Interventional Procedures in Whole Organ and Islet Cell Pancreas Transplantation

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ABSTRACT

Pancreas organ transplantation has been a therapeutic option for the treatment of diabetes mellitus for over a decade. More recently, percutaneous injection of isolated pancreas islet cells via the portal vein has been developed as an exciting minimally invasive alternative procedure to whole organ transplantation, and one where the interventional radiologist may play a major role. This chapter reviews the role of image guided intervention in the whole organ pancreas transplant and describes the evolving technique of percutaneous islet cell transplantation.

KEYWORDS: Whole organ pancreas transplantation, islet cell pancreas transplantation, percutaneous intervention

Objectives: Upon completion of this article, the reader should be able to understand (1) the range and nature of interventional procedures used in the management of common complications of whole organ pancreas transplantation and (2) the role of the interventional radiologist in percutaneous islet cell transplantation.

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Despite improvements in insulin therapy and delivery systems, diabetes mellitus remains one of the most important worldwide causes of renal failure, cardiovascular disease, retinopathy-associated blindness, and neuropathy.^{1,2} Whole organ pancreas transplantation has been used for the past 20 years as an effective means of endogenous insulin production. Patients may become insulin independent and have reversal of diabetic complications.³ Unfortunately, pancreas engraftment is a complex surgical procedure requiring multiple vascular and enteric anastomoses combined with heavy immunosuppression. It is associated frequently with major peri- and post-operative complications including hemorrhage, vascular thrombosis, leaking bowel anastomoses, acute

pancreatitis and infection.³ Acute rejection is another frequent complication of pancreas transplantation that may be difficult to confirm on clinical and biochemical evidence.^{4,5} In the past 10 years percutaneous image-guided core biopsy has become the standard method for the detection of rejection in the pancreas transplant.⁶ Recent reports in the literature have focused the future search for a cure for diabetes mellitus toward the percutaneous injection of isolated pancreas islet cells as a minimally invasive alternative to whole organ transplantation.^{7,8} As this procedure requires the percutaneous placement of an infusion catheter into the portal vein the interventional radiologist plays an important role in this process. This chapter describes the techniques for

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percutaneous biopsy of the whole organ transplant, percutaneous therapeutic options for allograft-associated complications and discusses the current development status of islet cell transplantation.

WHOLE ORGAN PANCREAS TRANSPLANTATION

Pancreas Biopsy

The diagnosis of rejection has been based on the histological assessment of allograft biopsies in most solid organ transplants. This approach has only more recently been applied to pancreas transplantation with the development of percutaneous needle biopsy of the pancreas allograft.⁹ Numerous non-invasive markers of pancreas rejection and function have been studied such as serum or urine levels of amylase, lipase, or anodal trypsinogen^{4,5,10} to screen for rejection, however none of these biochemical markers have shown adequate specificity on which to base treatment. Similarly, imaging studies such as magnetic resonance imaging or ultrasound have not shown adequate sensitivity or specificity to be used as the sole modality on which to base treatment decisions. Sonographically the most common finding in acute pancreas rejection is pancreatic enlargement and loss of marginal definition. Spectral Doppler sonography was initially thought useful for the detection of acute rejection, but has been shown to lack sensitivity compared with biopsy.¹¹ MRI scans have shown decreased parenchymal enhancement consistent with edema.¹² Prior to the adoption of biopsy of the pancreas allograft, patients who received simultaneous kidney and pancreas transplants from the same donor had the diagnosis of acute pancreas rejection based on the identification of acute rejection in the renal allograft. It has been shown that ~90 percent of rejection episodes in these patients occur simultaneously in both the kidney and pancreas, although pancreas rejection may occur without significant changes in the serum creatinine.¹³ In the past, the significantly lower graft survival rates of isolated pancreas transplants (pancreas after kidney and solitary pancreas transplants) were attributed, in part, to the difficulty of diagnosing acute rejection. The application of pancreas biopsy techniques, along with advances in immunosuppression has been credited with significant improvements in the results of isolated pancreas transplantation.¹⁴

Transplant Biopsy Techniques

Several different pancreas biopsy techniques have been described. The most common is the sonographically directed percutaneous needle biopsy of the allograft. This was first reported by Allen et al and allows a direct histologic diagnosis of acute rejection with a relatively

non-invasive technique.⁹ Other approaches include cystoscopic biopsy in the case of bladder-drained pancreas transplants, a surgical technique now less commonly used.¹⁵ In this technique the biopsy needle is directed through the duodenal bulb of the pancreas transplant into the pancreatic parenchyma through a cystoscope inserted into the bladder. This technique has the disadvantage of being more invasive. In recent years the technique of bladder drainage has fallen out of favor due to chronic complications relating to the effect of both pancreatic digestive enzymes in the urinary collecting system and urine reflux into the pancreas allograft. As described later in this chapter, CT directed percutaneous biopsies have been used on a less frequent basis. This approach may be utilized when sonographic identification of the pancreas transplant is difficult, or the presence of bowel interposition. The final alternative is a laparoscopic or open surgical biopsy.

ULTRASOUND-GUIDED BIOPSY

The use of percutaneous pancreas allograft biopsies has been limited by the perceived difficulty and uncertain safety of the procedure. Recently, however, two large series of percutaneous sonographically guided pancreas allograft biopsies have been reported and have shown a high degree of success with acceptable complication rates.^{6,16} Many transplant programs now routinely employ sonographically guided needle biopsies to assess pancreas transplant dysfunction. In this procedure the allograft is identified using standard sonographic equipment (a 3.5 megahertz transducer with an attached biopsy guide). In cases where the exocrine secretions are drained into the bladder, the pancreas can readily be identified in the right or left lower abdominal quadrant where the transplant duodenal C-loop is attached to the bladder. In these cases the body of the pancreas is relatively superficial, generally situated anteriorly within the peritoneal cavity. The now more commonly employed enteric drainage (drainage of the exocrine secretions into a loop of small bowel), results in the pancreas being placed more cephalad in the abdomen in a para-sagittal location. In this case the head of the pancreas is generally in a cephalad position and the body of the pancreas sits caudal and somewhat more deep within the abdomen (Fig. 1). Color duplex scanning is used to identify the major vessels, and to assess the adequacy of parenchymal perfusion in the allograft. If the venous anastomosis of the pancreas allograft is to the portal circulation, the allograft may sit quite deep within the abdomen and may be surrounded by small bowel or colon. On occasion, an adequate window for percutaneous biopsy requires the application of firm pressure with the ultrasound transducer under real time visualization; the bowel can be seen to slide off the pancreas allograft opening a window for percutaneous biopsy. Attempts to manipulate the bowel with a blunt trocar

Figure 1 Enteric-drained pancreas transplant frequently lies in a cranio-caudal axis in the right mid-abdomen (arrows). The head of the pancreas is generally in a cephalic position.

inserted through the abdominal wall have generally not been successful. A biopsy guide attached to the ultrasound transducer allows the tract of the biopsy needle to be easily visualized. It is highly recommended that the pancreas biopsy be done using real time sonographic imaging and a biopsy guide device (Fig. 2A). A site for the biopsy is identified either in the head or tail of the pancreas that avoids the major vascular structures. After localizing the pancreas and identifying the tract that the biopsy will take, the transducer is removed and the skin is sterilized and prepped. Lidocaine is injected subcutaneously and into the deeper muscular layers of the abdominal wall for local anesthesia. In our experi-

ence sedation is generally not required. An automated spring-loaded 18-gauge tru-cut biopsy device is used since smaller specimens provide tissue inadequate for histologic assessment. Typically these tru-cut biopsy devices have a 2 cm throw and a 1.7 cm specimen notch. Needles with an adjustable smaller notch and throw may be useful for small allografts. With the spring-loaded needle cocked, the transducer with the attached biopsy guide is replaced over the site previously selected. Under real time visualization, the needle is advanced to the surface without entry into the allograft. The needle is then fired and rapidly withdrawn (Fig. 2B). Firm pressure is held on the biopsy site for 5–10 minutes to decrease the potential for intra-abdominal bleeding. Generally, a single 18 gauge needle core biopsy of 1 cm length or greater is adequate for histologic assessment. The specimen is placed in formalin and processed for light microscopy. Electron microscopy or special histologic stains are generally not required. The pancreas biopsy specimen usually has a pale yellow or tan appearance and should hold together as a solid core that sinks to the bottom of the formalin container. A “stringy” specimen that floats on the formalin suggests adipose tissue and a sample that fragments suggests connective tissue or skeletal muscle.

Using these techniques, in a series of 426 biopsies reported from the University of Maryland, 88 percent of the specimens were adequate for histologic assessment.⁶ The rate of complications was low and similar to that reported for kidney allograft biopsies. In this series the most frequent complication was intra-abdominal bleeding. This occurred in eight patients (1.9%). In these patients the clinical presentation of intra-abdominal bleeding was abdominal pain. All patients presented within one hour following the procedure. Of these patients, half required a laparotomy to control the bleeding. One patient was managed laparoscopically and three were treated conservatively. One patient with a bladder draining pancreas transplant developed

Figure 2 (A) Ultrasound image through long axis of pancreas transplant (arrows). Biopsy probe guide and skin-allograft distance markers noted. (B) Ultrasound image after biopsy gun has been fired with needle tip position noted in body of pancreas (arrow).

self-limited hematuria after the procedure. There were four instances of an inadvertent biopsy of another organ, including liver, small bowel, and renal allograft. These patients required no specific treatment and the diagnosis was made retrospectively upon review of the histology of the biopsy. One patient developed a percutaneous pancreatic fistula that resulted in the only procedure-related graft loss in the series of 426 biopsies. It is of note that the majority of patients had more than one biopsy with 37 patients having four or more biopsies. Another report noted a successful tissue diagnosis in 98% of 232 ultrasound-guided biopsies of pancreas allografts with a complication rate of 2.6%.¹⁶

Histologic assessment of the pancreas allograft biopsy with acute rejection typically shows lymphocytic infiltrates. These first appear in the connective tissue septae of the allograft then later becoming apparent in the exocrine parenchyma. A well-defined grading scheme for pancreas allograft biopsies has been devised that correlates well with a graft outcome.¹⁷ With improved results of pancreas transplantation, biopsies are now often used to assess patients who present with hyperglycemia, but no evidence of pancreatic inflammation. This may be due to toxicity of the immunosuppressive medications or chronic rejection with loss of endocrine function of the allograft.^{18,19} A very small pancreas allograft identified by ultrasound in the setting of hyperglycemia is virtually diagnostic of advanced chronic rejection. Serial ultrasound images, if available, are useful and show progressive loss of pancreas mass. In this situation, a percutaneous biopsy is technically more difficult because of the smaller allograft size and generally is of little diagnostic utility. In addition to acute

and chronic rejection, other entities are occasionally seen on biopsy. These include post-transplant lymphoproliferative disorder or infections such as that due to cytomegalovirus.^{20,21} Acute pancreatitis of the transplant or drug-related islet toxicity may be histologically identified¹⁸ as well.

CT-GUIDED BIOPSY

As noted above, CT is not the first choice of imaging modality for guidance of pancreas allograft biopsy since the benefits of real-time guidance during the procedure are lost. This occurs in situations where the allograft may not be adequately visualized on US due to overlying gas in bowel or to the deep location of the transplant, especially in larger or obese patients. Another cause that may limit the use of US guidance is the high prevalence of colonic paresis and associated severe constipation in patients with diabetic autonomic neuropathy. In such situations a suitable anterior window may not be available for sonography, and a posterior retroperitoneal approach may mandate the use of CT guidance (Fig. 3A). CT has been successfully used for guidance of pancreas allograft biopsy in such circumstances, though lack of access due to interposed bowel has been noted in 20% of such referred patients.²²

The identification of the pancreas allograft on non-enhanced CT prior to biopsy may be difficult, especially for portal & enteric-drained grafts. Knowledge of the exact site of graft placement is very helpful, though some enteric-drained allografts may migrate within the mesentery. Oral contrast is given 2 hours prior to the biopsy procedure to opacify the adjacent small bowel. The duodenal C-loop of the allograft

Figure 3 (A) Composite of 4 sequential images during intermittent CT Fluoroscopy-guided biopsy of tail of pancreas transplant (arrows). Decubitus position used to open route between iliac bone and displaced bowel. No route for Ultrasound guided-biopsy could be obtained due to bowel gas. (B) CT image obtained 2 days post-biopsy show acute pancreatitis changes around pancreas transplant (arrows).

infrequently opacifies via retrograde contrast flow from the jejunum, but the metallic staple lines used to oversew the 2 ends of the C-loop are often visible. When overlying bowel precludes access to the transplant certain manipulations may displace bowel from the pathway such as left and right decubitus positioning of the patient. Compression bands or other devices may be used to displace bowel also. As with ultrasound, when available CT Fluoroscopy allows real-time or rapid intermittent imaging guidance during the biopsy procedure, thereby improving accuracy of needle placement and reducing the risk of bleeding or bowel injury (Fig. 3A). Biopsy needle type and size are similar to that described above for sonographic technique. Complications reported in association with CT guided biopsy include elevation of serum in amylase in 6% and significant bleeding in 3%.²² Acute pancreatitis infrequently occurs following biopsy but may be severe (Fig. 3B).

Fluid Collection Drainage

Post-operative fluid collections are frequently seen after pancreas transplantation. The majority of these are due to bleeding from the multiple vascular anastomoses fashioned during engraftment. Most are small and self-resolving seromas or hematomas, and may be simply observed. Other collections seen include pseudocysts, lymphoceles and urinomas (when a synchronously transplanted kidney is present).²³ In these immune-suppressed patients, abscess formation may rapidly develop. Imaging alone is unreliable for the characterization of these collections, and larger collections may be aspirated with US or CT guidance as appropriate.^{24,25} Some peri-transplant collections may be successfully drained with conventional percutaneous catheter techniques (Figs. 4A–D) but up to 70% of these may require subsequent surgical intervention.²⁴ This high rate may reflect a low threshold amongst many transplant surgeons to perform a “second look” laparotomy in patients with fluid collections or dysfunctional grafts, especially in the early post-engraftment phase.

Angiographic Techniques

Thrombosis of the main arterial graft that usually arises from the common iliac artery is a common cause of allograft loss. The vessel most commonly becomes occluded at or near its origin, and is not easily amenable to thrombolysis. Stenosis may occur at this anastomosis also, and there is anecdotal evidence for the value of percutaneous transluminal angioplasty in this setting.²⁶ Rare pseudoaneurysms, arterio-venous and aorto-enteric fistulae have been reported in pancreas allografts but usually require surgical repair.²³

ISLET CELL TRANSPLANTATION TECHNIQUE (ICT)

The portal venous system has become the site of choice for implantation of transplanted islets.²⁷ Any approach to the portal venous system could in theory be used for islet cell transplantation. In most cases the percutaneous transhepatic route is used, though in some institutions the preferred route of access is transvenous with the approach being via the internal jugular vein. As with other more invasive interventional procedures the patient is given intravenous sedation (combination of midazolam and fentanyl) and local anesthetic and the site of percutaneous entry and access tract are anaesthetized. The catheter used for the infusion of cells must have an inner lumen greater than 700 microns to avoid damage to the isolated islets from shear forces or excessive pressure during the transplant. The nominal reference diameter of islet is taken as 150 microns. In practice however preparations can include “islets” as large as 500 microns.

At the University of Alberta, the preferred approach is the right percutaneous transhepatic route and in fact all procedures have been performed by this approach. Sixty-eight ICT procedures performed at this institution have been reported previously.²⁸ Access is gained in an identical fashion as biliary access is gained for drainage purposes. Our access kit of choice is a 4-french stiffened micropuncture kit (Cook, Stouffville, Ontario, Canada), which is 15 cm long. The kit consists of a 4-french polythene catheter mounted on a plastic-coated metal stiffening core. The metal stiffener has a lumen that transmits a 0.018 inch guide wire. A mid-axillary line approach is used with the needle directed in a horizontal plane, oriented about ten degrees cephalad and is usually facilitated by ultrasound guidance to minimize the number of passes, reduce procedure time, and therefore mitigate complications. Bile duct or gall-bladder puncture was avoided in all 17 cases where it was used to guide portal vein access in the initial study performed at the University of Alberta.²⁸ A second or third order branch is typically entered. Following confirmation of the needle tip being in the portal venous system with minimal injection of contrast, access to the main portal vein is achieved. The 0.018 inch guide wire is introduced through the needle and advanced into the main portal vein. The combined delivery catheter and stiffening core are then advanced over the guide wire and into the portal vein. An initial pre-transplant portal vein pressure measurement is obtained. If the portal pressure is satisfactory (less than 20mm Hg mean) the transplant can proceed. A portal venogram is performed to assess patency of all branches and to evaluate distribution of flow (Fig. 5). The catheter tip is positioned in the mid portion of the main portal vein for the infusion of the islets allowing for even distribution to both lobes.

Figure 4 (A,B) CT images show fluid collection (arrow) on left side of pancreas transplant (arrowheads) in patient with fever and abdominal pain. A narrow window for percutaneous drainage was identified (curved arrow). (C,D) CT images show almost complete decompression of abscess collection (arrows) after drainage of purulent fluid via a 10Fr catheter placed using CT Fluoroscopy guidance.

The islet infusion is performed using a gravity-based closed infusion system. In our initial procedures the islets were injected in 50 ml aliquots using a 60 ml syringe but this was discontinued because of theoretical concerns that excessive shear strain was being exerted on the islets. The currently used 4Fr catheter system replaces the earlier use of a 7Fr Neff kit (Cook, Stouffville, Ontario, Canada), which was abandoned when the smaller caliber system was developed. In earlier cases no obliteration of the track was performed. However a small incidence of post procedural hemorrhage prompted the development of oblitative procedures for the tract. Initially gel-foam pledgets were used to occlude the parenchymal tract as the catheter was removed. Subsequently this was modified with the addition of alternat-

ing Gel-foam pledgets and embolic coils sequentially deployed in the tract. Techniques with cautery and laser ablation have been used, however the most recent development in our institution is the use of a combination of coils and Tisseel® tissue adhesive (Baxter Corporation, Mississauga, Ontario, Canada) to obliterate the tract. The catheter is withdrawn from the lumen of the portal vein branch, and having confirmed the catheter to be outside the vein, a coil is deployed (Fig. 6). The tissue adhesive is then injected through the delivery catheter as it is withdrawn over an approximate distance of 1 cm. Another coil is then deployed and the adhesive is injected as the catheter is withdrawn another 1 cm. Coils (3 mm × 2 cm) are deployed approximately every 1 cm (Fig. 6), with tissue adhesive being injected into the

Figure 5 Portal venogram is performed to assess patency of all branches and to evaluate distribution of flow. The catheter tip is positioned in the mid portion of the main portal vein for the infusion of the islets.

track between each coil until the catheter is withdrawn from the skin. The tissue adhesive is injected using a purpose designed dual-syringe injection device supplied with the Tisseel® kit. The components polymerize as they mix in the catheter forming a paste-like material that seals the track. Following the transplant procedure the patients are maintained on bed rest for 4 hours in the recumbent position. Initial placement of the patients in the right side down decubitus position has been abandoned because of lack of proven benefit from this positioning. The use of peri-transplant anticoagulant regimes and management of insulin regimes has been published elsewhere.²⁹

Figure 6 When the catheter is withdrawn from the portal vein, multiple coils (3 mm x 2 cm) are deployed within the track approximately every 1cm with tissue adhesive being injected into the track between each coil.

Figure 7 Absent enhancement due to complete portal vein thrombosis (arrow) is identified on CT scan in a patient one week after islet cell transplant infusion.

Portal vein thrombosis (PVT) is an infrequent but important potential complication of ICT (Fig. 7). This may result from injection of thrombogenic material in partially purified islet cell extracts. Anti-coagulant therapy and careful intra-procedural monitoring of portal vein pressure is used to avoid PVT. Improvements in islet cell purification and transplant techniques have resulted in PVT being encountered infrequently in the University of Alberta experience, seen in only one patient with right sided PVT and one other with transient segmental PVT.²⁸ Because of concerns about the risk of portal vein thrombosis the heparin dose administered with the islet cell preparation has been increased to 35U/Kg. Portal vein pressure is measured carefully during each ICT infusion. An association between increased portal vein pressure and multiple islet cell infusions has been noted and is of importance since most patients undergoing ICT will require an islet cell mass greater than that provided by a single donor pancreas to achieve exogenous insulin independence.³⁰ To date nearly all patients undergoing ICT have received multiple infusions. It is hoped that future refinements in technique and management of ICT may reduce the need for this.

Adjunctive Interventional Procedures

In the authors' experience and that at several other centers, no intentional adjunctive interventional procedures have been performed to date. Bucher et al reported a single case of a patient requiring embolization of an arterio-portal fistula following islet cell transplantation³¹ but no other cases of interventions following ICT have

been found in the literature. It seems reasonable to expect that a certain rate of complications will occur and the sequelae may require urgent therapy. Post procedural hemorrhage has occurred in several cases and this has required surgical intervention in four patients. In these instances the source has been from the liver capsule and one required partial hepatectomy for an intra-hepatic hemorrhage presumed to be arterial in nature. Other instances have been treated conservatively, with transfusion being required in several cases. There have been three instances in which episodes of vaso-vagal responses to the procedure were noted that responded to conservative management. Two of these episodes occurred in sequential transplants in one patient. The possibility of sudden hypoglycemia occurring during the transplantation or immediately afterwards should be considered, however, to date, this has not occurred in the University of Alberta experience.

CONCLUSIONS

This chapter has addressed the role of the interventional radiologist in the management of both whole organ and islet cell transplantation. The continued refinement of both techniques is likely to broaden the demand for these procedures, especially in view of the predicted better long-term management and avoidance of severe diabetic complications associated with pancreas transplantation. Islet cell transplantation in particular promises to become a minimally invasive, safe and repeatable image guided intervention that is likely to become widely available as interest in the technique grows at many transplantation centers. The contribution of the interventional radiologist to the success of a pancreatic transplant program should be emphasized.

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