The global trend for development of organ protection device to reduce secondary warm ischemic injury

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TOPICS

〔Abstract〕 The issue of cold-stored donor kidneys falling into a secondary warm ischemic state during vascular anastomosis in the recipient body has been a longstanding problem since the beginning of organ transplantation therapy. The authors have successfully developed an organ protector that suppresses secondary warm ischemia in cold-stored kidneys by using insulating materials based on polymer chemistry and thermodynamics. In this review, we introduced the development process and the functions of the product, Organ Pocket, the world's first organ protector for kidney transplantation, which was successfully developed through the realization of medical-industrial collaboration.

Introduction

Since the early days of organ transplantation, secondary ischemic injury during vascular anastomosis in the recipient body has been known to adversely affect postoperative donor organ function. Alexis Carrel, who was awarded the Nobel Prize in Physiology or Medicine in 1912 for his work on vascular suturing and transplantation of blood vessels and organs, aimed to recirculate blood as quickly as possible by rapidly completing anastomosis of the donor organ. Organs removed for transplantation are stored in cold conditions to prevent deterioration due to auto-metabolism; however, once the organ is introduced into the body, it is exposed to a secondary warm ischemic state until revascularization is completed, and blood recirculation begins. Therefore, transplant surgeons have focused on refining their vascular anastomosis techniques and quickly performing the procedure. Recipient surgeries have become less invasive, and speculative and robotic surgeries have become the focus of attention in the field of organ transplantation. Nonetheless, anastomosis is an extremely time-consuming procedure; therefore, reducing secondary warm ischemic injury is a major issue.

Kobayashi et al. were the first to develop a surgical technique to perform anastomosis while maintaining circulation of the removed organ[1),2)]. Since 2015, SCREEN Holdings Co., Ltd. have been focusing on the medical device business as a new field to explore, and have been researching and developing domestically produced organ perfusion and culture devices. In addition, they began working on the development of peripheral devices as part of a joint industry-university research project. As a result of their research, they succeeded in developing the world's first organ pocket to prevent secondary warm ischemia in the transplanted organs.

In this paper, we introduce the world's first "Organ Pocket" (Class I) medical device for transplantation, which was successfully commercialized in Japan through industry-academia collaboration based on a

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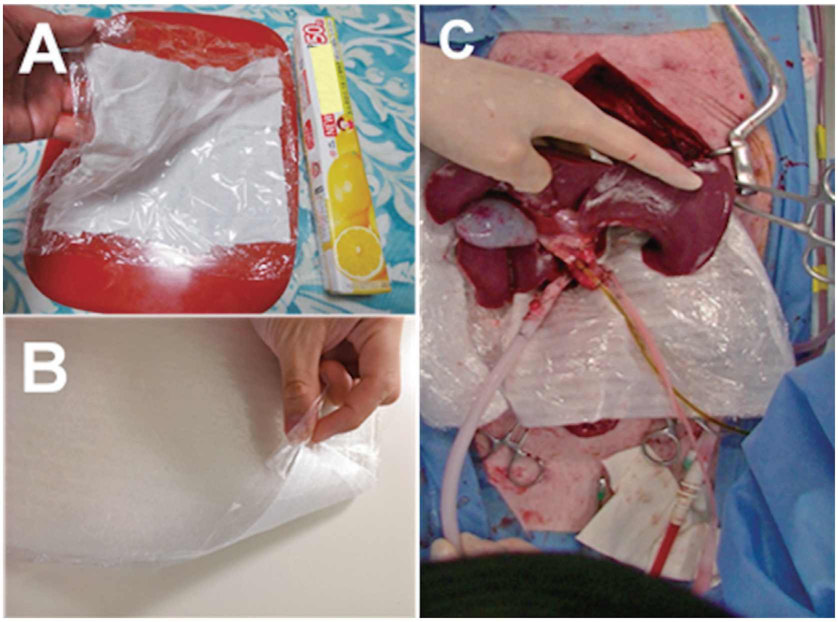


Fig. 1 Initial stage of development of "Organ Protection Sheet" with heat shielding effect
A. Sheet made from everyday materials. The inner surface is made of HEATTECH® cloth, and the outer surface is wrapped in Saran Wrap®.
B. Prototype type. The inside is made of polyethylene and the outside is made of silicon sheet.
C. Tested on a pig liver transplant.

global competition conducted during the development of this product.

Reason for Development

At the beginning stages of development in 2015, we came up with the idea of an "Organ Protection Sheet" with a thermal barrier effect, to prevent secondary warm ischemia (Fig. 1). In many medical device developments in academia, testing of new ideas tends to be delayed because the materials and design are considered in detail first; however, from the beginning, we repeated trials by hand using everyday items. Simultaneously, we tested active cooling, which uses cold water to cool the inside of the thermal barrier sheet.

These organ protection devices, such as the drawstring type that wraps the organs in a bag-like shape, were developed while applying for intellectual property patents, based on the company's strategy. Fig. 2 summarizes the documents related to patents. Finally, in 2020 and 2021, the company developed a patent application for containers of harvested organs.

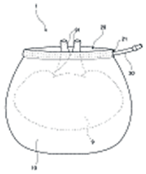
Global Competition

In the January 2018 issue of the *American Journal of Transplantation*, the authors reported the results of a preclinical study using a porcine kidney transplant model of a thermal barrier sheet that actively cools the inside of the sheet (Fig. 3)[3]. This idea was in line with the demands of the times, and was designed for robotic surgery with an active cooling function that allows cold ethanol to flow back to the inner surface of the sheet that encases the organ.

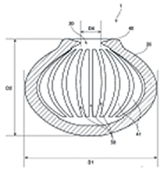
The authors initially thought of commercializing this idea without presenting it at conferences or submitting papers until it was realized; however, they were surprised by the competitiveness in this field. In response to this article, we wrote a letter to *Transplantation*

1. “Organ protection sheet“ Patent number: 6621381
Abstract: A sheet for protecting organs, comprising a flexible insulating layer and two waterproof layers adhered to the two main surfaces of the insulating layer.

2. “Organ storage bag and transplantation method“
Patent publication number: 2020-44287
Abstract: An organ storage bag for containing an organ, comprising an opening through which the organ can pass and a bag-shaped insulating sheet that holds the organ inserted through the opening, the insulating sheet having a pair of waterproof layers and an insulating layer located between the pair of waterproof layers.



3. ”Organ housing container“
Patent publication number: 2021-40938
Abstract: An organ housing container for storing organs, having an elastic, bag-shaped body having an opening, wherein the maximum width of the opening is smaller than the maximum width of the body in an unloaded state, and wherein the opening can be stretched to a state wherein the maximum width of the opening is larger than the maximum width of the body.



4. “Organ housing container“
Patent publication number: 2021-126384
Abstract: An organ housing container for storing organs, comprising an opening through which organs can pass, and a bag-shaped insulating sheet for holding organs inserted through the opening, the insulating sheet having an uneven inner surface.

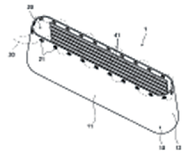


Fig. 2 Intellectual property strategy for organ protection sheets with thermal barrier effect
Part of a patent strategy for organ protection using silicone and elastomer is described. The patent for the protective sheet is registered and three other patent applications have been published.

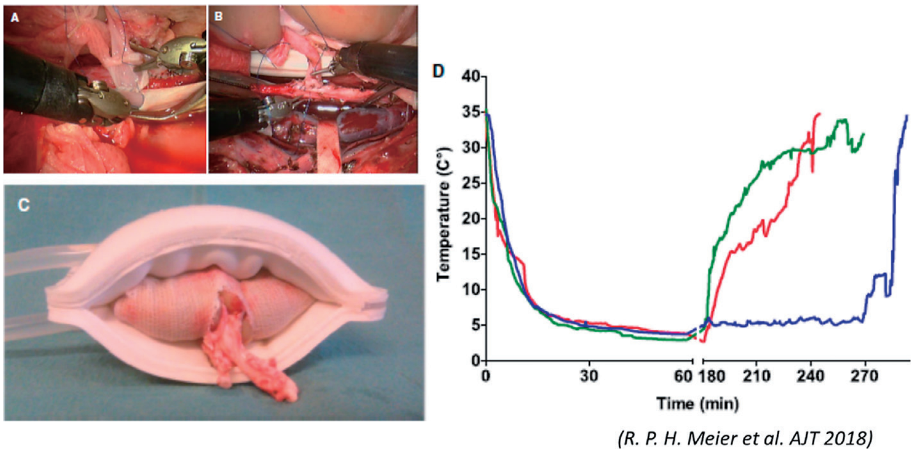


Fig. 3 Report on the intra-abdominal cooling system by MEIER et al.
A system to cool organs by actively circulating ethanol as a refrigerant fluid to suppress warm ischemic injury in robotic assisted kidney transplantation. The results of temperature and pathological analysis at the time of kidney transplantation and blood flow confirmation by MRI suggest that the system is more effective in protecting renal function after resumption of blood flow than conventional methods in cases of system adaptation[3).

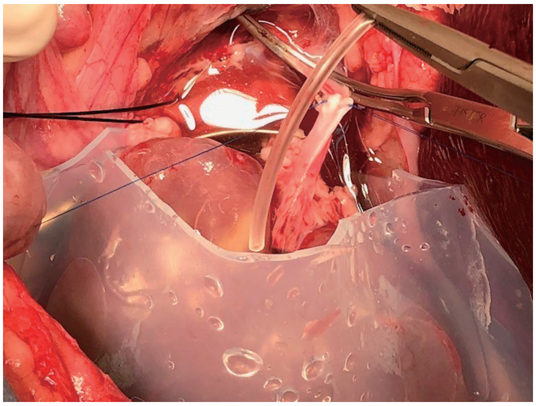


Fig. 4 Kidney housing made of medical grade silicon
Photograph of a laparoscopic renal arteriovenous anastomosis for a transplanted kidney. The upper part of the silicone container is open, and cold storage solution can be dripped through the tube.[4)]
Adapted from Kobayashi E, Torai S et al. Intra-abdominal Cooling System for the Transplanted Kidney. Transplant Direct 2019;5(4): e438. DOI:10.1097/TXD.0000000000000882 (Intra-abdominal Cooling System for the Transplanted Kidney: Transplantation Direct (lww.com) Fig. 1. Copyright © 2019 The Authors.

Direct, in which we introduced a silicon organ fixation device that could be used for long-term vascular anastomosis, with cold preservation fluid flowing through the organ even in the back shape (Fig. 4)[4)].

Subsequently, this group reported further studies showing the effectiveness of using the device during laparotomy (Fig. 5)[5)].

The authors conducted research and development using a porcine kidney transplant model, intending to apply the material of this organ fixation device to clinical kidney transplantation (Figure 6)[6)].

Initially, we developed an organ fixation device made mainly of biocompatible and insulating silicon materials for clinical transplantation. To verify the efficacy of the developed product, we evaluated the surface temperature of the donor kidney during vascular anastomosis and biochemical values at 7 days of survival in a pig kidney transplantation model, using a donor kidney with a 30-min circulatory arrest. Comparing the conventional method without the fixation device and the case with the organ fixation device, there was a difference of approximately 9℃ at 30 min after the completion of the vascular anastomosis (wearing group, 21℃; control, 30℃). In the 7-day survival evaluation, one patient died of primary non-function (PNF) on day 1 with the conventional method, but the patient with the organ fixation device survived until 7 days later, and serum BUN and creatinine returned to normal levels.

Surprisingly, it was recently discovered that Khan et al. in Australia worked on a similar project[7)]. They also attached an organ protection device (named "Jacket") to porcine kidneys to inhibit secondary ischemic injury and examined its insulating effect ex vivo. Using a 3D printer, Khan et al. fabricated and tested prototypes of silicon and urethane organ fixation devices. As a result, it was confirmed that the temperature of the donor kidney after 30 min was maintained at ~13℃ (control, ~25℃; wearing group, ~12℃), which was lower than that of the conventional method, similar to the results obtained by the authors.

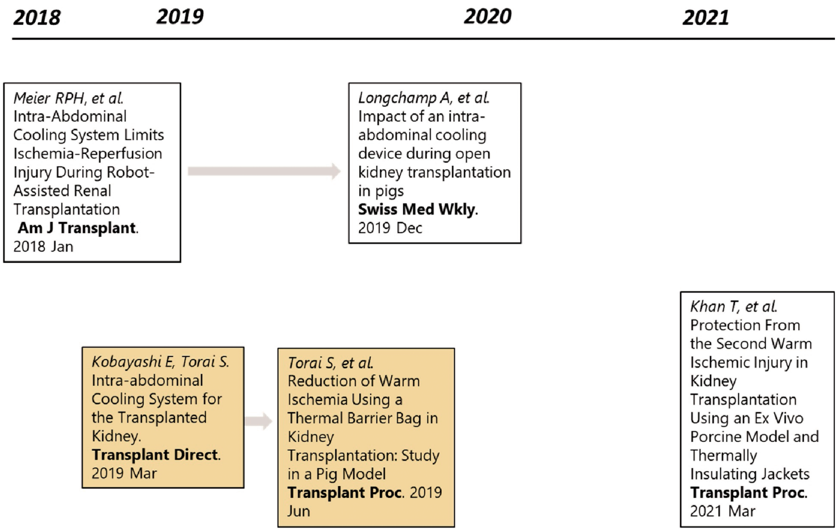


Fig 5 Development of a device to prevent secondary warm ischemia in the transplanted kidney during vascular anastomosis
A chronological list of research reports on reducing warm ischemic injury during vascular anastomosis in various countries.

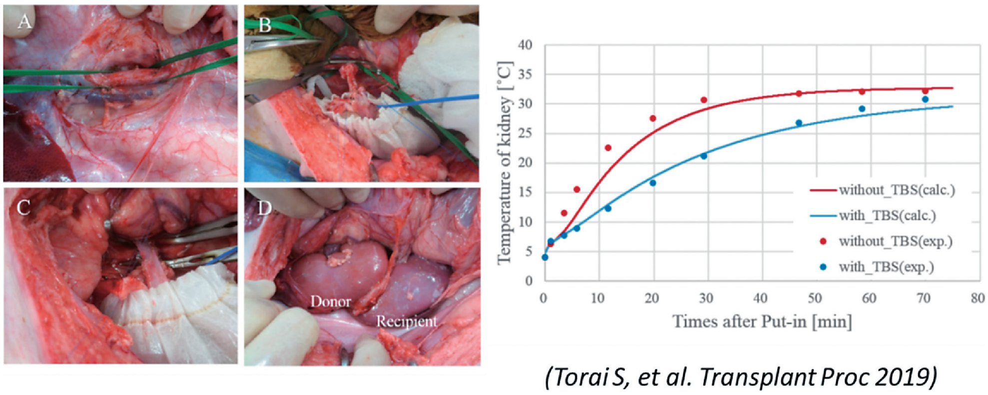


Fig. 6 Effect of organ protective equipment on warm ischemic injury during vascular anastomosis
In a pig model, when donor kidneys were transplanted 30 minutes after blocking the renal artery, a comparison of cases with and without the use of organ protection devices showed that the intraoperative increase in kidney surface temperature was suppressed and the prognosis was improved in the cases with the use of organ protection devices[6].
Reprinted from Transplant Proc 2019;51(5). Torai S, et al, Reduction of Warm Ischemia Using a Thermal Barrier Bag in Kidney Transplantation: Study in a Pig Model, P.1442-1450 (DOI: 10.1016/j.transproceed.2019.01.136.). Fig. 2, 4. Copyright © (2019), with permission from Elsevier.

Toward the launch of the world's first transplant organ protection bag

Silicon materials have been used in many medical devices because of their high biocompatibility; however, they pose a risk of damage to organs because of their high hardness and low elasticity. Therefore, the authors used an elastomeric gel material as the original material to protect the organs without damaging them, while maintaining the high insulation properties and conforming to the body. We succeeded in making it as soft and reversibly elastic as the human abdominal

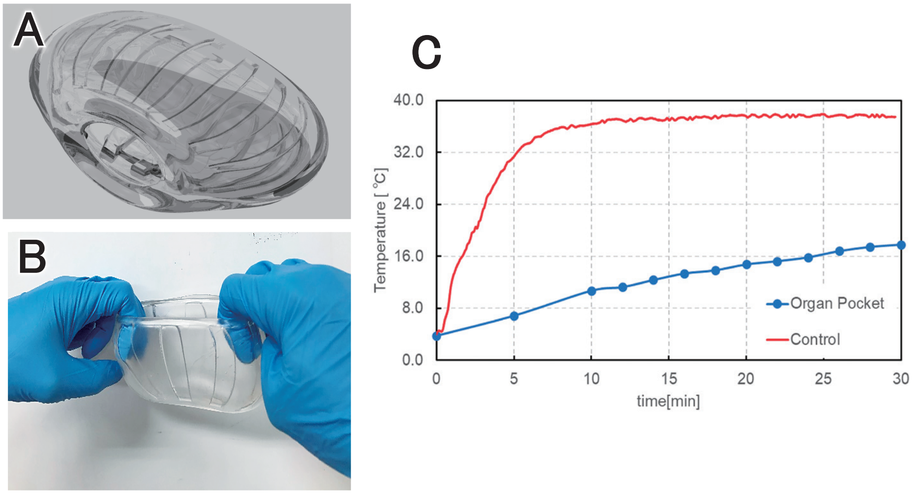


Fig. 7 The world's first organ protector "Organ Pocket" and performance test
A. Schematic view of the organ pocket made of ultra-soft elastomer. A. Overhead view of the Organ Pocket, which is made mainly of transparent and biocompatible insulating material and designed to be suitable for the kidney. C. Temperature change during anastomosis with the Organ Pocket. C. Temperature changes during anastomosis with and without the Organ Pocket.

cavity. In addition, to respond to donor kidneys worldwide, the average size of adult kidneys was calculated based on CT and MRI data from various countries (Fig. 7).

Using pig kidneys, the following experiments were conducted on the insulating and renoprotective effects of the newly developed organ pockets. Donor kidneys that had been cold-stored at 4℃ were removed from the organ storage solution and placed on a stainless-steel bathtub that had been warmed to 37℃, mimicking an abdominal cavity. To measure the temperature change in the donor kidney, a thermocouple was inserted from the ureter to the renal pelvis, and heated at 37℃ for 30 min. A cannula was inserted into the renal artery, and whole blood from the donor pig was circulated and perfused with a tubing pump for 45 min to measure the blood BUN and creatinine levels. The donor kidneys with (target group) and without (control group) organ pockets were compared. As shown in Fig. 7C, the results of the temperature measurement showed that the center of the kidney in the target group was 16℃ after 30 min, while it reached 37℃ in only 5 min in the control group. The difference in blood BUN and creatinine was also observed, with a maximum of 7.0 mg/L for BUN and 1.2 mg/L for creatinine in the target group and a maximum of 8.0 mg/L for BUN and 1.6 mg/L for creatinine in the control group. These results indicate that suppressing the heating of the kidney during vascular anastomosis preserves its function after blood reperfusion.

Conclusion

At present, the basic evaluation of the "Organ Pocket" has been completed, and a clinical study, titled "A single-center, open-label, uncontrolled, single-arm study on the safety and efficacy of the Organ Pocket thermal barrier bag in kidney transplant recipient surgery (First in human study)" is being conducted at the Department of Gastroenterology and Transplant Surgery, Hiroshima University Hospital by Professor Hideki Odan.

Acknowledgments

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