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Radiologic Aspects of Islet Cell Transplantation

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Abstract

Percutaneous transhepatic intraportal pancreatic islet transplantation is an experimental treatment for patients with type 1 diabetes. The radiologic aspects of pancreatic islet transplantation are described, including a review of interventional radiology, ultrasound, and fluoroscopy image-guided, minimally invasive techniques and procedure-related complications and their avoidance.

Introduction

Since the first described clinical attempt of slaughtered sheep pancreas transplant in a 13-year-old boy dying of diabetic ketoacidosis in 1894 [1], other islet transplantation approaches have been attempted over the years. These include the following: islet autografts in patients following near-total or total pancreatectomy, islet allografts in patients following total pancreatectomy, fetal islet allografts or xenografts in patients with type 1 diabetes, islet allografts in patients with type 2 diabetes, and islet allografts in patients with type 1 diabetes. The aim of this review paper is to expose the readers to the radiologic aspects of the procedures and techniques involved in islet cell allograft transplantation for the treatment of type 1 diabetes.

Islet Allografts for Type 1 Diabetes

Recent advances have led to post islet cell transplantation insulin independence rates of up to 80% at 1 year [2]. Multiple centers worldwide are now offering islet cell transplantation as an experimental treatment for select patients with uncontrolled, symptomatic type 1 diabetes. Since the year 2000, an estimated 500 patients with diabetes have received intraportal islet transplantation at 43 institutions [3].

The Authors' Institutional Experience

The Transplantation and Autoimmunity branch of the National Institutes of Health (NIH) National Institute of Diabetes and Digestive and Kidney Diseases established percutaneous islet transplantation as a clinical research protocol in May 1999. The aim was to reproduce in a new islet transplantation center the successful results reported by the Edmonton group [4•]. Six female patients with type 1 diabetes mellitus for at least 5 years and with undetectable arginine-stimulated C-peptide underwent islet cell transplantation in our institution. The main inclusion criterion was severe recurrent hypoglycemia. Pancreases were received at the NIH from regional organ procurement organizations and the United Network for Organ Sharing. The islet isolation process has been previously described [5]. Only islets with a maximal packed tissue volume of 10 mL or less and with islet purity of at least 30%, gram-stain negative and endotoxin negative were used for transplantation. The isolated islets were suspended in special medium 199 that also contained 50 U of heparin per kilogram of the recipient weight (in order to limit further thrombosis risk of the portal vein during infusion) for the first two patients and

one third that dose for the subsequent four patients. The remaining two thirds of the heparin dose (total remained 50 U/kg of the recipient body weight) was injected as a bolus into the portal vein just prior to islet infusion.

Validated techniques for culturing the islets following cell processing were not available at the time of the study, so all transplants were performed immediately, as soon as cell processing was complete. This required the teams to be on call, 24 hours per day. The interventional radiology teams were given notice that a pancreas was being evaluated and processed, and patients were brought in to the hospital for potential transplantation while cells were being evaluated for adequacy of quality and quantity. All potential recipients were fully evaluated and consented for an Investigational Review Board-approved protocol well before being contacted for possible transplantation. Communication between cell processing and the interventional radiology teams occurred at multiple stages during cell processing. Patients were brought to the interventional suite prior to the final islet counting and other assessments (eg, viability and endotoxin assays). Islet preparations deemed appropriate for transplant were infused via the portal vein. Patients were treated with daclizumab, sirolimus, and tacrolimus to prevent rejection.

Islet Cell Transplantation Technique (NIH Experience)

Standard intravenous conscious sedation (fentanyl and midazolam) was administered with routine hemodynamic, cardiac, and oxygen saturation monitoring. Glucose finger sticks were performed every 15 minutes throughout the entire procedure. The patient's abdomen was prepped and draped in sterile fashion. Prior to the transplantation, a comprehensive ultrasound of the patient's liver was performed in order to verify patency of the portal vein with normal hepatopetal flow, and normal Doppler signal. One percent lidocaine was administered locally subdermally with a 25G needle, followed by a 22G needle for anesthesia in a cylinder shape, down to the liver capsule. Under alternating ultrasound and fluoroscopic guidance, a peripheral portal vein tributary (usually on the right) was accessed (Fig. 1) with a special portal vein access set consisting of a 15- or 20-cm 21G or 22G needle, a stiffened and elongated coaxial 3F/4F micropuncture set (Cook Group, Bloomington, IN), and an 0.018-inch nitinol guide wire using a modified Seldinger single wall puncture technique. Successful peripheral portal vein access was confirmed with contrast injection. After exchange to a 0.35-inch guide wire (usually a Rosen), a 4.1 F Kumpe catheter (Cook Group) with 0.025-inch side holes cut near the tip was inserted and guided into the main portal vein with the tip on the hepatic side of the confluence of portal, splenic, and mesenteric veins. A dedicated digital subtraction preprocedural portal venogram was obtained to assess for normal portal vein flow and to verify catheter placement in the main portal vein (Fig. 2). Portal venous systolic and diastolic pressure monitoring was performed at baseline and at 5-minute intervals throughout the infusion. The islet preparation was divided into two to four 50-cm³ syringes. All syringes were continuously inverted slowly and simultaneously rotated throughout the procedure to minimize clumping and to keep the islets in suspension. The total heparin dose was divided into one third in the islet medium, and two thirds direct bolus injection into the portal vein. Total dose of heparin was 50 U of heparin per kilogram of the recipient weight for the first two patients and 35 U/kg for the subsequent four patients. Islets were slowly infused via syringe over 60 to 90 minutes using a three-way stopcock. Because the islets were denser than the suspension medium, they tended to spontaneously pellet to the dependent portion of the syringe if left at rest. In order to promote hemostasis at the conclusion of the procedure, collagen Gelfoam (Pharmacia & Upjohn, Kalamazoo, MI) pledgets were injected under real-time ultrasound guidance just below the hepatic capsule into the parenchymal track, while drawing back the 4.1 F Kumpe catheter. Special attention and care were invested to ensure the pledgets lodged in the liver parenchyma and not in the portal vein. The catheter was removed during track embolization (with the

placement of ~ 3-mm intraparenchymal Gelfoam pledgets) after waiting 60 minutes to let the heparin effect dissipate.

A postprocedure abdominal ultrasound survey was performed looking for free intraperitoneal, hepatorenal pouch, perihepatic or subcapsular fluid or blood. An ultrasound color Doppler analysis of the main, left, and right portal veins was performed to confirm continued patency. In the absence of symptoms, significant hemodynamic change, or other suspicious ultrasound findings, CT scans were not routinely obtained immediately following the procedures. A postprocedure ultrasound and Doppler evaluation were repeated within 24 hours after the procedure to assess for portal vein patency and bleeding. If there were clinical or radiographic suspicions, a CT was obtained as well.

Transplantation-related complications (NIH experience)

One patient experienced an intraperitoneal hemorrhage from the access track in the hours following the procedure (Fig. 3). This led to significant hemodynamic compromise requiring transfusion with 4 U of packed erythrocytes and supportive measures; however, bleeding stopped spontaneously without major interventions. This patient received heparin with the islets to decrease the risk of portal vein thrombosis, but did not receive protamine reversal.

A second patient presented 8 days following transplantation with watery diarrhea, diffuse abdominal pain, weakness, and hypotension. Ultrasound (Fig. 4) and CT scan at that time showed a complete left portal vein thrombosis and a nonocclusive right partial portal vein thrombosis. Although the mesenteric veins were patent, they were likely exposed to high pressures, as CT also demonstrated small bowel wall thickening. This patient received heparin and long-term anticoagulation with warfarin with near-complete recanalization of right portal vein with partial recanalization of the left portal vein on CT scan 10 months later.

A third patient experienced a hypoglycemic episode during islet transplantation and responded to a 50-mL infusion of 50% dextrose.

Results (NIH experience)

Following islet transplantation, no patient experienced any further serious hypoglycemic events, and insulin independence was achieved in three of six patients (in one patient after receiving only one islet transplantation). The remaining three insulin-dependent patients demonstrated islet cell functionality by measurable C-peptide and improved glycemia control (lower insulin intake, improved hemoglobin A_{1c}).

Worldwide islet cell transplantation publications

The past decade has witnessed the publication of multiple papers describing the islet cell transplantation experience at different centers addressing various procedural aspects, including complications [6–8], prevention of complications (bleeding) [9,10], technical aspects [11], current indications [12], progress and challenge [13], future opportunities [14], benefits and success [2,15•], follow-up, and clinical outcomes [15•]. Only two papers describing several centers' radiology role using the percutaneous-transhepatic intraportal technique have been published [16,17].

Procedure-related Complications

The Edmonton group published an important paper in *Current Diabetes Reports* addressing the risks of islet transplantation, as well as the long-term side effects of immunosuppressive drugs [7]. The authors addressed several important factors leading to transplantation-related complications, including the number of passes with the access needle through the liver before

the portal vein is successfully canalized, the number of overall transplantation procedures (total of 2–3 transplantations), and the manipulation of guide wires and catheters within the main portal vein. Significant bleeding (defined as a drop in hemoglobin more than 25 g/L or the need for transfusion or surgery) was seen in 9% of procedures [7]. Many of these patients received a loading dose of 325 mg of aspirin at the time of transplantation to mitigate the instant thrombotic islet reaction originally described by the Uppsala group [18]. These patients also received heparin (35 IU/kg) during the procedure, with the islet infusion and routine low molecular weight heparin for 10 days following the procedure. The bleeding risks were decreased later on, by avoiding aspirin for 2 weeks after transplantation. Puncture of the gallbladder with the 4F catheter is rare, and when encountered leads to abdominal pain but resolves spontaneously without surgical intervention. Despite heparin administration, partial portal vein thrombosis occurred in 3% of portal vein cannulations, and was treated with anticoagulation. One patient had an intrahepatic bleed that required partial hepatic resection. Liver function tests rose in 44% of patients, and usually resolved within 4 weeks. Abdominal pain related to the procedure resolved within a few days.

Owen et al. [8] reported their procedure-related complication experience for 68 islet cell transplantation procedures performed on 34 patients between March 1999 and May 2002. Potentially serious complications occurred in six of 68 (9%) procedures: two patients developed portal vein thrombosis and were treated with anticoagulation therapy; in one patient, this led to an expanding hepatic hematoma that required surgery. Four more patients experienced clinically significant perihepatic hemorrhage, with three of four patients requiring blood transfusions. Following these events, the authors initiated routine post-transplantation tract embolization using gelatin sponge pledgets. Routine tract embolization was discontinued later on with the introduction of a 4F delivering catheter (compared with the 5F catheters used by the authors in early stages).

Prevention of bleeding complications

A multivariate analysis of 132 cases in a single institution reported bleeding related to the islet cell transplantation procedure in 13.6% of the patients [9]. Cumulative transplant procedure number and heparin dose were independent risk factors for bleeding. The authors completed preventive bleeding procedures in all subsequent procedures ($n = 26$, $P = 0.02$) using either thrombostatic coils or tissue fibrin glue sealing the intraparenchymal liver track. Other authors reported the successful use of D-Stat (Vascular Solutions, Minneapolis, MN) (thrombin) to seal the catheter track under fluoroscopic monitoring to confirm adequate retraction of the catheter out of vein and into the liver parenchyma and real-time monitoring of a linear density within the track [10].

Other less common radiologic-guided islet cell transplantation techniques

A few published papers describe islet cell transplantation into organs other than the liver using various techniques, including CT-guided fine-needle intrathymic transplantation with simultaneous transhepatic intraportal injection [19]. The theoretic basis to this approach is that the thymus plays a central role in T-cell tolerance with animal experiments demonstrating that intrathymic donor cell injections induce a state of long-term unresponsiveness to transplanted organs and tissues, potentially inducing host tolerance toward the transplanted islet allografts. A case report of transplantation of islet cells via puncture of the kidney capsule under real-time ultrasound guidance has also been reported [20]. A combined CT and fluoroscopy-guided technique for percutaneous transhepatic catheterization of the portal vein on 44 patients was also described [21], as well as a transmesenteric approach, following a minilaparotomy [22].

In vivo imaging of islet cells

Imaging of the post-transplanted islets could play a major role when assessing islet engraftment and the early recognition of graft loss, thereby enhancing further understanding of graft survival and graft function. Today, insulin independence rates in islet transplanted patients are high, at the most experienced centers approximating 80% at 1 year, declining to 65% at 2 years [2]. The declining islet function raises concerns and the underlying causes are not well understood.

An international workshop was held at the NIH in 2003, under the title “Imaging the Pancreatic Beta Cell” and was published as an overview [23•]. The workshop discussed the development of novel in vivo imaging modalities and techniques of islet cell transplantation. Several of the techniques proposed included the use of targeted magnetic resonance contrast agents, such as lanthanides (Ln^{3+}) and manganese (Mn^{2+}), or magnetic imaging probes, such as superparamagnetic iron oxide nanoparticles. Positron emission tomography imaging could potentially be used with β -cell-specific antibodies or pharmacologic agents. Recently, noninvasive in vivo MRI techniques were described for post-transplant islet cell imaging in a small animal model. A few papers describe the successful use of iron-labeled allograft islets in rats to detect technical success of the transplantation procedure itself. Imaging as a surrogate for rejection and decrease in islet mass has also been described in rodent allogeneic models [24,25]. A more complex and specific approach has been developed in which isolated rat islets are cultivated with immunomagnetic particles (beads) against rat major histocompatibility complex class 1 antigens. The islets were then transplanted into the liver of syngeneic rats and islets were imaged by MRI [26].

Discussion

Although the radiologic procedural aspects are relatively simple, significant obstacles remain in the way of widespread adoption of islet cell transplantation techniques. The first and foremost is the limited islet supply, with multiple efforts underway, including education and legislation, as well as basic research so as to not rely on cadaveric donors. The steroid-free immunosuppressive regimens are not as innocuous as once hoped, and carry significant risk for life-altering side effects. These shortcomings should be viewed realistically as challenges, and not insurmountable obstacles.

Bleeding and thrombosis occur with a fairly low incidence, but are potentially significant risks. Both transfusion-dependent bleeding and portal vein thrombosis may occur and stain the apparent success of the technique. There is a fine balance between antithetical risks of bleeding and thrombosis in the immediate hours following transplantation. Until a technique or combination of pharmacologic maneuvers can be developed that addresses this balance, islet transplantation will carry these risks. Most thrombosis and bleeding risks are managed conservatively. It is suggested that the islet cells themselves cause portal system inflammation, and are likely thrombogenic [18]. The use of larger and stiffer catheters and wires may themselves irritate the portal vein endothelial wall, initiating platelet adherence and the coagulation cascade. Large devices may also increase risk of intraparenchymal bleeding. Extreme care must be taken to avoid traumatizing these vessels in diabetic patients with potentially abnormal vasculature. Further development and investigation of heparin-coated or low molecular heparin-coated wires and catheters could potentially decrease the overall thrombogenicity of the procedure leading to less complications. Furthermore, potential use of such pharmacologic maneuvers (ie, recombinant anti-tissue factor antibodies, or specific inhibition of the islet clotting cascade) could decrease portal vein clot risk.

The balance between thrombogenic factors and anticoagulation is very delicate and requires tight monitoring of portal vein pressures during the procedure as well as close clinical monitoring postprocedure. How do we interpret transient portal vein pressure elevations during

the procedure, since some elevation is normal? Is it associated with thrombosis? What is the threshold for aborting the procedure? Perhaps a multicenter registry or a consensus conference requiring the recording and reporting of portal vein pressures along with outcomes could shed light on these important topics. Nonhuman primate studies using the well-established diabetic model could also help refine preclinical questions regarding techniques and premedications, including immunosuppressives and anticoagulants [27]. Interventional radiology teams attempting this procedure should have the technical skills and appropriate equipment to deal with the complications, including diagnostic angiography with hepatic artery embolization (when uncontrolled hepatic parenchymal bleeding is encountered) or indirect portal vein thrombolysis via selective catheterization of the superior mesenteric artery (for portal vein thrombosis).

Conclusions

Islet cell transplantation is a multidisciplinary procedure that uses conventional interventional radiology techniques to treat diabetes with a minimally invasive, image-guided approach. However, the technique requires continued optimization and refinement to decrease risks, and there remains a significant incidence of postprocedural complications [6–8].

Studies comparing different image-guided and surgical techniques of islet cell administration should be performed. Central international registries should be initiated for the radiologic techniques alone and portal venous pressure monitoring. Being an integral part of the transplantation team, interventional radiologists are in a position to identify safer techniques to support this developing field.

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References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

• Of importance

•• Of major importance

1. Williams P. Notes on diabetes treated with extract and by grafts of sheep's pancreas. *BMJ* 1894;2:1303–1304.
2. Ryan EA, Lakey JR, Paty BW, et al. Successful islet transplantation: continued insulin reserve provides long-term glycaemic control. *Diabetes* 2002;51:2148–2157. [PubMed: 12086945]
3. Shapiro AM, Ricordi C. Unraveling the secrets of single donor success in islet transplantation. *Am J Transplant* 2004;4:296–298.
- 4•. Shapiro AM, Lakey JR, Ryan EA, et al. Islet transplantation in seven patients with type 1 diabetes mellitus using a glucocorticoid-free immunosuppressive regimen. *N Engl J Med* 2000;343:230–238. [PubMed: 10911004] Landmark paper describing the preliminary success with islet cell transplantation using a glucocorticoid-free immunosuppressive regimen, providing proof of the principle that islet transplantation can be reproducibly successful for at least 1 year.
5. Hirshberg B, Rother KI, Dizon BJ 3rd, et al. Benefits and risks of solitary islet transplantation for type 1 diabetes using steroid-sparing immunosuppression: the National Institutes of Health experience. *Diabetes Care* 2003;26:3288–3295. [PubMed: 14633816]
6. Bucher P, Mathe Z, Bosco D, et al. Morbidity associated with intraportal islet transplantation. *Transplant Proc* 2004;36:1119–1120. [PubMed: 15194389]
7. Ryan EA, Paty BW, Senior PA, Shapiro AM. Risks and side effects of islet transplantation. *Curr Diab Rep* 2004;4:304–309. [PubMed: 15265474]

8. Owen RJ, Ryan EA, O'Kelly K, et al. Percutaneous transhepatic pancreatic islet cell transplantation in type 1 diabetes mellitus: radiologic aspects. *Radiology* 2003;229:165–170. [PubMed: 12944593]
9. Villiger P, Ryan EA, Owen R, et al. Prevention of bleeding after islet transplantation: lessons learned from a multivariate analysis of 132 cases at a single institution. *Am J Transplant* 2005;5:2992–2998. [PubMed: 16303015]
10. Froud T, Yrizarry JM, Alejandro R, Ricordi C. Use of D-STAT to prevent bleeding following percutaneous transhepatic intraportal islet transplantation. *Cell Transplant* 2004;13:55–59. [PubMed: 15040605][Published erratum appears in *Cell Transplant* 2004, 13:475.]
11. Lakey JR, Burridge PW, Shapiro AM. Technical aspects of islet preparation and transplantation. *Transpl Int* 2003;6:613–632. [PubMed: 12928769]
12. Ryan EA, Bigam D, Shapiro AM. Current indications for pancreas or islet transplant. *Diabetes Obes Metab* 2006;8:1–7. [PubMed: 16367876]
13. Gaglia JL, Shapiro AM, Weir GC. Islet transplantation: progress and challenge. *Arch Med Res* 2005;36:273–280. [PubMed: 15925017]
14. Shapiro AM, Lakey JR, Paty BW, et al. Strategic opportunities in clinical islet transplantation. *Transplantation* 2005;79:1304–1307. [PubMed: 15912095]
15. Ryan EA, Paty BW, Senior PA, et al. Five-year follow-up after clinical islet transplantation. *Diabetes* 2005;54:2060–2069. [PubMed: 15983207] This paper addresses the longer-term follow-up data of islet transplant recipients, including short- and long-term complications. Most recipients who are rendered free from insulin therapy at 1 year after transplantation need to reinstitute insulin therapy within 5 years after transplantation.
16. Venturini M, Angeli E, Maffi P, et al. Technique, complications, and therapeutic efficacy of percutaneous transplantation of human pancreatic islet cells in type 1 diabetes: the role of US. *Radiology* 2005;234:617–624. [PubMed: 15591436]
17. Goss JA, Soltes G, Goodpastor SE, et al. Pancreatic islet transplantation: the radiographic approach. *Transplantation* 2003;76:199–203. [PubMed: 12865810]
18. Moberg L, Johansson H, Lukinius A, et al. Production of tissue factor by pancreatic islet cells as a trigger of detrimental thrombotic reactions in clinical islet transplantation. *Lancet* 2002;360:2039–2045. [PubMed: 12504401]
19. Arias-Diaz J, Vara E, Balibrea JL, et al. CT-guided fine needle approach for intrathymic islet transplantation in a diabetic patient. *Pancreas* 1996;12:100–103. [PubMed: 8927613]
20. Shuliang S, Guang DY, Xun Q, et al. Puncture guidance by two-dimensional ultrasonogram: new method of kidney capsule islet transplantation. *Transplant Proc* 1998;30:3421–3422. [PubMed: 9838508]
21. Weimar B, Rauber K, Brendel MD, et al. Percutaneous transhepatic catheterization of the portal vein: a combined CT- and fluoroscopy-guided technique. *Cardiovasc Intervent Radiol* 1999;22:342–344. [PubMed: 10415226]
22. Osama, Gaber A.; Charnsuddin, A.; Fraga, D., et al. Insulin independence achieved using the transmesenteric approach to the portal vein for islet transplantation. *Transplantation* 2004;77:309–311. [PubMed: 14742999]
23. Paty BW, Bonner-Weir S, Laughlin MR, et al. Toward development of imaging modalities for islets after transplantation: insights from the National Institutes of Health Workshop on Beta Cell Imaging. *Transplantation* 2004;77:1133–1137. [PubMed: 15114073] This paper summarizes the consensus among investigators in the field, that an accurate and reproducible in vivo measure of functional islet mass is critically needed in order to allow the assessment of islet engraftment and the early recognition of graft loss, leading potentially to greater improvements in islet graft survival and function.
24. Kriz J, Jirak D, Girman P, et al. Magnetic resonance imaging of pancreatic islets in tolerance and rejection. *Transplantation* 2005;80:1596–1603. [PubMed: 16371931]
25. Evgenov NV, Medarova Z, Dai G, et al. In vivo imaging of islet transplantation. *Nat Med* 2006;12:144–148. [PubMed: 16380717]
26. Koblas T, Girman P, Berkova Z, et al. Magnetic resonance imaging of intrahepatically transplanted islets using paramagnetic beads. *Transplant Proc* 2005;37:3493–3495. [PubMed: 16298639]

27. Neeman Z, Hirshberg B, Tal MG, et al. Pulmonary angiography for the diagnosis of thromboembolic events in the non-human primate. *Transplantation* 2004;78:1025–1029. [PubMed: 15480169]

Figure 1.
Ultrasound-guided access of the right portal vein (*white arrow*) with a 21G Chiba needle.

Figure 2.
Portal venogram. Good positioning of 4.1 F Kumpe catheter (Cook Group, Bloomington, IN) tip within the main portal vein.

Figure 3.
Arterial phase CT scan demonstrating hepatic parenchymal bleed (*white arrow*).

Figure 4.
Ultrasound image demonstrating thrombus in the portal vein (*white arrow*).