Editorial Commentary

Dueling with the dual artery blood supply in pancreas transplantation: why replace the Y?

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Comment on: Ferrer-Fàbrega J, Cárdenas G, Sapena V, *et al.* Validation of the Back-table Graft Arterial Anastomosis between the Splenic Artery and Superior Mesenteric Artery: Arterial Complications after a 21-year Single-center Experience of Pancreas Transplantation. Ann Surg 2023. [Epub ahead of print]. doi:10.1097/SLA.0000000000006188.

Keywords: Arterial complications; backbench reconstruction; early graft loss; thrombosis

Submitted Apr 12, 2024. Accepted for publication Jun 28, 2024. Published online Jul 17, 2024.
doi: 10.21037/gs-24-121
View this article at: https://dx.doi.org/10.21037/gs-24-121

The history of vascularized whole organ pancreas transplantation has been marked by innovations in surgical techniques in response to an unacceptably high early (within 3 months of transplant) relaparotomy rate resulting in significant morbidity and inferior allograft survival. During the first few decades following its introduction, the "developmental" period of pancreas transplantation was characterized by modifications and improvements in surgical techniques in response to the frequently encountered postoperative complications that were potentially allograft and life threatening (1-3).

At the new millennium, rates of surgical complication after pancreas transplant ranged from 25–50% including allograft pancreatectomy for vascular thrombosis in 5–10% of cases (1-4). Most pancreas transplant programs internationally retrieve the pancreas and prepare the allograft on the backbench using a Y-graft reconstruction of the splenic and superior mesenteric arterial inflow (5,6). In addition, the pancreas allograft is usually implanted through a transperitoneal approach with systemic venous drainage and some form of gastrointestinal exocrine drainage (4). Although surgical complication rates have decreased with time, some centers continue to report rates of early re-exploration of 20–40% (7-9). The objective of pancreas transplantation is to restore normal glucose homeostasis by transplanting functioning islet cells, which represent approximately 2% of the total mass of the pancreas in humans, yet most post-operative complications originate from the remaining 98% "non-endocrine" portion of the pancreas (i.e., pancreatitis, leaks, and vascular issues), which are of particular concern because they can ultimately result in allograft loss, morbidity, and death as well as contribute to increased costs of health care, and may affect the kidney allograft as well (7-9).

With improving surgical outcomes with time, the management of exocrine secretions no longer remains the "Achilles' heel" of pancreas transplantation and vascular complications have now emerged as the most relevant surgical complication in the context of early re-exploration and allograft loss (4,7-12). Currently, 5% to 7% of pancreas transplants are still lost as the result of early technical failure with rates of re-exploration ranging from 12% to 44% (7-15). In the current era, allograft thrombosis remains the leading etiology of technical failure, accounting for 80% of early technical pancreas allograft losses (7-16). Potential risk factors for surgical complications following pancreas transplantation include:

- Donor factors: age >45 years, body mass index (BMI)

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>30 kg/m^2, cerebrovascular accident as cause of death, donation after circulatory death, massive volume resuscitation leading to parenchymal edema, fatty infiltration of the pancreas (5,15,16).

- ❖ Procurement and preservation factors: surgical injury, over-flushing of the allograft, prolonged cold ischemia times (>14–16 hours) (17).
- ❖ Recipient factors: older age, absence of uremia, history of thrombosis or hypercoagulable state, vascular disease, BMI >30 kg/m^2 (15,16).
- ❖ Technical considerations: suboptimal surgical technique, small or diseased vessels, surgeon experience, pancreas retransplantation, reoperative surgery (15,16).
- ❖ Post-operative factors: prolonged or severe allograft pancreatitis, hypotension, not administering anti-coagulation or anti-aggregate agents (1,3,7-12,15,16).

Unfortunately, analysis of risk factors is made challenging due to the multitude of variables involved in the pathogenesis of early thrombosis of the pancreas allograft. As imaging studies have improved, the reported incidence, or more appropriately the increasing awareness of, "partial thrombosis" (referred to as "peripheral thrombosis" by the authors of the study) has increased but intervention may not always be required (18). A histopathologic analysis of explanted pancreas allografts that have failed early following transplantation suggested that in at least 1/3 of cases, the etiology for allograft thrombosis was, indeed, rejection (19,20). Therefore, the traditional differentiation between immunologic and nonimmunologic allograft failure is sometimes unclear.

Consequently, it is important to once again emphasize that the key factors for reducing technical complications after pancreas transplantation include appropriate selection of donors and recipients; meticulous allograft retrieval, backbench preparation, and implantation technique specifically attempting to minimize cold and warm ischemia; proper medical management including appropriate use of anti-coagulation and evidence-based approaches to immunosuppression; and assiduous post-operative care to ideally prevent or at least identify and address complications in a timely fashion. It is worth mentioning that the approach to antibody induction and the technique of transplant does not appear to directly impact on the rate of early complications. Although still an ongoing issue, the rate of early technical complications after pancreas transplantation has decreased over time to 10–20% in some reports (9).

Currently, approximately 5% of all pancreas transplants are lost to early vascular thrombosis, which is most frequently venous rather than arterial in origin (3,10-12,18). In most instances, early allograft thrombosis is not directly related to vascular anastomosis suturing technique or other technical problems but rather to the low-flow state of the pancreas, local and systemic hypercoagulability, pancreatic edema which may impair flow in the microcirculation, and many other donor and recipient factors. The pancreas allograft is particularly predisposed to vascular complications because of the dual arterial blood supply that requires a complex back-bench vascular reconstruction, intrinsically low microcirculatory flow, and the need to rely on collateral flow through the inferior pancreaticoduodenal artery and branches of the splenic artery (SA) to fully vascularize the pancreas. Reperfusion injury, pancreatitis, and tissue edema can increase capillary resistance further contributing to the hypercoagulable environment within the pancreas allograft with resulting increased risk for microvascular thrombosis. The underlying diabetes is characterized by a prothrombotic state which, in association with direct injury to the endothelium during organ recovery and transplantation, may promote macrovascular thrombosis. Furthermore, the pro-inflammatory environment associated with brain death, resuscitation, organ preservation, and ischemia-reperfusion can stimulate aggregation and deposition of platelets. From a technical perspective, vascular thrombosis may result directly from anastomotic technique with intimal flap or dissection leading to arterial thrombosis or from kinking of the vessel for venous thrombosis, leading to proponents of the opposing approaches for either shortening the portal vein or adding an interposition graft.

Management of early thrombosis of the pancreas allograft usually mandates re-exploration with allograft pancreatectomy, although there have been several case reports of allograft salvage depending on the nature and extent of thrombosis and the condition of the pancreatic parenchyma (1-3,7-12,21-23). Pancreas allograft rescue is certainly possible in the setting of partial thrombosis, but only rarely achieved in the setting of complete vascular occlusion and only if managed immediately (21). Urgency is necessary in the setting of suspected thrombosis to prevent a partial thrombosis propagating to complete thrombosis, prevent the systemic consequences of an infarcted organ, and to prevent pulmonary emboli if the portal vein was drained to the systemic venous circulation. In addition to surgical re-exploration, other interventions may include systemic anti-coagulation (particularly in the setting of partial venous thrombosis), percutaneous interventional

thrombolysis or thrombectomy with or without stent placement, surgical thrombectomy, and partial resection of the thrombosed/necrotic portion of the allograft. Nevertheless, outcomes for salvage and rescue attempts in the setting of symptomatic vascular thrombosis remain dismal, with allograft pancreatectomy ultimately indicated despite these heroic attempts (1-3,7-12,21-23).

Vascular thrombosis persists as the most common indication for early allograft pancreatectomy. Because early diagnosis is so important in order to salvage the allograft, most management protocols in the perioperative period involve frequent (perhaps hourly) monitoring of serum glucose levels for at least the first day or two, surveillance imaging (such as duplex ultrasonography) of the allograft, and some method of thrombosis prophylaxis such as heparin or low dose aspirin. Early or late arterial complications include an arterial pseudoaneurysm, which can occur at any of the vascular anastomotic sites and may be technical or may occur in the setting of surrounding infection (13,24). Arterial stenosis resulting in pancreas allograft failure is extremely rare. Other chronic vascular complications include late arteriovenous thrombosis or fistula and arterioenteric fistula, which tend to occur in the setting of chronic rejection or a failing pancreas allograft (13). In contrast to early vascular complications, late arterial complications are often managed by endovascular techniques.

In this seminal study by Ferrer-Fàbrega and colleagues from the Barcelona group, the authors report a large single-center experience (>400 pancreas transplants) spanning 21 years (25). Importantly, they introduce a unique method of arterial reconstruction of the pancreas allograft applied in 376 cases [arterial splenomesenteric anastomosis (ASMA)] that involves only a single end-to-end anastomotic reconstruction on the backbench between the distal superior mesenteric artery (SMA) and the proximal SA, which they compare to 31 cases of the more conventional Y-graft arterial reconstruction of the donor pancreas (that involves two separate end-to-end anastomoses on the backbench) performed at their center. Of note, the ASMA technique places the two arterial systems in series, so that a complication involving either artery places both vascular distributions of the pancreas in jeopardy. In comparison, the Y-graft technique has two separate arterial anastomoses that can independently develop issues. The lack of reconstruction of the proximal SMA that is maintained with an aortic cuff limits options for adjusting and optimizing the length of the arterial segment that will be anastomosed to the iliac artery. Without the inclusion of reperfusion photographs, it is difficult for the reader to imagine how the pancreas would ultimately lie and how the SMA and SA would be positioned beneath the pancreas and around the portal vein compared to the more familiar Y-graft reconstruction.

It should also be emphasized that this procedure requires an *in-vivo* dissection of the distal SMA (with ligation of jejunal branches) at the time of organ recovery following removal of the liver. Therefore, it is not compatible with simultaneous intestinal recovery and may prolong the extraction time of the pancreas and kidney allografts. In addition, an aortic cuff surrounding the origin of the SMA must be preserved, which often is not consistent with liver removal in the setting of an accessory or replaced right hepatic artery originating from the SMA. The approach used for ASMA reconstruction in this series was to dissect the right hepatic artery to its origin from the SMA, transect at this level and repair the defect, preserving the aortic cuff with the proximal SMA. This would be a controversial approach from the perspective of many liver transplant centers that currently insist on preserving the origin of the right hepatic artery along with the proximal SMA for reconstruction to the celiac axis. Transecting the SMA at this level, preserving the inferior pancreaticoduodenal branches, remains consistent with Y-graft reconstruction and would also be possible with inclusion of a donor iliac artery extension graft to the proximal SMA for ASMA. Many liver transplant centers, particularly in the era of living donor liver transplantation, will currently also accept right hepatic arterial reconstruction to the donor gastroduodenal artery as a safe alternative, in which case dissection and transection to the level of the SMA is unnecessary. To summarize, the described reconstruction technique is only possible when the donor and recipient teams are from the same center and/or agreement is secured between the liver and pancreas teams regarding the disposition of the blood supply to each organ.

In the current study, the authors report a slightly lower arterial complication rate with their dueling techniques (7.9% ASMA versus 12.9% Y-graft) and graft salvage rates (53.3% ASMA versus 50% Y-graft) that were comparable (25). With a median follow-up of 129 months, 10-year patient and pancreas graft survival rates were 92.5% and 70.5%, respectively. Of the 30 cases of arterial complications in the ASMA group, 15 (4%) represented acute thrombosis compared to 3 cases (9.7%) in the Y-graft group. Not specifically reported in the manuscript but presented in the

supplementary material, the majority of the thromboses in the ASMA were central, three involved the vein as well as the artery (suggesting a non-technical issue from the reconstruction perspective), and five required allograft pancreatectomy compared to only 1 of the 3 thromboses in the Y-graft group in a case of pancreas retransplantation. Also of note, stenosis was only seen in the ASMA group and involved the SA anastomosis to the SMA in half of cases. The only early pseudoaneurysm occurred at the SA/SMA anastomosis in an ASMA recipient, which was managed with an endovascular stent that subsequently occluded resulting in allograft loss at 15 months. Late pseudoaneurysm only occurred in the ASMA group with two occurring at the SA/SMA anastomosis and three at the iliac artery anastomosis. There were three arterioenteric fistulae including one in the Y-graft group, and two late thromboses, both in the ASMA group, all in the setting of chronic rejection. Finally, there was one arteriovenous fistula in the ASMA group.

Strengths of the study include a large number of pancreas transplants at an experienced center using an innovative technique of arterial reconstruction in the majority of cases with long-term follow-up, granular data, and excellent outcomes. It is also worth noting that as of May 2016 this group has preferentially switched to a novel technique of retrocolic pancreas transplantation with exocrine drainage via a duodeno-duodenostomy. The discussion that the most successful management of late arterial complications occurs with nonoperative techniques (endovascular and anti-coagulation) is another important finding of this study. Unfortunately, because of the large disparity in size between groups according to method of backbench arterial reconstruction, a valid statistical analysis could not be performed. It would be interesting to know if their arterial complication rate decreased over time (with increased experience) and if the Y-graft group was specifically clustered in a particular era. Were there any differences in outcomes when comparing simultaneous pancreas-kidney (SPK) transplantation (n=340) to solitary pancreas transplants (n=28), or when comparing primary pancreas transplantation (n=368) with pancreas retransplantation (n=39)? These are relevant questions because it is well established that the risk of early thrombosis is higher in solitary pancreas transplantation as well with pancreas retransplantation compared to primary SPK transplantation.

Given the variability in organ recovery techniques and anatomic considerations, it is premature to accept the authors' conclusion that this technique should be considered "for first-line back-table reconstruction" or that it is a "more easily reproducible technique". Although this statement may be true at the transplant center in Barcelona, the safety and utility of this technique needs to be validated at other centers before it can be generally accepted.

However, the authors are to be congratulated on providing a unique and innovative experience that is a paramount contribution to the literature on pancreas transplantation. Although the focus of this study was primarily on arterial reconstruction techniques and arterial complications, it is important to emphasize that most early vascular complications are venous in origin following pancreas transplantation. In the absence of an adequate arterial bifurcation graft from the donor, if recognized prior to allograft retrieval, one may consider using this novel technique to reconstruct the pancreas allograft. Therefore, it represents an important addition to the repertoire of the pancreas transplant surgeon that deserves further consideration and study.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Gland Surgery*. The article has undergone external peer review.

Peer Review File: Available at https://gs.amegroups.com/article/view/10.21037/gs-24-121/prf

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-24-121/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Fridell JA, Stratta RJ. Dueling with the dual artery blood supply in pancreas transplantation: why replace the Y? Gland Surg 2024;13(7):1159-1163. doi: 10.21037/gs-24-121