glucagon administration was used to maintain physiological blood glucose levels (targeted range of 3.5–6.5 mmol l−1) in response to continuous glucose measurements. An integrated dialysis unit has been incorporated for physiologic electrolyte balance and removal of metabolic waste products from the blood. The perfusion machine is fully automated obviating the need for constant presence of personnel. Continuous movement of the liver, in an effort to mimic diaphragm oscillations, is also integrated into the system. In other words, for a liver in the contraption, it's almost like it never left the body.



The Wyss perfusion machine replaces the functions of various organs in order to keep the donor liver alive outside of the body.

From poor to good in three days

The liver graft disclosed an immediate clearance of lactate and increasing bile production as well as low release of transaminases, which decreased after 24 hours (peak AST of 791 U/ L and peak ALT of 587 U/ L. Acute cytokine levels in the perfusate also remained low. Liver function, measured by factor V synthesis, improved continuously from 33% at the start of perfusion to 54% within the first 24 hours of perfusion.



Liver performance parameters during ex situ normothermic machine perfusion

Pre-reperfusion (baseline) histology of the tumor in segment 1, which became available at this time, revealed a perivascular epithelioid tumor with no features of malignancy. After viability testing, the decision was taken to consider this liver for transplantation after consultation with an international advisory board.

The patient

The potential recipient was a 62-year-old male patient who suffered from advanced cirrhosis, severe portal hypertension and multiple and recurrent hepatocellular carcinoma (HCC). He had a near-zero chance to receive a graft in time and had no available living donation.

Following his consent, the organ was transplanted by standard technique. A biopsy taken 60 minutes after reperfusion demonstrated no signs of reperfusion injury and no necrotic areas. No reperfusion syndrome was observed. The patient was extubated in the operating room and transferred to the intensive care unit.

Postoperative course

After transplantation, there was a very low degree of graft injury with minimal release of liver enzymes (peak ALT = 138 U/L and peak AST = 309 U/ L) and normal serum bilirubin. The recipient experienced acute kidney failure, leading to short-term hemofiltration, possibly related to a combination of hypovolemia and nephrotoxicity of one of the antibiotics (possibly vancomycin) and hypoalbuminemia (14 g/L). On postoperative day 5, a small anastomotic bile leak required an endoscopically placed stent in the CBD, which was removed 4 weeks later. The patient was discharged 12 days after transplantation. Immunosuppression with calcineurin inhibitor (tacrolimus) dose targeting low levels of 2–3 µg/ L, mycophenolate mofetil (CellCept, 500 mg twice daily) and tapering dose of steroids was used.

Post-operatively, he did very well. MRCP done 6 months after transplantation showed completely normal intrahepatic bile ducts without any dilatation. ERC was performed at 11 months after transplantation due to an asymptomatic short anastomotic biliary stricture. This ERC disclosed a perfectly preserved intrahepatic biliary tree, and laboratory tests rapidly normalized after placement of a temporary stent. One year after the trailblazing procedure, the team reported that the organ recipient was still doing exceptionally well. "The patient rapidly recovered a normal quality of life without any signs of liver damage," the research team at Liver4Life said.

Professor Pierre-Alain Clavien with the patient at discharge after transplant.

Saving more lives

"I am very grateful for the transplant," the 62-year-old organ recipient said in a statement. "Due to my rapidly progressing tumor, I had little chance of getting a liver from the waiting list within a reasonable time."

“Our therapy shows that by treating livers in the perfusion machine, it is possible to alleviate the lack of functioning human organs and save lives,” said Pierre-Alain Clavien, Director of the Department of Visceral Surgery and Transplantation at University Hospital Zurich. "The success of this unique perfusion system - developed over a four-year period by a group of surgeons, biologists and engineers - paves the way for many new applications in transplantation and cancer medicine helping patients " He also believes the perfusion machine technology could one day be used for other organs.

“The interdisciplinary approach to solving complex biomedical challenges embodied in this project is the future of medicine,” said Mark Tibbitt, professor of macromolecular engineering at ETH Zurich. “This will allow us to use new findings even more quickly for treating patients.”

The next step for the Liver4Life project is to review the procedure on other patients and demonstrate its efficacy and safety in the form of a multicenter study. "Its success would mean that in the future, a liver transplantation, which usually constitutes an emergency procedure, would be transformed into a completely elective procedure. In addition, those involved in basic research continue to look for ways of treating other liver diseases outside the body with drugs, molecules or hormones."

Transplant Vignettes

The Child Turcotte Pugh SCORE – *More than CHILD’s play!*

Dr Johns Shaji Mathew
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In the mid 1900’s cirrhosis had attained the status of a deadly disease. Disease progression resulted in uniformly poor outcomes with little chance of cure or alleviation of advanced symptoms. Patient’s with variceal bleeding had extremely high rates of mortality. This prompted surgeons of the time to take an aggressive approach to its treatment.

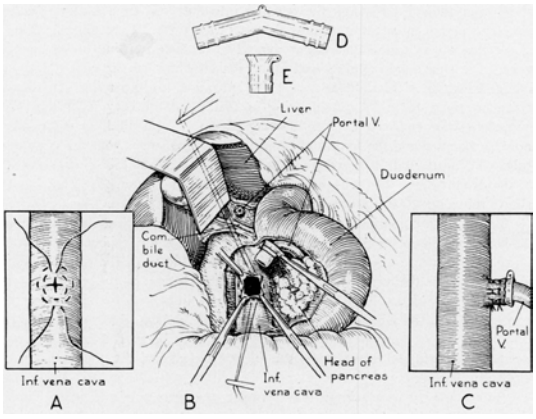
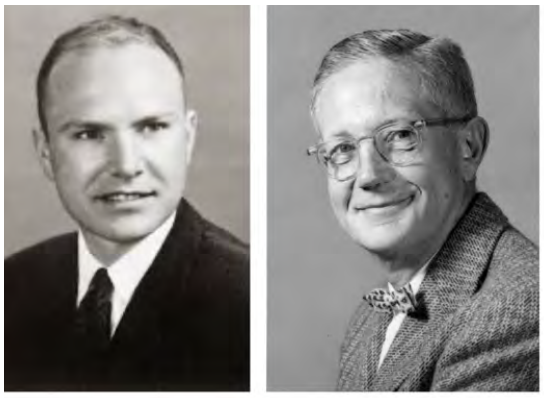


Illustration demonstrating the use of vitallium tubes to create a surgical portosystemic shunt. Emergency portosystemic shunts were the only treatment option available in the early 1900. Vitallium tubes provided a safe method of creating a vascular anastomosis as Carrel’s technique of vascular anastomosis was yet to be universally adopted. (From Blakemore & Lord. Ann Surg 1945)

Encouraged by the use of Vitallium tubes for creating porto-caval shunts by Blakemore and Lord, Allen Oldfather Whipple (of Whipple's procedure fame) re-introduced porto-systemic shunts in the treatment of portal hypertensive bleeds. Whipple primarily described and advocated the technique of porto-caval anastomoses. Multiple variations of the shunt were conceived later on by eminent surgeons. However, shunt surgery in portal hypertension had a major drawback; although the surgery was effective in controlling the bleeding, the outcomes were severely impacted by post procedure liver failure and encephalopathy. As one later observer claimed "in comparison with those who do not undergo surgery, patients with shunts bleed less, flap more and yet live longer". However, there were some patients who did very well with the shunt procedure. Selecting the right patient for shunt surgery became very important.

Surgeons such as Robert R Linton, William V McDermont and Cyril Shaldon all devised methods for patient selection. However, it was in 1964 that Charles Gardner Child III and Jeremiah George Turcotte from the Department of Surgery at the University of Michigan, Ann Arbor devised a classification based on the severity of liver disease for stratification of patients undergoing shunt surgery (Figure 1). Patients were categorized into Class A (Minimal), B (Moderate) and C (Advanced) based on serum bilirubin, albumin, neurological disorder (hepatic encephalopathy), ascites and nutritional status. These variables were selected based on clinical experience. Child and Turcotte performed actuarial survival analysis to demonstrate statistically significant differences in 3-year and 10-year survival rates between the groups.



Drs Jeremiah Turcotte and Charles Gardner Child III

Looking back, the score has had its share of controversies. George E Wantz and Mary Ann Payne, previous colleagues of Child, had in fact described the classification 2 years (1961) before in the New England Journal of Medicine. However, with the publication of Child's paper, their contribution was almost forgotten and even Dr Turcotte started calling it the Child's score. Perhaps the score should have been called Wantz-Payne-Child-Turcotte criteria to give all these researchers their due.

TABLE 1. CRITERIA FOR CHILD-TURCOTTE CLASSIFICATION

Group designation	A	B	C
Serum bilirubin[a] (mg·%)	Below 2.0	2.0–3.0	Over 3.0
Serum albumin (gm·%)	Over 3.5	3.0–3.5	Under 3.0
Ascites	None	Easily controlled	Poorly controlled
Neurological disorder	None	Minimal	Advanced "coma"
Nutrition	Excellent	Good	Poor, "wasting"

Table I.—GRADING OF SEVERITY OF LIVER DISEASE

CLINICAL AND BIOCHEMICAL MEASUREMENTS	POINTS SCORED FOR INCREASING ABNORMALITY		
	1	2	3
Encephalopathy (grade)*	None	1 and 2	3 and 4
Ascites	Absent	Slight	Moderate
Bilirubin (mg. per 100 ml.)	1–2	2–3	>3
Albumin (g. per 100 ml.)	3·5	2·8–3·5	<2·8
Prothrombin time (sec. prolonged)	1–4	4–6	>6
For primary biliary cirrhosis:— Bilirubin (mg. per 100 ml.)	1–4	4–10	>10

* According to grading of Trey, Burns, and Saunders (1966).

The original scoring system developed by Child and Turcotte and the modified score developed by Pugh replacing nutrition with prothrombin time

In 1973, R. N. H. Pugh from King's College Hospital in London modified the original scoring system. Pugh et al adjusted the limits for serum albumin, defined the encephalopathy grading system and substituted normalized ratio (INR) for nutritional status, thereby eliminating the most subjective element in the scoring system. Quoting Pugh et al, "*Our method of grading the severity of liver disease is more flexible than that originally described by Child (1964), in which a low serum albumin alone was sufficient to place a patient who otherwise had good liver function into Grade C*". Each of the five parameters were given points ranging from 1 – 3 leading to the calculation of the Child-Turcotte-Pugh (CTP) score (5 - 15). CTP A was scored from 5 to 6, CTP B from 7 to 9 and anything more than 10 as CTP C. The same paper discussed the operative mortality in each of the three classes; A at 29%, B at 38% and C at 88% (Figure 3).

Needless to say these modifications made the score more reliable and robust, and helped it stand the test of time. The CTP score is widely used even now in clinical practise with some authors claiming that the CTP score is better than the MELD score in predicting mortality.

There is no doubt that the CTP score continues to be useful in prognosticating patients with cirrhosis. Recent reports suggest that nutritional assessment (in the form of sarcopenia) and objective parameters measuring frailty are useful in prognosticating patients suffering from cirrhosis. It ironic that nutritional status, a parameter in the original CT score and later removed from the CTP score has now found new relevance in hepatology practice.

Tricks of the Trade

Safely reducing transplant cost using a modified back table graft flush technique in LDLT

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Back table flushing of the graft with a cold preservative solution is an essential step for prevention/reduction of Ischemia-Reperfusion (IR) injury in liver transplantation, whether it is living donor or deceased donor liver transplantation. UW (University of Wisconsin), HTK (histidine-tryptophan-ketoglutarate), IGL-1 (Institute Georges Lopez) are the commercially available preservative solutions that are commonly utilized for this purpose.

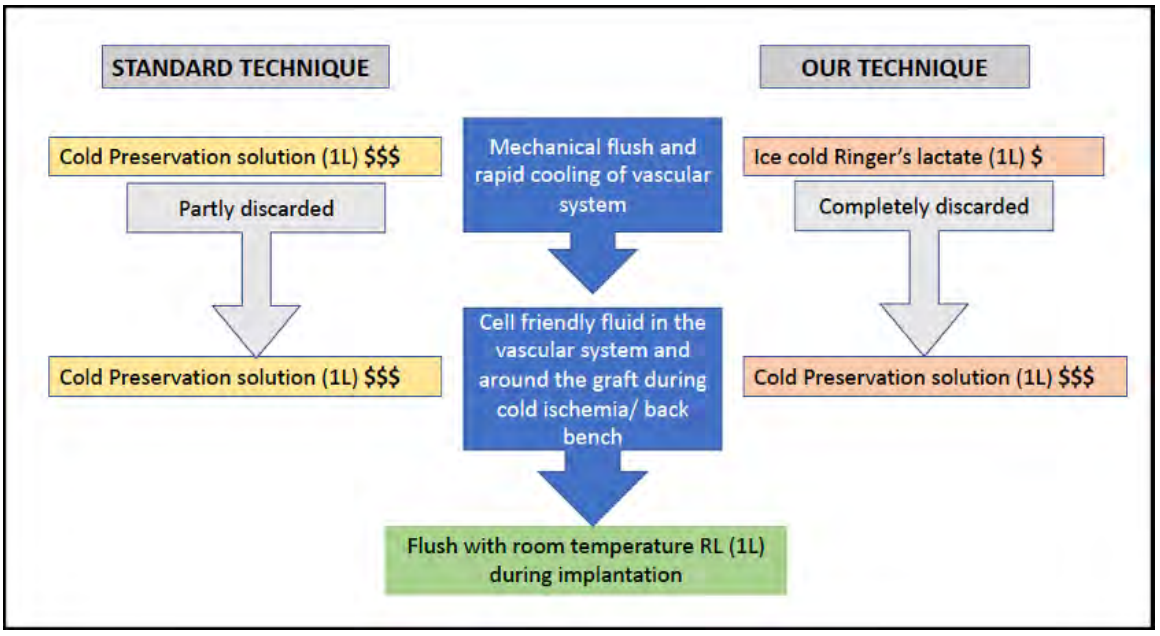
Back table flushing process has two components: (a) flushing out donor blood from the graft (b) cooling of organ and creation of a homeostatic environment for the graft during the period of cold storage. Preservative solutions are used for both these purposes. However, these preservative solutions are expensive; currently a 1-litre bag of IGL-1 costs 38,000 INR in Delhi. Although no evidence-based recommendation has been made regarding

the volume of preservative solution to be used during LDLT; the general practice is to continue flushing via portal vein till the effluent from the hepatic veins is clear and free of blood. In our experience, at least 1.5 to 2 liters of preservative solution is required for this purpose. Since, 500 ml bags of UW or IGL are not freely available, one ends up using at least 2 bags of these solutions that amounts to an expenditure of about 76000 INR per LDLT which is a substantial part of the total cost of consumables used during the procedure.

Liver transplantation is an expensive endeavour and despite the cost of LDLT in India being relatively lower compared to the rest of the world, it still remains beyond the reach of majority of Indian population. Keeping the cost of LDLT low is therefore a goal that all transplant centers strive for. One way cost cutting can be achieved is by reducing the volume of preservative solution used in each transplant. Since, the first component of back table flushing procedure is mechanical flushing out of the blood from the graft; we hypothesized that one does not need to use an expensive preservative solution for this purpose.

This can be achieved by simply using a cold crystalloid solution. Therefore, we started using 500 ml of cold (4° C) Ringer's lactate (RL) solution for the initial flush followed by 1 liter flush with UW or IGL solution via the portal vein, thereby saving 1 liter of preservative solution per LDLT. This equates to a cost saving of at least 38000 INR per transplant. We started this practice nearly 4 years back and have used it in more that 600 living donor liver transplants.

Till date we have not observed any evidence of increased incidence of IR injury as a result of this modified flushing technique. No difference has been observed in the pattern of post liver transplant liver function tests when compared with the results of standard flushing technique. We have used this flushing technique for all types of grafts including grafts from relatively older donors and donors with fatty livers (10% macrovesicular fat) without any detrimental effect on post-transplant graft function.



Journal club

Pediatrics

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Liver transplantation of partial grafts after ex situ splitting during hypothermic oxygenated perfusion—The HOPE–Split pilot study

Guillaume Rossignol et al. Liver Transplantation. 2022; 28:1576–87.

Aim: The authors designed a clinical pilot study (IDEAL stage 2a) to assess feasibility and safety, preservation characteristics and early outcomes of adult and pediatric LT with partial grafts after ex situ splitting with concurrent HOPE(HOPE-Split) compared with a cohort, which included all consecutive pediatric and adult recipients transplanted with liver grafts split during ex situ during static cold storage (the Static–Split group)

Methods: The primary safety endpoint was based on the number of liver graft–related adverse events (LGRAEs) per recipient, including primary nonfunction, biliary complications, hepatic vascular complications, and early relaparotomies. Secondary endpoints included preservation characteristics and early outcomes. Whole grafts were considered for splitting based on donor age, body mass index, intensive care unit stay, no-flow time, and donor biology. The Donor Risk Index and Balance of Risk (BAR) score were used to stratify pretransplantation donor–recipient matching.

Results

Sixteen consecutive HOPE–Split liver transplantations (8 HOPE–Split procedures) were included and compared with 24 Static–Splits. All HOPE–Split grafts were successfully transplanted. Mean LGRAE per recipient was similar in both groups (0.31±0.60 vs. 0.46±0.83; p = 0.78) and split duration was not significantly increased for HOPE–Split (216 vs. 180min; p = 0.45). HOPE–Split grafts underwent perfusion for a median of 125min, which significantly shortened static cold storage (472 vs. 544min; p = 0.001), whereas it prolonged total ex vivo preservation (595 vs. 544 min; p = 0.007). HOPE reduced neutrophil infiltration on reperfusion biopsies (p = 0.04) compared with Static–Split. The majority of HOPE–Split grafts presented with grade 0–2 (none to mild) IRIs (n = 11, 68.8%) and no grade 4 IRI was observed. The Static–Split grafts showed a higher overall grade of IRI with two cases of grade 4 (severe) IRI. Early posttransplantation outcomes were comparable in pediatric recipients. Serum transaminase peak, bilirubin levels, and factor V normalization are presented in Figure 2. No graft loss or recipient death was encountered in the HOPE–Split group during the median follow-up of 7.5months

The concept : Split-liver transplantation (SLT) has been developed to increase the number of available grafts and offer a rapid access to transplantation for pediatric recipients. In situ liver graft splitting during procurement is a technically and logistically challenging procedure. Consequently, ex situ liver splitting remains frequently performed. As a result of technical aspects nherent to the ex situ split, these partial grafts have prolonged static cold storage time, which negatively impacts graft survival despite the use of optimal donors.

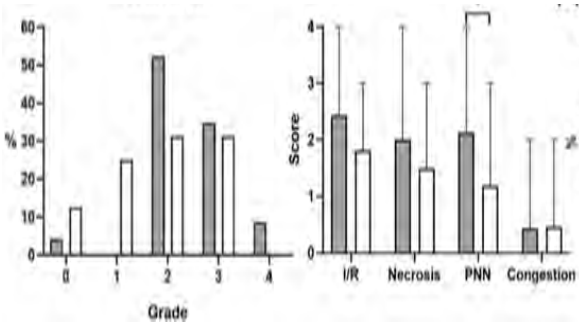

Figure 5 1A, Histological analysis of IRI. Overall IRI grade in the HOPE–Split and Static–Split groups. 1B. Detailed histological analysis of IRI in the HOPE–Split and Static–Split groups.

Ex situ machine perfusion strategy has been shown to mitigate ischemia/reperfusion injury (IRI) of liver grafts by reducing static cold storage and uploading cellular energy levels with a positive impact on post transplantation outcomes. The use of HOPE may also benefit partial grafts from ex situ splits and possibly improve outcomes in both pediatric and adult recipients.

Our take : Previous reports from Spada et al and Thorne et al presented technical aspects of split livers during machine perfusion in single cases. A major limitation of the current study is the small sample size and the short follow-up. In line with the IDEAL frame- work on surgical innovation, this study is a mandatory step to assess feasibility and safety of the HOPE–Split procedure in the routine clinical setting.

Indeed, following stage 1, which consists in a proof-of-concept focussing on the description of a new technique, stage 2a aims at developing and refining the technique and reporting short-term outcomes from a single-center prospective cohort. The data acquired form the stage 2a study will help design future large-scale trials, which will need to confirm the presented outcome data. Another limitation is that HOPE–Split was evaluated in well-selected donors and recipients. The next step would be to evaluate this procedure in higher-risk SLT scenarios for which HOPE may present a superior clinical benefit as shown for marginal whole grafts.

In conclusion, this is the first study to evaluate HOPE in both pediatric and adult SLT in the routine clinical setting. HOPE–Split appeared as a feasible and safe procedure without jeopardizing early postoperative outcomes sand possibly suggests improved preservation compared with static ex situ splitting. These preliminary results will allow to set up large-scale trials on the use of machine perfusion in pediatric and split-liver transplantation.

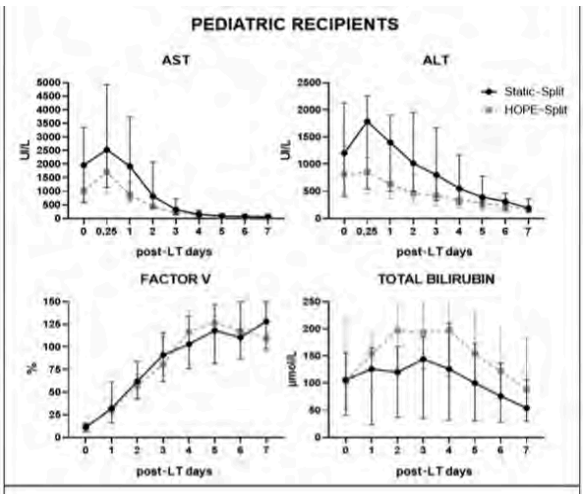

Figure 2 Serum ALT, AST, factor V, and total bilirubin of pediatric recipients during the first PODs in the HOPE–Split and Static–Split groups

Surgery

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Sequential hypothermic and normothermic machine perfusion enables safe transplantation of high-risk donor livers

Van Leeuwen OB et al.

Am J Transplant. 2022; 22: 1658– 1670.

Summary

The advent of dual hypothermic oxygenated machine perfusion ([D]HOPE) and normothermic machine perfusion (NMP) have improved discard rates of sub-optimal livers worldwide. DHOPE has been shown to improve ischemia-reperfusion injury (IRI) and reduce the risk of non-anastomotic strictures (NAS) and early allograft dysfunction (EAD). NMP allows for viability testing but some reports have shown that it may be associated with IRI and NAS especially in the setting of high risk DCD livers. This paper highlights the use of sequential DHOPE and NMP to mitigate the risk of IRI and enable safe transplantation of high risk livers.

This is a prospective observational cohort study of patients transplanted with initially discarded livers following sequential DHOPE and NMP between Jan 2017 to March 2021. HBOC (Hemoglobin-Based Oxygen Carrier)-based perfusion solution was used for NMP till Jan 2019 and RBC-based solution was used subsequently. All livers underwent one hour of DHOPE followed by NMP until completion of recipient hepatectomy, if the liver met viability criteria (See Table 1). In total, 54 livers were perfused and 34 transplanted during this period. Of them, 53 met the hepatocellular viability criteria and 34 met the cholangiocellular viability criteria and were transplanted.

The study reports a graft and patient survival rate of 95% and 100% at the end of 1 year. There was no difference in outcomes between the HBOC solution (n=12) and RBC-based solution (n=22). Two patients required re-transplantation (1 in each group) for chronic rejection and venous outflow issues. Only 1 patient had NAS (8%) while 12 patients (35%) had anastomotic biliary strictures (no difference between HBOC and RBC groups). Four patients (12%) had bile leak. There were no cases of primary non-function or hepatic artery thrombosis. Acute rejection occurred in 3 patients (9%) and chronic rejection developed in 2 patients (6%). Mean hospital stay was 17 days and 18 days respectively in the 2 groups.

Our Take:

In comparison to other randomized trials, this study shows exciting results with excellent graft and patient short to mid-term outcomes. A recent trial by van Rijn et al. reported in NEJM on 160 patients (78 DHOPE vs 78 static cold storage) for DCD livers resulted in 6% NAS, 12% post reperfusion syndrome and 26% EAD for DHOPE group compared to 18%, 27% and 40% respectively. The VITTAL clinical trial from the UK reported 22 liver transplants

following NMP after viability testing with 100% 3-month graft survival. They reported 4 cases of NAS (18%) compared to one (2.3%) in the control group. Of them, three (30%) were in the DCD group (n=10). The TRaNsIT study which was a systematic analysis of NMP studies revealed a 0-20% rate of biliary complications.

One limitation of the current study is the lack of randomization. The reason for switching from HBOC to RBC-based NMP oxygen carrier was the availability and approval of RBC-based solution. Selection bias is also an important factor since patient safety is always the primary factor for study design. However, the significant reduction of NAS (64%) and post reperfusion syndrome (57%) demonstrates that a short duration of DHOPE can be extremely beneficial prior to NMP.
The major benefit of this protocol is the ability to allow for viability testing of NMP while reducing the risk of NAS in DCD livers related to end-ischemic NMP. Cost may also be a limiting factor, which this study does not take into consideration. In an ever expanding field of machine perfusion in liver transplantation, this may yet be a major breakthrough to obtain the best results by using both types sequentially and mitigating the risks of either while reaping the benefits of both.

	Parameter	Green zone	Orange zone	Red zone
Hepatocytes	Bile production (ml)	≥ 10[a]	5 to 10	< 5
	Perfusate lactate (mmol/L)	< 1.7	1.7 to 4.0	> 4.0
	Perfusate pH	7.35–7.45	7.25 to 7.35	< 7.25
Cholanglocytes	Bile pH	> 7.45	7.40 to 7.45	< 7.40
	ΔpH	> 0.10	0.05 to 0.10	< 0.05
	ΔHCO_3^- (mmol/L)	> 5.0	3.0 to 5.0	< 3.0
	ΔGlucose (mmol/L)	< −5.0	−3.0 to −5.0	> −3.0

TABLE 1 Criteria used to determine viability during 2.5 h of NMP
The green zone includes the four original viability criteria.
Orange zone represents potentially acceptable values.
Red zone indicates values that do not meet the viability criteria.

Parameters to assess graft viability during normothermic machine perfusion

ANESTHESIA

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Associations of sarcopenia with graft failure and mortality in patients undergoing living donor liver transplantation.

Ji-Hoon Sim et al
Liver Transplantation. 2022; 28:1345–1355.

This is a retrospective study done by Asan Medical Center, Seol by Department of Anesthesia and radiology on the association of sarcopenia with graft failure and mortality in patients who underwent living donor liver transplant (LDLT) between the years Jan 2008 to Jan 2018.
Primary outcome was to see the result of sarcopenia versus non sarcopenia patients post liver transplant and it was assessed based on graft failure in short term 60 days and 180 days and long term 1 year and overall time frame.
Secondary outcome was to see the mortality of sarcopenia patients versus non sarcopenia patients during short term 60 days and 180 days and long term 1 year and overall time frame.

Results

Out of 3068 LDLTs, 2816 patients were analyzed while 252 recipients aged <18 years and >60 years, emergency surgery, re-transplant, and missing CT scan data were all taken as exclusion criteria. Among 2816 recipients 2507 were in non sarcopenic group and 309 recipients were in sarcopenic group.

60-day, 180-day, 1-year, and overall **graft failure** were 2.4%, 4.5%, 6.9%, and 15.7%, respectively. M**ortality rates** in the recipients at 60 days, 180 days, and1 year and overall were 2.0%, 3.9%, 6.0%, and 14.6%, respectively.

Sarcopenia group had statistically significant difference in **demographic variables** (age, sex, BMI, HCC, CRF, CTP, MELS score), **etiologies** (HBV, HCV, Alcohol), higher WBC counts, INR and BNP levels and lower hemoglobin levels and sodium levels.

Intraoperative variables were also statistically significant in sarcopenia groups such as postreperfusion syndrome, total crystalloids, urine output, intraoperative CRRT, massive blood transfusion.

	Non-sarcopenia group, n = 2507	Sarcopenia group, n = 309	Total, n = 2816	p value
	Graft outcome			
60-day graft failure	51 (2.0)	17 (5.5)	68 (2.4)	<0.001
60-day mortality	44 (1.8)	12 (3.9)	56 (2.0)	0.01
180-day graft failure	97 (3.8)	31 (10.0)	128 (4.5)	<0.001
180-day mortality	83 (3.3)	27 (8.7)	110 (3.9)	<0.001
1-year graft failure	156 (6.2)	38 (12.3)	194 (6.9)	<0.001
1-year mortality	135 (5.4)	34 (11.0)	169 (6.0)	<0.001
Overall graft failure	369 (14.7)	72 (23.3)	441 (15.7)	<0.001
Overall mortality	346 (13.8)	66 (21.4)	412 (14.6)	0.001

Limitations: It was a retrospective study done in one large medical center where they do more than 300 liver transplants per year and hence the surgical results vary with other centers. Also the skeletal muscle index varies with different races and ethnicities and hence needs to be adjusted when applied.

Takeaway points:

Sarcopenia is a preoperative significant independent risk factor which may be a strong predictor of the surgical prognosis in LDLT recipients. 50% of Indian liver patients are sarcopenic and they may have postoperative sepsis, neurological complication, longer ICU stay and ventilator support. 20-35% of cirrhotic patients have sarcopenic-obesity due to myo-steatosis.

Liver frailty index has been recently used for evaluation. But CT has emerged as the gold standard method. An axial CT image at L3 level including all skeletal muscle area taken and later excluding visceral and subcutaneous fat to get a value and this is adjusted to the height to get skeletal muscle index **(SMI**). Based on the SMI cut-off, sarcopenia has been defined as 39.9 for men and 28.9 for women.

Accelerated starvation, hyperammonemia, insulin resistance, reduced testosterone, endotoxemia from gut translocation, chronic inflammation all leads to sarcopenia in cirrhosis. The link between immunity, inflammation, and adipocytokines has been suggested major mechanism by which sarcopenia affects patient survival. Imbalance of adipokines and myokines lead to senescence of natural killer lymphocytes and due to impair immune system risk of sepsis related death is high. Sarcopenia is also associated with nutritional deficiency which reflects poor health and vulnerability and hence graft is easily damaged by ischemic perfusion and also susceptible to post operative inflammatory response.

Sarcopenia is an optimizable factor prior to transplant and with the help of life style modifications, nutritional therapy and exercises the postoperative outcomes can be improved.

Commentary

ERAS in Live Donor Liver Transplant - Its relevance and applicability in India

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Enhanced recovery after surgery (ERAS) is an evidence-based program of care that has changed age-old surgical stereotypical practices to achieve early post-operative recovery for patients undergoing major abdominal surgery. Considering its advantages, efforts are being made to implement it in the field of liver transplantation (LT), despite the complexity and intricate nature of the surgical procedure.

Recently ERAS Society recommendations for LT were developed using an e-Delphi method involving experts from 12 international centres (Brustia et al Transplantation 2022). The Consensus recommended patient screening and treatment for malnutrition, careful consideration for omission of nasogastric tube and abdominal drain among other things. Anaesthesia techniques to facilitate early extubation, early oral intake, mobilization, glycemic control and multimodal-balanced analgesia were strongly recommended postoperatively. The review highlighted that the highest level of evidence was available for only 13 of 22 items of ERAS pathways for LT. A need for consensus in certain areas of controversies such as intraoperative surgical caval anastomosis techniques, transfusion of blood products or concentrates and antifibrinolytics, type of hemodynamic monitoring to be used, choice of either restricted fluid therapy, goal-directed therapy or liberal fluid therapy and anticoagulant prophylaxis were identified.

Protocol for ERAS

For implementation of ERAS, pre-operative counselling of the patient, management of decompensations and nutritional optimisation are essential. Ambulatory patients with decompensated chronic liver disease (CLD) could be admitted one day prior to elective Living donor liver transplantation (LDLT) as postoperative infections are usually more in those who have preoperative hospital stay. Anaesthetic techniques favouring early extubation are used at our center, including preoperative premedication for anxiolysis and intra-operative goal-directed transfusion of fluids and blood products. Avoidance of caval cross clamping and creation of temporary portocaval shunt along with minimisation of cold ischemia times help to mitigate the reperfusion syndrome. On-table extubation is often considered in electively scheduled LDLTs in Child A and B recipients when hemodynamics are stable with evidence of

good graft function. Early discontinuation of positive pressure ventilation is considered an important step as it helps to optimize circulation to neo-liver graft. However, if the duration of surgery exceeds 8-10 hours and there is considerable transfusion of fluids and blood products during the surgery, recipients are electively ventilated for 6-8 hours followed by spontaneous weaning. This allows for the assessment of improving liver function tests prior to de-escalating ventilatory support and does not hamper implementation of other components of ERAS.

Following transplant, physiotherapy to mobilise all limbs and early removal of invasive lines and NG tube is very important, as early as on the first postoperative day (POD). On the second POD, more aggressive chest and limb physiotherapy is instituted and the patients are encouraged orally as there is gradual recovery from paralytic ileus. This is followed by conversion of intravenous injections and fluids to oral form as enteral acceptance improves by POD 3. Patients are ambulated out of bed with the help of a physiotherapist. As the appetite improves and oral acceptance increases, dietary options need to be improved with direct interaction with the dietician. Arrangements to have the recipient interact with the family- especially with the donor, initially over video cameras and then personally helps to keep the morale of the patients up As the levels of immunosuppression stabilize and abdominal drain output reduces, abdominal drains are removed. Fluid mobilisation is also achieved to make the patients euvolemic, ambulatory and ready to be shifted from ICU.

The CLBS experience

Between January 2019 and May 2022, 76 out of 616 adult patients operated for decompensated CLD in our unit were shifted to the ward from ICU/HDU within 7 days after LDLT, as against our historical average stay of 14 days. 107 of 616 recipients were discharged within 15 days of transplant from the hospital, as against the average hospital stay of 26 days. Notably, none of them required ICU readmission. Out of the 76 adult recipients shifted early from the ICU, only 20 patients were transplanted for HCC The distribution of disease severity based on Child's score was A- 7, B-26, C-43.

Out of the 107 discharged early from the hospital, 18 patients were operated for HCC and the distribution of Child A:B:C was 12:40:55. 47 patients out of the 107 had been selected for tracheal extubation on table at the end of surgery.

ERAS for LDLT in the India scenario

Ethanol and non-alcoholic steatohepatitis (NASH) related liver disease comprise the major burden of CLD undergoing LDLT. Most of our patients present for LT with advanced decompensated liver disease after exhausting all medical management options. Ours being a tertiary transplant referral centre, a large proportion of our patients at the time of transplant either have high (model for end stage liver disease) MELD (>25) or are those who develop acute on chronic liver failure needing organ support.

In LDLT graft size, GRWR, graft steatosis and outflow reconstruction too affect immediate post-operative outcome. Due to non-availability of suitable donors, marginal grafts from available relatives

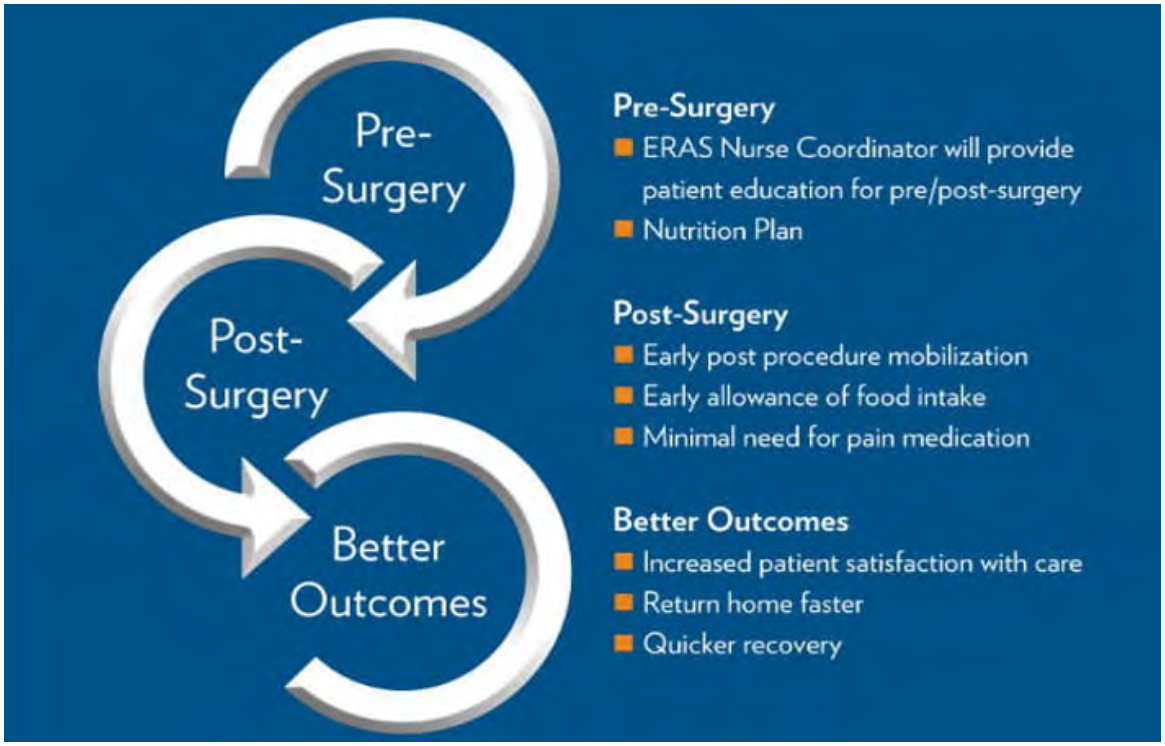
may be the only option. Recipients are older (age>50 years), overweight (BMI>28), and suffering from comorbidities like Diabetes Mellitus & Hypertension which cause end organ damage. These factors need to be considered when planning to perform tracheal extubation early or on table even in stable low MELD patients who were otherwise considered optimal for implementation of ERAS.

In the presence of adequate arterial and portal venous flow on intraoperative doppler ultrasonography, evidence of a functioning graft, stable hemodynamics, early extubation can be considered. However overnight ventilation is often the norm when the duration of surgery is >10 hours and/or in the presence of massive intraoperative transfusion of blood and blood products (>1 total blood volume).

The Indian scenario brings its own set of issues with regards to implementation of ERAS. In the absence of subsidized healthcare and where a family member is also the donor, families are neither willing to have their relative shifted out from the ICU or discharged from the ward before their package is exhausted. During preoperative counselling, the advantages of ERAS need to be explained in the success of the surgery along with provision of modification of charges in discussion with the administration. The other administrative hurdle that the transplant team often faces in shifting patients from the ICU is that the step-down unit or ward many not be adequately staffed or equipped. But as the understanding and realization of the benefits and feasibility of ERAS is growing, we can gradually overcome the challenges and try and implement ERAS in more patients to reap the benefits.

The ERAS pathway and its benefits in liver transplantation

(Ref Medical University of South Carolina)



Book Launch

Textbook of Liver Transplantation- The first *India-centric* reference guide for liver transplantation

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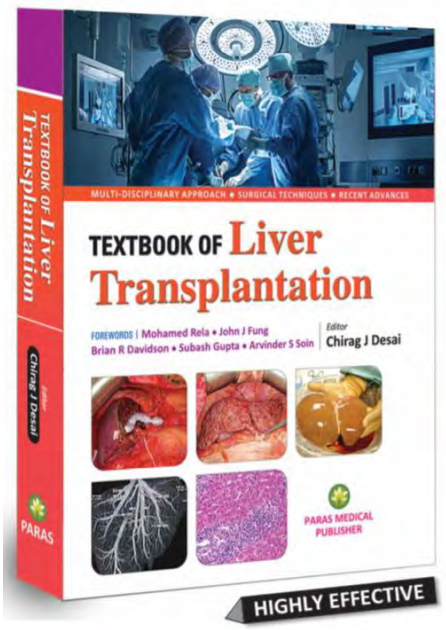
Chief Consultant and Program Director, Department of GI, Hepatobiliary and Liver Transplant Surgery, Apollo Hospitals, Ahmedabad, India

Hepatobiliary and liver transplant surgery has emerged as a new subspecialty within Surgical Gastroenterology and abdominal surgery. Surgical trainees are increasingly attracted to this new field. Similarly numbers of specialist hepatologists, anaesthetists and intensivists is also increasing. Transplant radiology, interventional radiology and liver pathology are now becoming rapidly developing fields. Structured fellowships and teaching programs in this specialty are being developed both in India and abroad. Management of a liver transplant recipient requires a multi-disciplinary approach and mastery of liver transplantation requires one to have an in-depth knowledge of the basic sciences. Currently, there is paucity of a textbook which encompasses details of all the aspects of liver transplantation.

This first edition of the **Textbook of Liver Transplantation** brings together over 150 expert authors from India, UK, USA, South Korea, Singapore, Canada and Taiwan, covering medical and surgical aspects of both deceased donor as well as living donor liver transplant in adult as well as pediatric patients. All the authors are experts in their field and have contributed on a subject which is their core strength.

This book offers focused guidance in a highly templated, easy-to-consult format. The chapters follow an easily readable pattern and are filled with high quality illustrations. This book has 15 sections and 75 chapters starting from basic sciences, role of allied branches, living and cadaver donor surgery, care of a recipient and surgical techniques, and complications. The chapters on surgical techniques have high resolution multicolour images, which gives it a look of Atlas of Surgery.

Liver transplant for specific indications and ethical as well as administrative issues related to liver transplantation. The book also contains chapters on allied specialties such as radiology, pathology, anesthesiology and critical care medicine. Cutting-edge techniques such as laparoscopic and robotic donor liver surgery, ABO incompatible LT, DCD donors, domino liver transplant, auxiliary liver transplant are also explored in this textbook.
This book is dedicated to all the organ donors and their families for giving new lease of life to people with end stage disease.



The textbook is available on Amazon.co.in

Jumble Puzzle

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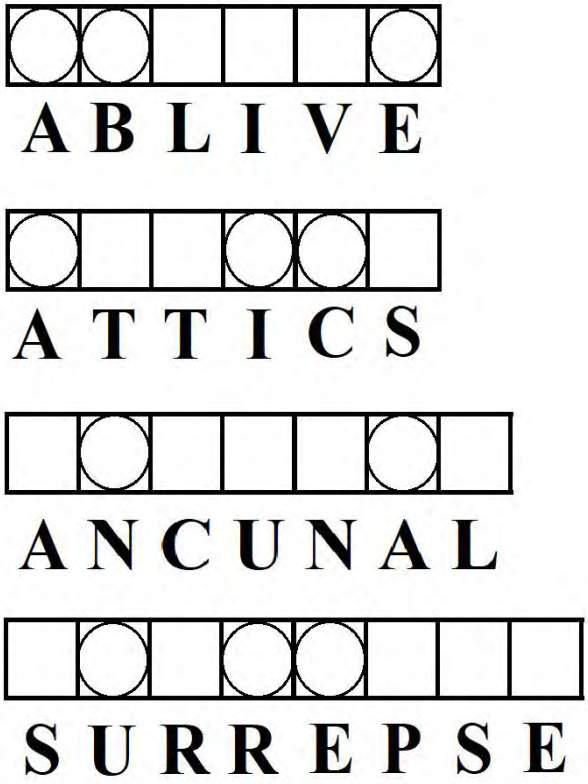

When the only offer option available was a discarded organ, what the patient needed was a _____ _____!!

NOW ARRANGE THE CIRCLED LETTERS TO FORM THE SURPRISE ANSWER, AS SUGGESTED BY THE ABOVE CARTOON.

ANSWER HERE: ☐☐☐☐☐ ☐☐☐☐☐☐

TODAY'S THEME: PERFUSION

Solution on Page 8 of this issue