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Pancreas preservation for pancreas and islet transplantation

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Abstract

Purpose of review—To summarize advances and limitations in pancreas procurement and preservation for pancreas and islet transplantation, and review advances in islet protection and preservation.

Recent findings—Pancreases procured after cardiac death, with in-situ regional organ cooling, have been successfully used for islet transplantation. Colloid-free Celsior and histidine-tryptophan-ketoglutarate preservation solutions are comparable to University of Wisconsin solution when used for cold storage before pancreas transplantation. Colloid-free preservation solutions are inferior to University of Wisconsin solution for pancreas preservation prior to islet isolation and transplantation. Clinical reports on pancreas and islet transplants suggest that the two-layer method may not offer significant benefits over cold storage with the University of Wisconsin solution: improved oxygenation may depend on the graft size; benefits in experimental models may not translate to human organs. Improvements in islet yield and quality occurred from pancreases treated with inhibitors of stress-induced apoptosis during procurement, storage, isolation or culture. Pancreas perfusion may be desirable before islet isolation and transplantation and may improve islet yields and quality. Methods for real-time, noninvasive assessment of pancreas quality during preservation have been implemented and objective islet potency assays have been developed and validated. These innovations should contribute to objective evaluation and establishment of improved pancreas preservation and islet isolation strategies.

Summary—Cold storage may be adequate for preservation before pancreas transplants, but insufficient when pancreases are processed for islets or when expanded donors are used. Supplementation of cold storage solutions with cytoprotective agents and perfusion may improve pancreas and islet transplant outcomes.

Keywords

islet isolation; islet transplants; pancreas preservation; pancreas procurement; pancreas transplants

Introduction

Pancreas and islet transplants are two options for patients who, because of serious diabetic conditions, will benefit from β-cell replacement. The numbers of clinical pancreas transplants have increased exponentially and outcomes have improved markedly, especially during the past two decades [1]. The improvements in outcomes are attributed to better recipient care with respect to surgical techniques and immunosuppressive regimens and to better organ procurement and preservation protocols. In this review, we summarize the

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recent literature regarding the current state-of-the-art in pancreas procurement and preservation. Our focus is on pancreas preservation before islet isolation, which appears to have more stringent requirements than pancreas preservation for whole-pancreas transplants, due to the added stresses experienced by the islets during the isolation and purification process. In addition, we provide a brief review of current advances in islet protection and preservation during isolation and culture.

Pancreas procurement

There are several well established techniques for multi-organ procurement. The two main techniques for pancreas are en-bloc procurement, and in-vivo dissection [2].

In a recent report, Brockmann *et al.* [3•] performed a meta-analysis of the literature on organ procurement for transplants and favored rapid en-bloc removal of the abdominal organs with separation on the back table. Dalle Valle *et al.* [2] reported that pancreas grafts procured by in-vivo dissection and in-situ separation maintained excellent quality. Dalle Valle noted that successful in-vivo dissection was influenced by the experience and ability of the operating surgeons, more so than when the back-table technique was used, suggesting that the back-table technique might be preferred in the absence of a dedicated team of experienced surgeons.

The techniques described above are most likely sufficient for organ procurement from brain-dead donors, but they may be inadequate for procurement of organs from donors after cardiac death. The increasing demand for, and limited availability of, organs for transplants have prompted the use of pancreases procured from donors after cardiac death [4]. Such pancreases have also recently been successfully processed for islets and used for clinical islet transplants in Japan [5,6••,7,8•]. The in-situ regional organ cooling system originally developed for kidney procurement [9] was modified for pancreas procurement [8•]. After confirmation of brain death, a double-balloon catheter is inserted into the aorta through the femoral artery; the tip of the double-balloon catheter is placed above the level of the celiac axis [9]. Ultrasound is used to confirm balloon placement. In order to prevent warm ischemic damage, regional in-situ cooling of the pancreas and kidney is achieved by infusion of a hypothermic preservation solution. The flush is initiated immediately after the donor's cardiac arrest and continued until organ procurement is complete. A venous catheter is also placed in the inferior vena cava via the femoral vein to vent the perfusate.

Pancreas preservation for pancreas transplantation

The two main methods used for experimental and clinical organ preservation are static cold storage, which we will simply refer to as cold storage, and machine perfusion [10–20,21•, 22•,[23]–[34],[35]•,36,37•,38–44]. The hypothermic pulsatile machine perfusion technique originally developed by Carrel and Lindbergh in 1935 [45–47] has been widely used for clinical kidney transplants [48] but not for clinical pancreas preservation.

Early experiments with canine segmental pancreas grafts, reported by Florack *et al.* [16], demonstrated that failure rates with machine perfusion were 30% at 24 h and 40% at 48 h. There were no failures at 24 and 48 h with cold storage. These results, along with the complexities associated with machine perfusion of the pancreas, have made cold storage the preferred and most widely used method for pancreas preservation [44].

Pancreases preserved with cold storage and transplanted immediately as vascularized grafts nearly always restore insulin independence in the recipient. When pancreases are preserved for islet transplantation, two to three donor pancreases may be required per recipient to achieve insulin independence [49], in some but not all centers [50].

The need for more than one donor pancreas per recipient for islet transplants may be attributed to at least three problems: first, to the lower quality of pancreases selected and offered for islet transplants compared with those organs offered for whole-pancreas transplantation; second, to exposure of islets to a series of damaging physicochemical stresses during isolation that may amplify the damage caused during cold storage; and third, to the further damage of islets during purification and culture [38].

University of Wisconsin solution (UWS) has been the standard preservation solution for pancreas transplantation for almost 20 years [36]. Recently, multiple reports have suggested that other preservation solutions may be effective alternatives to UWS [18–20,22•].

In 2006, Englesbe *et al.* [21•] reported the results of a multicenter study using histidine-tryptophan-ketoglutarate (HTK). The study population consisted of 77 consecutive pancreas recipients: 41 were in the UWS group and 36 were in the HTK group. Pancreas graft function, at 90 days posttransplant, the technical graft loss rates, and the pancreatic leak rates were similar between the groups, with no significant differences in postoperative amylase and lipase levels. Similarly, in 2007, Becker *et al.* [22•] reported no significant differences in patient survival or graft survival between UWS ($n = 47$) and HTK ($n = 48$) groups. Furthermore, peak lipase on postoperative day 1, serum amylase and C-reactive protein were not significantly different between the two groups. Some reports, including the one by Becker *et al.* [22•], have indicated that HTK-flushed pancreata appeared more edematous [18–20,21•,22•]. However, this edema did not appear to impair early graft function [22•].

Celsior, an extracellular, low-viscosity preservation solution originally designed for heart transplantation has also been used for experimental pancreas [23–25] and other organ preservation [26–32]. For whole-pancreas transplantation, the use of Celsior has been controversial [23–25]. Baldan *et al.* [24] demonstrated that Celsior was an effective alternative to UWS for pancreas procurement in a pig autotransplant model, whereas Uhlmann *et al.* [25] reported, using the same model, that the use of Celsior was associated with increased ischemia-reperfusion injury, when compared with UWS. Recently, in a pig allotransplant model, Garcia-Gil *et al.* [33] demonstrated that lipid peroxidation after reperfusion of pancreases preserved in Celsior and UWS was similar.

The first prospective, randomized study comparing UWS ($n = 50$) with Celsior ($n = 50$) for clinical pancreas transplants was recently reported by Boggi *et al.* [34]. The authors demonstrated that Celsior and UWS had similar safety profiles for pancreas preservation. Another study reported by Manrique *et al.* [35•] comparing Celsior ($n = 28$) with UWS ($n = 44$) for pancreas preservation demonstrated that 2-year recipient survival rates, 2-year graft survival rates, pancreas leakage rates, and clinical graft pancreatitis rates were similar in both groups.

Pancreas preservation for Islet transplantation

UWS has been used since the 1980s as the pancreas preservation solution [36] for clinical islet transplants. Salehi *et al.* [37•] recently reported that islet yields from human pancreases preserved in HTK or UWS were equivalent. A recent study by Hubert *et al.* [51•], demonstrated that the islet isolation yields, as measured in islet equivalents per gram pancreas, from pancreases preserved with Celsior solution were 2.1-fold lower than those obtained when UWS was used ($P < 0.05$). Based on these results, Hubert *et al.* [51•] suggested that colloid-free preservation solutions might be suboptimal for pancreas perfusion and cold storage prior to islet isolation and transplantation [38].

Two French groups recently demonstrated the possibility of clinical application of solution de conservation d'organes et de tissus (SCOT), which has been shown to have some immunoprotective effects on islet cells. SCOT, an extracellular solution containing polyethylene glycol (PEG), is an oncotic agent, which may induce immunocamouflage of the graft's surface antigens [52]. In addition, Hubert *et al*. [51•] demonstrated that cell swelling and pancreas edema were not significant following 12 h of cold storage with SCOT, compared with UWS – a finding that may be related to the presence of PEG. Giraud *et al*. [53] demonstrated that SCOT could improve islet yield when used during isolation and could prolong islet allograft survival without immunosuppression when used for culture, as compared with control solutions.

There is consensus among the major islet transplantation centers that islet yields and quality can be improved with better pancreas procurement techniques and by the use of cold-preservation techniques that are not necessarily needed for whole-pancreas transplants. The two-layer method (TLM) for pancreas preservation is an example of a coordinated effort to improve islet yield and quality by improving pancreas oxygenation during preservation. In 2002, the University of Minnesota [38], University of Miami [39], and University of Alberta [40,41] reported that the TLM improved islet yield and increased islet transplant opportunities. Since then, the TLM has been widely used by islet transplant centers worldwide.

The mechanisms by which the TLM improves human islet yield and quality are not fully understood. A standard explanation is the improved oxygenation of the pancreas during cold storage with the TLM. It has been suggested that during islet isolation and transplantation, apoptosis is initiated and executed mainly through the mitochondrial and mitogen-activated protein kinase (MAPK) pathways [54–56]. Matsuda *et al.*, using a rat model [57], and Ramachandra *et al.*, using human pancreases [58••], demonstrated improved islet yield from pancreata preserved with the TLM. These results may be attributed to inhibition of apoptosis mediated by the mitochondrial pathway.

Noguchi *et al.* [59•], using a pig model, reported that the islet yield from pancreases preserved with the TLM using a modified ET-Kyoto solution (Otsuka Pharmaceutical Factory, Inc., Tokyo, Japan) was significantly higher when compared with the TLM using UWS. Interestingly, Noguchi *et al.* found no significant difference in islet viability, in-vitro or in-vivo function between the two preservation methods [59•]. They also recently demonstrated improvements in islet isolation using M-Kyoto solution [60•] instead of UWS [61] for ductal injection. They hypothesized that M-Kyoto solution is less likely to inhibit collagenase activity than UWS [62].

Brandhorst *et al.* [63], demonstrated that a simpler preservation method, the one-layer method (OLM), using oxygenated perfluorocarbon, could be used as an alternative to the TLM. They suggested that short-term storage in oxygenated perfluorocarbon improved the in-vitro but not the in-vivo function of pig islets that were damaged by warm ischemia. Three hours of additional pancreas 'oxygenation' with the OLM significantly increased ATP content in pig islets exposed to 30 min of warm ischemia, resulting in recovery of in-vitro function but not in significant improvements in posttransplant function [64•]. These observations are quite interesting as the perfluorocarbon does not contain any substrate for ATP regeneration, does not contain any additives with antioxidant properties, and does not include any of the compounds that are expected to prevent cellular edema during cold storage.

In contrast to observations by Brandhorst *et al.* in the porcine model, Kuroda's group [65], using a rat transplant model, demonstrated that pancreata damaged by 30 min of warm

ischemia were restored after 3 h of TLM preservation [63]. These discrepancies may be explained by species-dependent differences in pancreas size and texture [66•]. Porcine and human pancreata are much thicker, and are often covered by significant amounts of fat, as compared with canine pancreases. Papas *et al.* [67], using a porcine model, demonstrated that only 15% of the total pancreatic volume was oxygenated during TLM preservation with oxygen-saturated perfluorocarbon, suggesting the need for substantial improvement in pancreas oxygenation and preservation, even when the TLM is used.

In a recent large-scale clinical study, the Edmonton group [68•] demonstrated no beneficial effect of the TLM with preoxygenated perfluorocarbon on islet isolation and islet transplant outcomes ($n = 75$). In addition, the Uppsala group [69••] recently reported results from 200 islet isolations, and found that the TLM did not improve islet isolation or clinical outcome posttransplant.

The 2007 Annual Report of the Collaborative Islet Transplant Registry (CITR) [70] provided information on islet characteristics with regard to pancreases preserved by the TLM or UWS. The data were collected from the 31 active islet transplant programs in North America from 1999 to 2006. According to the data, islet yields did not significantly differ between pancreata preserved with the TLM (366,467 ± 11,418, $n = 161$) or UWS (390,532 ± 7,440, $n = 330$). Additional information on islet viability did not reveal any substantial differences between the two groups. The membrane integrity tests, however, utilized for generating the reported viability data are known to be insensitive [71]. In addition, the retrospective analysis reported by the CITR did not indicate the exact methods of perfluorocarbon oxygenation in the TLM, (saturated compared with continuous oxygen supply), the duration of cold ischemia in the two groups, or any relationship or overlap between the pancreas procurement teams and the processing and infusion teams.

The different perfluorocarbon oxygenation methods (presaturated without replenishment compared with continuous oxygen supply) are unlikely to explain the controversial findings on the benefits of the TLM in pancreas preservation. Even in the best-case scenario for oxygenation (perfluorocarbon continuously bubbled and fully saturated with oxygen), the oxygen penetration depth cannot be expected to exceed 1 mm, leaving a large portion of human and porcine pancreata oxygen-limited [66•,67].

It is hypothesized that more sophisticated preservation protocols may be necessary and should replace cold storage, with or without TLM, in order to improve islet yields and quality. This is supported by recent data [73•] indicating that machine perfusion of porcine pancreases for 24 h improved isolation yields by approximately threefold compared with cold storage and by approximately two-fold compared with fresh procurement. The mechanisms behind these improvements are unclear; it has been suggested that edema caused by perfusion may facilitate more efficient islet isolation [73•]. In addition, intermittent capillary perfusion at low flow rates may facilitate pancreas preservation by maintaining better functional capillary density, compared with cold storage [74]. Capillary perfusion may be important for pancreas transplants, but may be less of an issue for islet transplants.

The implementation of recently developed tools for pancreas and islet quality assessment [71,72•] is expected to contribute to more thorough and sensitive evaluation of existing, as well as much-needed new, pancreas preservation strategies, and perhaps help answer some of the long-standing questions in the field.

Islet protection and preservation

Goto *et al.* recently exploited the ability of perfluorocarbon to store high amounts of oxygen to better oxygenate islets during the isolation process [75•]. They demonstrated that the use of oxygenated perfluorocarbon during islet isolation resulted in improved islet yield and quality, which suggests that hypoxia during islet digestion may damage islets [75•].

Ichii *et al.* [76••] demonstrated that the addition of nicotinamide to the processing medium significantly improved islet yield and increased the success rate of isolation. Nicotinamide, a cytoprotective compound, may ameliorate injuries caused by oxidative stresses and various cytokines. In addition, nicotinamide supplementation of the processing medium reduced the islet production of tissue factor, which may trigger thrombotic reactions after portal islet infusion. Nicotinamide also reduced the islet production of macrophage chemoattractant protein (MCP-1), which has a potent chemotactic activity for monocytes. Korsgren's group [77] demonstrated that nicotinamide supplementation of culture medium was effective in reducing both tissue factor and MCP-1 production by islets, which led to the inhibition of the instant blood-mediated inflammatory reaction when islets came into contact with blood.

Islet isolation activates the c-Jun NH2-terminal kinase (JNK), a member of the stress-activated group of MAPKs [55,56]. Noguchi *et al.* investigated the efficacy of a JNK inhibitory peptide (JNKI) to inhibit cell apoptosis in islets isolated from pancreata preserved with the TLM [78,79]. They demonstrated that JNKI prevented islet cell apoptosis induced immediately after isolation and that JNKI improved islet yield and islet graft function after 1 day of culture [78,79]. Similar findings were recently reported by Ito *et al.* using an inhibitor of p38 MAPK during islet preservation [80].

Conclusion

The management of donor pancreas preservation affects clinical outcomes in pancreas, and especially islet, transplant recipients. In-situ regional organ cooling may protect the pancreas from warm ischemic injury when managing donors after cardiac death. Colloid-free preservation solutions such as Celsior and HTK, have been demonstrated to perform comparably to UWS when used for pancreas preservation for subsequent pancreas transplants. Colloid-free preservation solutions were reported to be inferior to UWS for preservation of pancreases intended to be used for islet isolation. Pancreas preservation for islet isolation and transplants may have different requirements: cold storage with or without the TLM may be insufficient. Recent studies with large numbers of pancreases did not demonstrate significant differences in islet yields and in clinical islet allotransplant outcomes with pancreases stored with TLM when compared with cold storage. Pancreas size and texture variations and methods of perfluorocarbon oxygenation may influence the oxygenated volume fraction and the quality of the preserved pancreas. Agents that block stress-signaling pathways and that may interfere with apoptosis, such as JNK and p38 inhibitors, may improve islet yield and quality. Nicotinamide supplementation of the medium has also been reported to be effective for preserving islets. The lack of real-time, quantitative objective tools for assessing the quality of pancreases during and after cold storage and the quality of islets after isolation has hindered progress. The recent development and implementation of such tools [71,72•] is expected to contribute significantly, in the near future, to needed advances in preservation of pancreases to be used for islet isolation and transplantation.

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