Editorial

Predicting early graft loss in pancreas transplantation using novel imaging techniques: are we there yet?

Samrat Ray[1]^, Trevor W. Reichman[1,2]^

[1]Ajmera Transplant Centre, Toronto General Hospital, University Health Network, Toronto, ON, Canada; [2]Department of Surgery, University of Toronto, Toronto, ON, Canada

Correspondence to: Trevor W. Reichman, MD, PhD. Associate Professor, Department of Surgery, University of Toronto, 585 University Ave., Toronto, ON M5G 2N2, Canada. Email: Trevor.Reichman@uhn.ca.

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Introduction

Since its inception in 1966 at the University of Minnesota, pancreas transplantation has witnessed major milestones in evolution of surgical techniques, immunosuppression regimen and more recently, machine perfusion for optimising graft utilisation (1). The last two decades have witnessed a steady increase in pancreas graft survival rates, with 5- and 10-year survival rates now exceeding 80% and 70%, respectively, in many centers worldwide (2). However, duodenal anastomotic leaks still continue to be the major contributor to early graft losses after pancreas transplantation, with rates of graft loss being as high as 20–25% in the first year after transplantation (3). Precarious pancreato-duodenal vasculature, along with standard graft procurement steps that involve ligation of gastroduodenal artery contribute to further jeopardising the vascular supply to the duodenum, leading to a risk of anastomotic failure (4). Besides this, there could be other systemic factors such as advanced age of the recipient, recipient body mass index (BMI), long term pre-transplant immunosuppression that have been proven to be potential contributors to development of duodenal anastomotic leaks after pancreas transplantation (3).

With the advent of imaging techniques like dynamic contrast enhanced ultrasound (DE-US), indocyanine green (ICG) fluorescence angiography, hand-held vital microscopy (HVM) and more recently Hyperspectral imaging (HSI), there has been rising interest in intra-operative assessment of graft vascular integrity to predict the outcome of solid organ transplantation (5,6). Utilisation of these modalities in pancreas transplantation is a challenge, owing to the limitation of cold ischemia time of the graft *ex vivo*, sensitivity of the organ to handling and above all the technical challenge to accurately predict the complex microcirculatory pattern of the graft.

The article titled "*Intraoperative reperfusion assessment of human pancreas allografts using hyperspectral imaging*" by Sucher *et al.* from Germany aimed to study the role of HSI as a technology to identify early onset of tissue mal-perfusion and hypoxia by real-time assessment of pancreatic graft microcirculation. As an addendum to this well-structured study, we would like to address a few viewpoints regarding the applicability of this novel technology in pancreas transplantation.

HSI *vs.* other modalities of graft perfusion assessment

Intra-operatively, subjective signs such as brisk bleeding from the graft parenchyma and duodenal mucosal

^ ORCID: Samrat Ray, 0000-0002-5701-2593; Trevor W. Reichman, 0000-0002-2303-1606.

edges, capillary refill of the duodenal wall and pinkish red appearance of duodenal mucosa indicate good graft perfusion. This could further be complimented with presence of a strong arterial waveform on intra-operative doppler ultrasonography. However, intra-observer variability and the inability to demonstrate microcirculation limit the use of this technology for accurately predicting the graft perfusion in pancreas transplantation. Handheld vital microscopy (HVM) using the principle of direct visualisation of circulating RBCs within the vessel lumen showed some initial promise in assessing hepatic dynamic microcirculation, but is limited in its applicability in pancreas due to high sensitivity to motion induced blurring and technical expertise required by the operator (7). ICG fluorescence angiography proved valuable in decision-making strategies in small bowel anastomosis, as evidenced by the promising results of the multicentre PILLAR II trial (8). One of the earliest evidence of its applicability in pancreas graft perfusion assessment came in 2008 by Sanchez *et al.* (Baylor, Dallas group) who could demonstrate the use of ICG fluorescence combined with the SPY imaging (Novadaq, Toronto, Canada) in identifying low blood flow states of the transplanted grafts in animal models (9). More recent evidence of its applicability came from the French group (Panaro *et al.*), who studied the role of ICG angiography in evaluating duodenal stump vascularity in 5 patients undergoing kidney-pancreas transplantation and found promising results (10). However, inability to delineate perfusion beyond the area of anastomosis and the fear of anaphylaxis (dye related) and invasiveness of the technique might limit its wide applicability to pancreas transplantation. HSI, on the other hand offers the advantage of pixel-wise analysis of chemical changes in the tissue, with real time assessment of tissue oxygenation, hemoglobin and water concentration. Its ability to map perfusion changes over a wider area in the tissue and the ease of technical set-up and non-invasiveness offer some of the advantages over ICG angiography. However, a major limitation of the technique is the absence of an objective threshold to make a surgical judgement to differentiate between an undisturbed *vs.* borderline *vs.* restricted anastomotic healing due to disturbed tissue oxygenation and microcirculation. Another limitation that has already addressed by Sucher *et al.* is the applicability of the technique only intra-operatively (11). It is a well-known fact that besides surgical technique and intra-operative tissue vascularity various other systemic factors like compromised cardiovascular state or poor wound healing due to underlying diabetes mellitus in these patients might affect anastomotic healing. Therefore, predicting the outcome of duodenal anastomosis just based on the intra-operative HSI findings might not be accurate or adequate. In the series of 3 patients by Sucher *et al.*, all were under the age of 50 years and in the normal range of BMI, with presumably no underlying cardiovascular conditions (not addressed in the article) (11). This could account for a favorable result of anastomosis in these patients based on the intra-operative HSI findings, accounting for a selection bias.

Future applicability of HSI

Currently, HSI has been used mostly as a guidance tool for precision colorectal surgeries, especially in setting of neoplastic diseases post chemoradiotherapy, where identification of areas of compromised microcirculation could play a significant role in intra-operative decision making. A recent study by Moulla *et al.* (Germany) demonstrated its use in decision making in patients undergoing pancreatoduodenectomy, by evaluating liver and gastric perfusion, especially in patient with Coeliac artery stenosis (CAS) (12). The recent introduction of the TIVITA® MINI technology (Diaspective Vision GmbH, Am Salzhaff, Germany) has opened the avenue of exploring this novel technology laparoscopically as well, though much of it is still unexplored currently (13). In the realm of solid organ transplantation, another potential area of its applicability could be real-time assessment of the graft microcirculation, while on-pump in machine perfusion, which is one of the futures of solid organ transplantation to optimise graft utilisation. Normothermic machine perfusion in pancreas grafts has been only studied so far in animal and a few human discarded grafts (including our centre; unpublished yet), where the biggest challenge has been achieving the most physiological state of perfusion for the graft (in terms of vascularity and parenchymal homeostasis) at the end of 3–5 hrs of being on pump (14). The challenge would be increased many fold in extended criteria grafts with longer warm (Donation after cardiac death) and cold ischemia times (animal models, still under trial). Combining machine perfusion and HSI might be technically feasible, with the main challenges being ensuring sterility while capturing the images and still maintaining an adequate distance for optimum resolution. Theoretically, the low penetrating ability of the technology might limit an accurate delineation of microcirculatory disturbances at a deeper tissue level (15). But, rapid reproducibility of the results

(within 10 minutes) and presumably higher reliability compared to other available methods of tissue oxygenation assessment (oxygen tension probe, oxygen extraction ratio in perfusate, tissue succinate levels) make it a promising complimentary tool in the armamentarium of machine perfusion in pancreas transplantation.

To summarise, HSI is a promising novel tool for intra-operative assessment of pancreas graft microcirculation and oxygenation and perfusion of the duodenal anastomosis. However, a multifactorial background of anastomotic pathophysiology and healing calls for evaluation of other important factors affecting anastomotic integrity rather being reliant on HSI alone for surgical decision making. Applicability of this novel tool in a larger and more heterogeneous cohort of pancreas transplant recipients and its possible integration with machine perfusion in pancreas transplantation would be the potential areas to explore in future.

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Footnote

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