A Novel Device to Preserve Intestinal Tissue Ex-Vivo by Cold Peristaltic Perfusion

Raja R. Narayan*, Natalie E. Pancer, Brian W. Loeb, Kristi Oki, Andrew Crouch, Spencer Backus*, Yusuf Chauhan, Roger Patrón-Lozano, Manuel I. Rodriguez-Davalos, John P. Geibel, Richard E. Fan* and Joseph P. Zinter

Abstract— **In the past two decades, much advancement has been made in the area of organ procurement and preservation for the transplant of kidneys, livers, and lungs. However, small intestine preservation remains unchanged. We propose a new preservation system for intestinal grafts that has the potential to increase the viability of the organ during transport. When experimented with porcine intestine, our device resulted in superior tissue quality than tissue in standard of care.**

I. Introduction

The small intestine remains the least commonly transplanted organ despite continuing need [1]. While patients with short bowel syndrome or intestinal failure can be supported with total parenteral nutrition (TPN) for a period of time, eventually this can lead to further complications such as depletion of central venous access and/or cholestatic liver disease [1].

Intestinal transplantation (ITx) is an effective alternative for patients using TPN but its use has faced significant obstacles in the past relating to issues of immunosuppression, limited surgical technique, as well as issues inherent to the organ procurement and preservation process [2]. With the advent of the immunosuppressant tacrolimus and innovative surgical devices such as the gastrointestinal anastomosis (GIA) stapler, the rate of successful small bowel transplants has increased [3]. Between 1990 and 2010, 2035 intestinal transplants were performed with a high of 198 in 2007 [4]. Survival of patients with ITx has also increased dramatically over time; however, it is still lacking when compared to survival of most other transplant patients [5].

ITx is a cost-effective treatment for patients with intestinal failure or patients who are dependent on TPN, yet despite its potential to increase patients' standard of life, intestinal transplantation is rarely done [2]. Postoperative complications such as primary graft failure, acute rejection, and necrosis along the grafted loop of bowel limit its effectiveness and therefore its performance [6]. Much of this morbidity is believed to occur due to poor preservation of the small intestine during transport, during which time the intestine degrades due to the build up of reactive oxidizing species and other waste products.

Little has changed in the crucial intermediary step of keeping tissue viable for transplantation [6], keeping the overall number of bowel transplantations low, keeping recipient outcome quality poor, and lengthening waiting times. Thus, there exists significant interest in optimizing the process of small intestine procurement, preservation, and transportation.

We sought to develop a device that could preserve intestinal tissue during this period by pumping a cold preservation solution through the intestinal lumen and vasculature. This treatment would limit buildup of harmful waste products inherent to bowel. Additionally, minimization of mechanical stress and trauma to the organ is essential to extending the time for ex-vivo transportation and ultimately, availability of small intestine. We hypothesized that our device would lead to a lesser degree of necrosis than that seen with the current standard of care.

II. Methods

A. Device Design

As part of a project-based design course, an intestinal preservation system was built (Fig. 1). A standard 28-quart cooler was chosen as the device foundation. Ice, as opposed to active cooling, was employed due to its inexpensive nature, availability, and efficiency at cooling. Peristaltic pumps were used for fluid flow since the fluid does not contaminate the pump head, only the tubing, which can be easily cleaned or replaced for reusability. An exterior box housed the electronics, including potentiometers, power

*Member of the Institute of Electrical and Electronics Engineers
§Research supported by the Yale University Center for Engineering, Innovation, and Design.
RR Narayan is with the Yale School of Public Health, New Haven, CT 06510 USA (phone: 510-427-7511, email: raja.narayan@yale.edu).

BW Loeb, K Oki, S Backus, RE Fan, and JP Zinter are with the Department of Mechanical Engineering, Yale University, New Haven, CT 06510 USA (email: brian.loeb@yale.edu, kristi.oki@yale.edu, spencer.backus@yale.edu, richard.fan@yale.edu, and joseph.zinter@yale.edu).

NE Pancer, A Crouch, and Y Chauhan are with the Department of Biomedical Engineering, Yale University, New Haven, CT 06510 USA (email: natalie.pancer@yale.edu, andrew.crouch@yale.edu, and yusuf.chauhan@yale.edu).

JP Geibel, MI Rodriguez-Davalos, and R Patrón-Lozano are with the Department of Surgery, Yale University School of Medicine, New Haven, CT 06510 USA (email: john.geibel@yale.edu, manuel-rodriguez-davalos@yale.edu, roger.patron-lozano@yale.edu)

switches, lithium polymer (LiPo) batteries, and a liquid crystal display (LCD) screen showing flow rate, temperature, and time data (Fig. 2)

The peristaltic pumps were characterized and their properties were used to program the microcontroller to adjust the pumps at different speeds (Fig. 3).

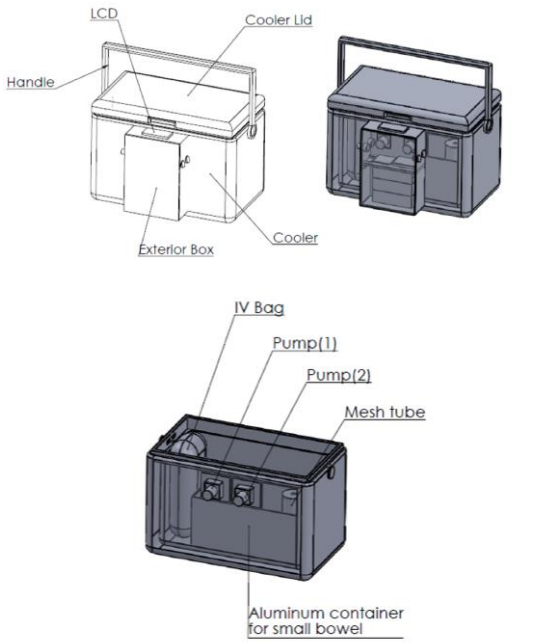

Figure 1. Outside of device schematic (top), inside of device schematic (middle), and picture of device (bottom).

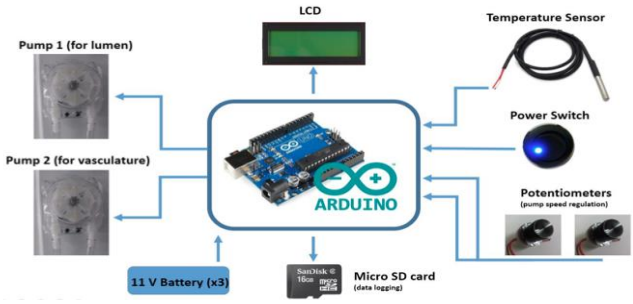

Figure 2. Schematic diagram of electronics in device.

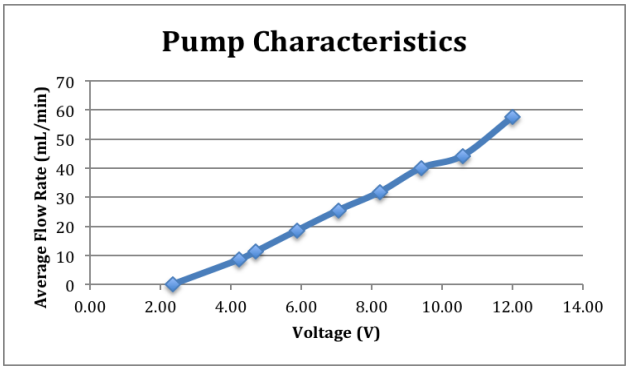

Figure 3. Pump characterization of flow rate versus voltage.

B. *Surgical Technique*

Details of the procurement technique have been described before [7]. One porcine specimen was used for this experiment. Eight meters of porcine intestine were harvested (4 meters from the distal end and 4 meters from the proximal end) and stored in a manner consistent with the standard of care to serve as a control. This tissue was placed in a plastic bag in an insulated cooler, surrounded by ice. The residual 3 meters of porcine intestine that remained en bloc were installed in the device.

C. *Experimental Treatment*

The intestine inside the device was kept at 4-8 ºC, which is the standard of care for transportation of organs. The device utilized 2 peristaltic pumps running at 160mL/min. Tubing from the first pump conducted 0.9% saline solution from a 1L IV (intra-venous) bag through a closed system into the proximal end of porcine small intestine while tubing from the distal end of the intestine returned the fluid to the pump. A second pump and tubing conducted saline into the arterial inlet of the small intestine, the superior mesenteric artery. The intestinal tissue sat in a cold saline bath that collected solution from microperforations in the vasculature as well as the main venous outlet. This solution was passed through a metal screen before being delivered through a 180µm filter to tubing that returned the solution to the second pump (Fig. 4). Tygon tubing was used in the device, and Christmas tree connectors were used along with sutures to connect the intestine to the tubing. Temperature and flow rate were monitored for 8 hours.

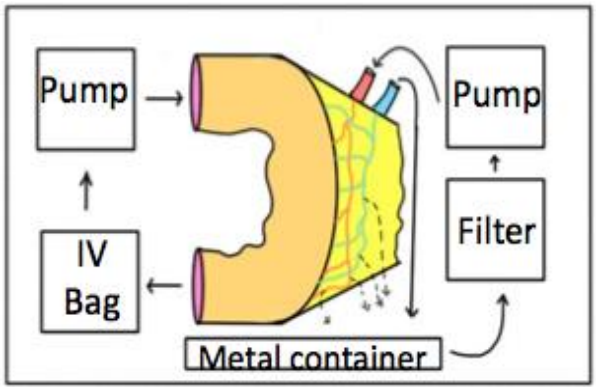

Figure 4. Schematic of open and closed loop systems.

III. Results

Circuitous flow was achieved through both the lumen and vasculature. After eight hours, the experimental lumen had not distended or suffered any apparent physical damage. Meanwhile the control, which had not been flushed out, had a visible buildup of waste products and several sections of the bowel had collapsed upon itself (Fig. 5).

The organ was kept at a constant temperature of 4 and 8°C during the 8 hour experiment (Fig. 6). This demonstrates that ice as a passive cooling method is effective at keeping the organ at the desired temperature.

Two histology images stained with hematoxylin and eosin are to the right (Fig. 7). The control image shows significant inflammation, while the experimental tissue has almost none. The control tissue had signs of focal early ulceration, which the experimental tissue did not have. Overall, there was significantly less epithelial damage in the experimental tissue than in the control. According to these parameters, our device preserved the intestine better than the standard of care.

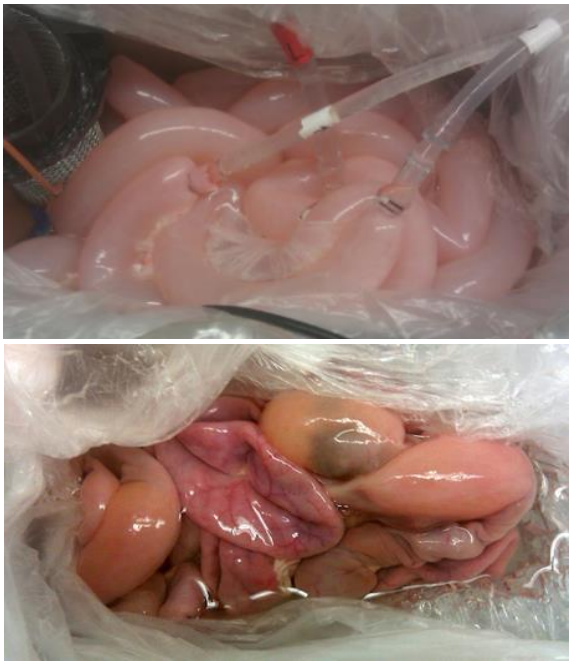

Figure 5. Experimental (top) and control (bottom)intestinal tissue.

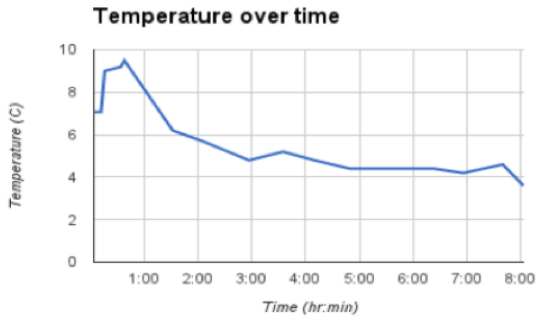

Figure 6. Time versus temperature graph during 8 hour experiment.

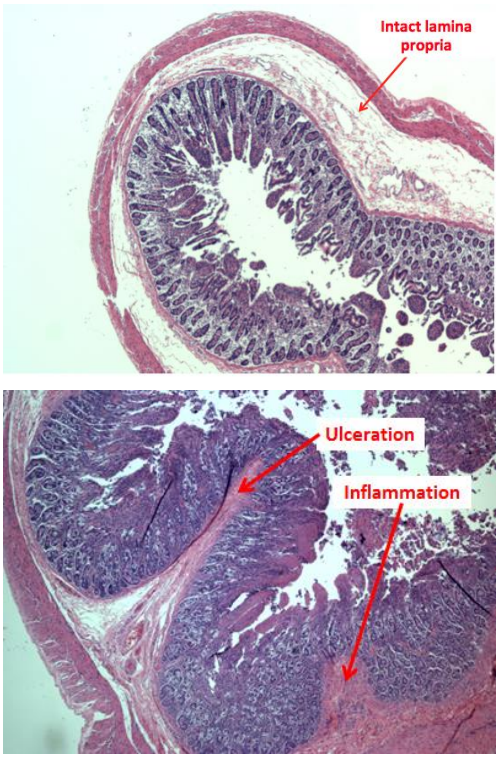

Figure 7. Histology images of experimental (top) and control (bottom) intestinal tissue.

IV. Conclusion

Better preservation of the intestine during transport can make transplant procedure more viable, thus markedly improving patient care for those with intestinal disorders. Our device fills this unmet clinical need. While the standard of care solely keeps the intestine cold using ice within a cooler, our innovation - perfusion of both the intestinal lumen and vasculature - increases tissue preservation. Pathological analysis showed that after 8 hours, the experimental tissue in the device had noticeably less inflammation and ulceration than the control, which had been placed in the standard of care.

To implement perfusion within a cheap, simple, and transportable device, peristaltic pumps were used to flush perfusate through the intestinal lumen in a closed circuit, and through an open circuit in the vasculature. The system also cools the organ between 4-8 ºC using ice, and displays time, flow rate, and temperature, enabling user control of flow rate. It is lightweight and small enough for conventional travel, capable of being carried by one person. Finally, the device operates for at least eight hours to ensure an adequate travel window.

Acknowledgment

The authors would like to thank the Yale Animal Resources Center and Yale Environmental Health and Safety for their oversight in ensuring that all porcine experiments

were performed ethically and economically.

REFERENCES

[1] Khan FA, Tzakis AG. Intestinal and Multivisceral Transplantation. In: Transplantation, Ginns, Cosmi, Morris (Eds). Malden: Wiley-Blackwell, 1999:422.

[2] Fishbein, Thomas M. "Intestinal transplantation." *New England Journal of Medicine* 361.10 (2009): 998-1008.

[3] Nickkholgh, Arash, et al. "Intestinal transplantation: review of operative techniques." *Clinical transplantation* 27.s25 (2013): 56-65.

[4] Health Resources and Services Administration, Organ Procurement and Transplantation Network. Transplants by Donor Type, Intestine, April 4, 2014. Accessed on April 7, 2014.

[5] Khan FA, Selvaggi G. Overview of intestinal and multivisceral transplantation. UpToDate. (Accessed September 17, 2013).

[6] United Network for Organ Sharing: 2002 Annual Report of the U.S. Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients: Transplant Data 1992–2001. Rockville, MD, Department of Health and Human Services/Health Resources and Services Administration/Office of Special Programs/Division of Transplantation, 1.

[7] Casavilla A, Selby R, Abu-Elmagd K, et al. Logistics and technique for combined hepatic-intestinal retrieval. Ann Surg 1992; 216:605– 609.