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EDITORIAL

# Pancreas allocation in the era of islet transplantation

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Have we reached the era of islet transplantation in the history of finding a cure for type 1 diabetes, and is vascularized pancreas transplantation becoming a thing of the past? The enthusiasm for islet transplantation seems to be increasing, both from transplant physicians or patients with type 1 diabetes, and is ranking high on the agenda of major funding agencies [1]. Recent updates of the International Islet Transplant Registry have shown increasing numbers of islet transplant procedures being performed at increasing numbers of institutions worldwide, with the magic figure of 100 patients transplanted in a single year reached in the year 2002 (*M. Brendel, XXth International Congress of the Transplantation Society, Vienna, 2004*). Performance of the first successful islet transplant procedure with islets isolated from a living related donor was recently reported from Japan [2].

These spectacular achievements are of course the direct consequence of the breakthrough results of the Edmonton group that have put islet transplantation back into the spotlight since the turn of the century [3]. Insulin independence rates at 1 year almost matching those of vascularized pancreas transplantation were obtained by an astute protocol combining steroid-free immunosuppression and sequential islet infusions from multiple donors, and emphasizing the need for improving several meaningful variables for islet isolation, such as donor selection, pancreas procurement and ischemia times.

After the original excitement rightfully generated by the Edmonton protocol, the sobering fact that the rate of insulin independence had dropped to below 25% at 5 years (*J. Shapiro, XXth International Congress of the Transplantation Society, Vienna, 2004.*) has led the islet transplant community to consider a number of issues that must be addressed. A significant islet loss occurs during the isolation procedure or the early engraftment period and determines the need for multiple donors. There is a decline in long-term metabolic function of the islet graft in a vast majority of patients. The toxicity profile of the current immunosuppressive regimen, including a worrisome deterioration of kidney function, has been deemed unacceptable by some [4]. The reproducibility of the Edmonton results has not been optimal, the limiting factor being the technically challenging procedure of islet isolation and purification [5,6]. There is an urgent need for tools to monitor the islet graft, such as surrogate markers of rejection.

With these open questions, islet transplantation, although considered a standard-of-care procedure in some countries, is still at a stage of 'coming of age', with approximately 1000 cases performed worldwide in total.

In comparison, the established, 'mature' vascularized pancreas transplant procedure, with a worldwide experience of over 20 000, is credited with insulin independence rates of 85–90% at 1 year, with a better sustained function in the long-term. For this reason, the question of donor pancreas allotment for vascularized organ transplantation versus islet of Langerhans isolation, addressed by the paper of Ridgway et al. [7] in this issue of *Transplant International*, is of great and immediate interest. Current features of pancreas and islet transplantation are shown on Table 1.

In what one could be tempted to view as a fierce competition between two procedures, a preliminary comment must be that islet and pancreas transplantation should be merely seen as two different therapeutic options of beta cell replacement for patients with type 1 diabetes. These two approaches do not indifferently apply to all candidates for beta cell replacement, and procured pancreata cannot be indifferently allocated to either method of processing. In fact, the coexistence of these two approaches can allow to increase the number of beta cell replacement procedures actually performed by expanding both the pool of acceptable donor pancreata and the target population with type 1 diabetes.

Tentative criteria for selecting the best beta cell replacement procedure for one given candidate and for allocating one given pancreas to the best processing option are shown on Tables 2 and 3. These should be seen as smooth guidelines, likely to be slightly adapted according to local preferences and to evolve with forthcoming experience. The foremost reason for preferring islet over pancreas transplantation obviously lies in the minimally invasive character of the former, which increases its appeal to the patient but also makes it feasible in a candidate otherwise unable to withstand pancreas transplantation for cardiac and/or respiratory reasons. Interestingly, the current preferred target population is extremely different in the two procedures. Pancreas transplantation is done chiefly together with a kidney transplant procedure in patients with advanced type 1 diabetes that led to terminal nephropathy, and is undisputedly considered as such as a life-saving procedure in chronically ill patients [8–12]. In contrast, since the publication of the Edmonton results, islet transplantation has been performed almost exclusively in patients with 'brittle' type 1 diabetes and preserved kidney function, in an attempt to improve daily metabolic control and prevent the occurrence of severe hypoglycemic events [13]. The specificity of this indication and the need for multiple donors needed to reproducibly achieve insulin independence, in the current

**Table 2.** Contra-indications and exclusion criteria for pancreas or islet transplantation.

| Recipient criteria | Pancreas transplantation | Islet transplantation |
|---|---|---|
| Age | <50 years | <65 years |
| Severe heart or respiratory disease | None | |
| Severe mesenteric and ilio-femoral angiopathy | None | |
| Daily insulin requirements | No limit | <50 U/day<br><0.7 U/kg/day |
| Body weight | No limit | <70 kg (female)<br><75 kg (male) |
| Body mass index (BMI) (kg/m$^2$) | No limit | <26 |
| Thrombophilia/Coagulation disorders | | None |
| Liver disease (chronic hepatitis), liver hemangioma | | None |

**Table 1.** Comparative current features of islet and pancreas transplantation.

| | Pancreas transplantation | Islet transplantation |
|---|---|---|
| First case performed | 1966 | 1974 |
| Worldwide experience | >20 000 cases | Approximately 1000 cases |
| Preferred procedure | Simultaneous pancreas-kidney transplantation (SPK) | Islet transplant alone (ITA) |
| Surgical approach | Laparotomy<br>General anesthesia<br>Major procedure | Interventional radiology<br>Local anesthesia<br>Minimally invasive |
| Number of donors required | 1 | ≤3 |
| Insulin independence: | | |
| at 1 year | 85% | 80% |
| at 3 years | 80% | 50% |
| Complications | Common–severe:<br>Graft thrombosis<br>Peritonitis<br>Graft pancreatitis | Less common–milder:<br>Portal vein thrombosis<br>Bleeding |
| Mortality | Low (up to 4%) | Exceptional |

**Table 3.** Criteria for pancreas allocation to islet or whole organ transplantation.

| Donor criteria | Pancreas transplantation | Islet transplantation |
|---|---|---|
| Age | 5–45 (50) years | 18–65 (70) years |
| History of: Alcohol abuse/ chronic pancreatitis/diabetes | None | None |
| Blood glucose | | <16, 7 mmol/l (3 g/l) |
| Body mass index (BMI) (kg/m$^2$) | <25 (30) | >22 |
| Prolonged CV collapse or arrest (>30 min) | None | None |
| High vasopressors | Acceptable | No |
| Hospitalization (ICU) | | <7 days |
| Criteria for splanchnic hypoperfusion: (elevated liver function tests or serum creatinin) | | <2× upper limit of normal |
| Serum amylase and lipase | <2× upper limit of normal | <2× upper limit of normal |
| Maximum total ischemia time | 18–24 h | 8–12 h |

context of severe organ shortage, are leading to a redefinition of success criteria for islet transplantation. Single donor solitary islet transplantation could be considered successful when normalization of metabolic control (i.e. normalization of HbA1c and disappearance of hypoglycemic events) with evidence of islet graft function (i.e. serum C-peptide positivity and a decrease in exogenous insulin requirements), even in the absence of insulin independence, are obtained [14].

To comment on a few discriminating parameters from the donor criteria viewpoint, overweight and older donors are associated with an increased rate of technical complications in vascularized pancreas transplantation [15,16], but are acceptable for islet isolation and transplantation up to the age of 65–70. Obese donors are excellent islet donors in terms of yields, provided they have no history of type 2 diabetes [17–19]. Pediatric donors, and up to the age of 18–20, are poor islet donors, because islets are difficult to extract by enzymatic digestion in this age population [18], whereas they have been credited with excellent function after whole pancreas transplantation [20]. Finally, the pancreas sensitivity to ischemia is especially critical for islet isolation. An optimal total ischemia time below 8 h should be kept, which make it problematic to ship organs over long distances. Fortunately, the two-layer method of pancreas preservation, in which the pancreas is kept in a container at the interface between the preservation solution and oxygen-loaded perfluorochemical, can extend the time of preservation and even rescue organs with prolonged cold ischemia [21].

The study of Ridgway et al. [7] shows that there is a large discrepancy between current practices and opinions of health professionals working in the field of pancreas and islet transplantation in the UK. In particular, 35% of consulted institutions stated having an active pancreas transplantation program. Yet, as the authors rightly point, there was a gross underutilization of donor pancreata in the UK in the study period, with 47 pancreata being transplanted of a total of 704 donors (7%), which does not compare favorably with the 21% donor utilization rate reported in the United States for vascularized pancreas transplantation for the year 2004 [22].

It is a clear sign of the current appeal of islet transplantation that 45% of surveyed institutions expressed their will to start an islet transplantation program in a near future. However an uncontrolled multiplication of islet transplantation programs is neither a realistic nor a desirable prospect, for reasons of costs and efficiency. The financial burden on national health systems of building a state-of-the-art islet production facility with strict enforcement of current good manufacturing practice (cGMP) rules has been estimated at 1–2 million Euros and is too heavy to allow their indiscriminate proliferation. Additionally, the steep learning curve that has to be faced for the technically challenging procedures of islet isolation and purification implies that time will be required before newly established facilities are able to produce islet preparations of sufficient quality for human transplantation [23]. This also means that during this period of training and building up experience, a number of pancreata will be wasted, when they could have been successfully processed at experienced institutions. Finally, the multiplication of islet transplant centers implies that a critical mass of patients will not be achieved in several programs, with an ensuing lack of experience in islet transplantation and patient follow-up [24,25].

One answer to this problem is to develop multicenter networks for islet transplantation, in which one experienced centralized institution serves as the islet production facility for all centers participating to the network. The feasibility of the concept of remote islet isolation and transplantation was first demonstrated in 1997 by the report of the Portland-Minneapolis collaboration in a setting of autologous islet transplantation [26], and has been reproduced and validated since, either in bilateral collaborative efforts or within the framework of multicenter networks [24,25,27,28].

The GRAGIL consortium, a Swiss-French collaborative effort initiated in 1997, was the first operating multicenter network designed for islet transplantation, based on an already experienced islet processing facility located at the University of Geneva, and a shared donor pool and com-

mon waiting list in a network of transplant centers. The network is currently composed of eight university centers in France, namely Besançon, Grenoble, Lyon, Strasbourg, Dijon, Nancy, Marseille and Montpellier, and Geneva in Switzerland. The first patient was transplanted in 1999, and as of December 2004, islets isolated from pancreata harvested in Switzerland and three organ-sharing regions in France have been transplanted into 52 patients throughout the network [27,29].

The publication of the paper by Ridgway et al. [7] is a timely reminder that rules and regulations are required in order to optimize utilization of donor pancreata. This implies the decree of clear guidelines for appropriate allocation of organs for pancreas versus islet transplantation, and rationalization of the number of pancreas and islet transplant centers and the structure in which they operate. In this regard, the Council of Europe is currently working on recommendations to its member states on pancreas allocation and limitation of the number of islet production facilities, along the principles developed above. The purpose of such regulations is ultimately the benefit of patients suffering from type 1 diabetes and who are in need of this precious resource.

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