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Pancreas Preservation for Pancreas and Islet Transplantation: A Minireview

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ABSTRACT

Pancreas preservation by cold storage using University of Wisconsin solution was the mainstay method used for pancreas transplantation during the past 2 decades. Other solutions, such as HTK, Celsior, and SCOT 15, could not demonstrate any advantage for short preservation periods. But the advent of clinical islet transplantation and the larger use of controlled non–heart-beating donors have prompted the transplantation community to develop methods for increasing pancreas graft quality while preventing ischemic reperfusion damages. Oxygenation by 1- or 2-layer methods during pancreas preservation, as well as the use of perfluorocarbons, might increase the islet yield. Based on the former methods, there is a renewed interest in machine perfusion and oxygenation in pancreas preservation for pancreas transplantation and islet preparation.

Outcome after whole organ pancreas transplantation has consistently improved over the past 20 years; islet transplant results are also improving steadily.[1] The reasons are multifactorial, including improved immunosuppression,[2] prophylaxis against infections and thrombosis,[3] and modifications in surgical[4] and islet preparation techniques.[5] In addition, improvements in organ preservation have undoubtedly had a significant impact on outcome.[5,6] That has been achieved by cooling the pancreas organ down to 4–8°C and maintaining a milieu of reduced metabolism at low temperatures. But the pancreas has certain unique anatomic aspects. First, when procured for a whole-organ transplant, the pancreas is taken with a segment of duodenum. The bowel (duodenum) is more prone to cold ischemic injury than other abdominal organs. Second, the pancreas is a low-flow organ, as compared with the kidney, so it is more susceptible to barotraumas from aggressive cold perfusion after the aorta is cross-clamped. Therefore, preservation tools and methods for whole-organ pancreas transplantation are not valid for islet transplant preparations. Indeed, cold storage may be adequate for preservation before pancreas transplants, but insufficient when pancreases are processed for islets or when expanded-criteria donors are used. Supplementation of cold storage solutions with cytoprotective agents and machine perfusion may improve pancreas and islet transplant outcomes in the future.[7]

PANCREAS PRESERVATION FOR TRANSPLANTATION

The 2 main methods used for experimental and clinical pancreas (organ) preservation are static cold storage and machine perfusion.[7] The hypothermic pulsatile machine perfusion technique, originally developed by Carrel and lately popularized by Belzer,[8] has been widely used for clinical kidney transplants but not for clinical pancreas preservation.

Early experiments with canine segmental grafts, reported by Florack et al,[9] demonstrated that failure rates with machine perfusion were 30% at 24 hours and 40% at 48 hours. There were no failures at 24 and 48 hours 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.[7]

For cold storage of pancreas transplants, the first solutions used were Collins,[10,11] Sacks,[12] and Euro-Collins.[13] But University of Wisconsin solution (UW)[14,15] became and has been the standard preservation solution for pancreas transplantation for almost 20 years.[7] Recently, multiple reports have suggested that other preservation solutions may be effective alternatives to UW (Table 1).

Studies comparing histidine-tryptophan-ketoglutarate (HTK) solution with UW have demonstrated similarities between both solutions in the context of low-to-moderate flush volume and short cold ischemia time (≤10 h) for HTK.[16–19] In contrast, other studies in pancreata flushed

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Table 1. Preservation Solutions

Component (mmol/L)	EC	UW	HTK	Celsior	SCOT 15
Na+	10	28	15	100	143
K+	113.4	125	18	15	5
Ca++			0.015	0.26	1.7
PO_4	57.6	25	9		
HCO_3	10				25
Glucose	194				11
Raffinose		30			
Lactobionate		100		80	
Gluthation		3		3	
Allopurinol		1			
HES		50 g/L			
PEG 20					15 g/L
Viscosity	1.18	3.156		1.15	1.05

Abbreviations: *EC, EuroCollins; UW, University of Wisconsin; HTK, histidine-tryptophane-ketoglutarate; SCOT, Solution de Conservation d'Organes et de Tissus.*

with HTK found a higher incidence of postoperative complications, including graft pancreatitis, use of octreotide, and a decreased rate of insulin independence at hospital discharge.[20–22]

Celsior, an extracellular, low-viscosity preservation solution originally designed for heart transplantation, has also been used for experimental pancreas preservation with controversial results: effective alternative to UW according to Baldan et al,[23] versus increased ischemia-reperfusion injury according to Uhlmann et al.[24] For other organs, such as lung[25] and liver,[26–28] Celsior solution gave similar clinical results. The first prospective randomized study comparing UW and Celsior for clinical pancreas transplants was reported by Boggi et al,[29] demonstrating similar safety profiles for pancreas preservation. That was also reported by Manrique et al[30]: 2-year graft survival rates, pancreas leakage rates, and clinical graft pancreatitis rates were similar using either solution. That is also true for kidney preservation.[31]

A new preservation solution, SCOT 15 (Solution de Conservation d'Organes et de Tissus), which contains an extracellular ionic composition including polyethylene glycol (PEG) as a colloid, was recently used by Hauet et al,[32] for experimental organ preservation, but clinical data for pancreas preservation are still lacking.

PANCREAS PRESERVATION FOR ISLET TRANSPLANTATION

UW has also been used since the 1980s as the pancreas preservation solution for clinical islet transplants.[33] After other preservation solutions became available, Salehi et al[34] reported that islet yields from human pancreases preserved in HTK or UW were equivalent. Another study by Hubert et al[35] demonstrated that the islet isolation yields from pancreata preserved with Celsior were 2.1-fold lower than those obtained with UW. That study suggests that colloid-free preservation solutions might be suboptimal for pancreas perfusion and cold storage before islet isolation and transplantation.

In contrast, Giraud et al[36] demonstrated the possibility of clinical application and advantages of using SCOT, which could increase islet yield and reduce graft immunogenicity in pancreatic islet transplantation. Using SCOT, the same authors eventually improved the islet isolation process from pancreata of non–heart-beating donors[37] in a murine model.

Based on that early experience, there is a 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.[7] The 2-layer method (TLM) for pancreas preservation is an example of a technique for improving islet yield and quality by increasing pancreas oxygenation during preservation. Based on several studies,[38–40] TLM has been widely used by islet transplant centers worldwide, but the mechanisms by which it improves human islet yield and quality are not yet fully understood. It has been suggested by Matsuda et al[41] that TLM cold storage protects isolated islets against apoptosis through the mitochondrial pathway. Noguchi et al,[42] with a pig model, reported that the islet yield from pancreata preserved with TLM and a modified so-called classic solution was significantly higher than with TLM using UW. They hypothesized that their own solution is less likely to inhibit collagenase activity than UW.[43] Therefore, TLM could be a promising technique for both pancreas and islet transplantation[44] while using other preservation methods.

The basic principle of TLM is the use of a cold storage solution, mainly UW, in combination with an oxygen carrier solution, the perfluorocarbons (PFC), which have a higher specific gravity. Therefore the PFC solution settles at the bottom and the UW is above it. The pancreas is suspended at the interface of the 2 solutions (Fig 1). Oxygenation of the PFC for 40 minutes before pancreas placement is sufficient to maintain adequate O_2 concentrations for up to 24 hours. The oxygenation must be done with a gaseous pressure of 10–12 mm Hg and a flow rate of 50–100 mL/min. After that period, pancreata can be transported without the oxygenating apparatus. Moreover, it has been shown that maintaining the temperature of the medium at 8°C rather than 4°C results in superior islet function.[6] The beneficial role of oxygenation for improving pancreas quality and islet isolation was also experimentally demonstrated by Hackl et al[45] using simple preoxygenation of different preservation solutions (UW, HTK, Celsior) and by Scott et al using persufflation.[46]

Therefore, using the 1- and two-layer methods, using perfluorocarbons, which are inert solutions with a high capacity for dissolving oxygen, or oxygenation with other tools, these methods have been proving to be successful for pancreas preservation by cold storage. Taking into account that PFCs can be formulated as an emulsion, there is a huge renewal of interest in using the emulsion for continual

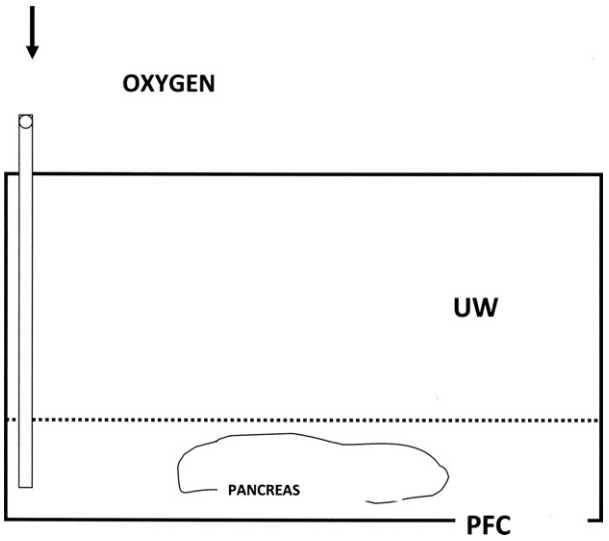

Fig 1. The 2-layer method: University of Wisconsin (UW) solution is above and perfluorocarbons (PFC) solution below.

machine perfusion or as simple flush solution.[47] Indeed, Taylor et al[48] reported that islet isolation from juvenile porcine pancreas after 24-hour hypothermic machine perfusion (HMP) preservation can be successfully achieved; HMP is well tolerated, leading to moderate edema but no loss of function of the harvested islets. Moreover, the edema appears to aid in enzymatic digestion, producing a greater yield and purity of islets compared with pancreas subjected to 24 hours of static cold storage. In parallel, Karcz et al[49] have developed a model of machine perfusion for porcine pancreata that is simple, reliable, and protects graft histopathologic integrity. The model can be used in further studies to improve the quality of pancreas preservation and to assess the condition of and improve the viability of borderline pancreatic grafts.

CONCLUSION

With the number of pancreas transplants increasing and the advent of clinical islet transplants, a significant shortage of pancreata will appear soon. Better preservation methods than just cold storage of donor pancreata will be needed. Because controlled non–heart-beating donors (NHBDs) may be a potential source for pancreata, other preservation methods might be foreseen. Indeed, with NHBDs, significant ischemic damage and postoperative complications might especially occur with prolonged preservation using cold storage.[50,51] The use of TLM has shown promise in prolonging clinical pancreas preservation times and ameliorating warm ischemic insult.[6]

Therefore, there is an urgent need to get access to the TLM technology not only for pancreas preservation for islet transplantation, but also for pancreas transplantation. The machine perfusion technique is also a pancreas preservation method that needs to be reevaluated in the light of new technologies using other perfusion fluids, temperatures, and oxygenation for conditioning the pancreatic graft.

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