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Human Pancreas Hypothermic Oxygenated Machine Perfusion for Islet Isolation in Clinical Settings: A Prospective Study of its Viability

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Introduction

A select group of people who have had type 1 diabetes for a long time can benefit from allogeneic transplantation of pancreatic islets. Most transplanted patients can achieve improved glycemic control with modern immunosuppressive regimens. Pancreases with less favorable donor characteristics are left for islet isolation in the Eurotransplant region, where pancreas transplantation vascularized is the preferred option. As a result, more pancreases have been accepted for isolation from donors who meet extended criteria (ECDs), such as donors who donated after a circulatory death (DCDs). DCD procedures represented 34% of all multi-organ donation procedures in the Netherlands in 2010, rising to 59% in 2019. Since DCD kidneys and livers have been shown to be more susceptible to the adverse effects of warm and cold ischemia, the utilization of DCD organs is thought to carry additional risks. Islet isolation from DCD donors has been shown to yield 87 000–100 000 IEQ less than from DBD pancreases. As a result, DCD pancreases frequently benefit more from donor characteristics: younger age, more frequently male donors, and no recent cardiac arrest history resulted in comparable viability and function after islet isolation. After pancreas transplantation, it has been demonstrated that prolonged cold ischemia time (CIT) is an independent risk factor for technical failure. In DCD pancreases, it is hypothesized that these negative effects are even more pronounced. During islet isolation from a donor pancreas, in addition to cold ischemia, multiple physiochemical stress factors result in the loss of islets. Reducing damage during preservation is one way to extend the CIT without sacrificing quality. As an alternative method for carrying out this function, hypothermic machine perfusion (HMP) has been proposed. After kidney transplantation, HMP has been shown to decrease delayed graft function (DGF) and improve the quality of higher-risk livers prior to transplantation. Oxygenated HMP was recently shown to be capable of adequately preserving pancreatic tissue. However, there has not yet been a comprehensive examination of the effects of oxygenated HMP on human islet isolation and subsequent days in culture. By using oxygenated HMP for six hours, we hypothesized that we could safely extend the CIT of human DCD pancreas [1].

Methods

This study included ten pancreases from human multi-organ donors in the Netherlands. The Medical Ethical Committee of the University Medical Centre Groningen issued a statement of no objection for this study. The "Declaration of Istanbul on Organ Trafficking and Transplant Tourism" states that the clinical and research activities adhered to the Declaration of Istanbul's guiding principles.

Transport of the organs the pancreas was obtained by the regional multi-organ recovery teams using the no-touch method, as previously mentioned. In the beginning, SCS flushed all pancreases before storing them in the University of Wisconsin Cold Storage Solution. In order to prepare for perfusion, the DCD pancreases were transported in UWS under hypothermic conditions to the machine perfusion facility at the University Medical Center Groningen (UMCG).During transport to the islet isolation facility at the Leiden University Medical Center (LUMC), oxygenated HMP was performed. DBD pancreases were transported directly (SCS) to the LUMC's islet isolation facility. CIT was calculated as the amount of time passed from the donor's aortic cold flush to the pancreas' initiation of ductal enzymatic perfusion, which included oxygenated HMP [2].

Oxygenated hypothermic machine perfusion When the pancreases arrived at the UMCG, they were prepared to be connected to the portable pressure-controlled dual perfusion device. In short, the spleen was removed, the gastroduodenal artery was ligated, and the superior mesenteric and splenic arteries were cannulated for separate 25 mmHg perfusion. To ensure passive drainage of perfusion fluid into the reservoir, the portal vein was left open. One liter of Machine Perfusion Solution from the University of Wisconsin which was oxygenated by delivering 100 percent oxygen at a fixed flow rate of 100 milliliters per minute through hollow fibber oxygenators. Inside an insulated box that was surrounded by melting ice, the pancreas was placed in a plastic organ holder with a net. Throughout the entire transport, the ambient temperature remained between 4 and 7 degrees Celsius [3].

Edema and apoptosis markers were examined by independent researchers upon arrival at the isolation facility for visible macroscopic edema in the HMP and SCS pancreases. Using a 12G needle biopsy (Bio-feather), tissue samples (ventral head and tail) were taken from the HMP pancreases shortly before the start of HMP and from both the HMP and SCS groups shortly before islet isolation.San Possidonio, Medax, Italy). The examples were fixed in 4% paraformaldehyde, consequently implanted in paraffin, and cut into areas of 4 µm. To assess morphological shifts, light microscopy of H&E-stained sections was carried out. A custom logarithm in Image-Pro Premier 9.1 (Media Cybernetics, Silver Springs, MD) was used to measure edema by comparing the area of interstitial tissue to the area as a whole. Insulin has been immunofluorescently stained procedure was used [4].

Islet isolations A modified version of the semi-automated procedure that was previously described was used to isolate pancreatic islets at the LUMC. Both HMP- and SCS-preserved pancreases had identical isolation protocols. The level of processed tissue was determined by the mass of the pancreas after peri-pancreas tissue analyzation (pancreas mass) short the tissue mass leftover in the Ricordi chamber after assimilation, isolated by the pancreas mass. Images of samples (more than 20 islets) from each fraction were used to count the embedded and non-embedded islets following purification. An islet was said to be embedded if exocrine tissue covered more than half of its perimeter. To calculate the percentage of embedded islets, the fraction of islets was divided by the isolation's total IEQ, multiplied by that fraction's IEQ, and added to all other fractions. The results were confirmed by a second investigator who was blind [5].

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Discussion

Hypothermic machine perfusion was used to successfully preserve human DCD pancreases in this study. After oxygenated HMP, this study demonstrates that it is possible to prolong the cold ischemia time by isolating a sufficient number of viable islets from discarded human DCD pancreases that are clinically relevant. These pancreases would typically be rejected for clinical islet isolation based on the characteristics of the donor. However, following HMP, we were able to isolate a sufficient number of functional, viable islets and demonstrate proper functionality both in vitro and in vivo [2].

There are numerous factors that influence the outcome following isolation as well as graft function following transplantation: characteristics of the donor, methods of procurement and preservation, and the protocol for islet isolation, culture, transplantation, and engraftment. Because they lack endogenous antioxidants, pancreatic islet cells are known to be highly susceptible to oxidative stress. This stress can eventually result in the production of reactive oxygen species after a period of extreme stress. Proof recommends that the oxidative pressure during pancreas acquirement and the separation system can prompt on going impeded islet capability after transplantation. SCS is the current industry standard for the preservation of donor pancreases following multi-organ donation, whether for islet isolation or whole organ transplantation. Albeit straightforward and reasonable, stretched out SCS time definitely prompts the collection of intracellular poisons and ATP exhaustion, on account of leftover metabolic movement without even a trace of oxygen. The logistical challenges of an islet isolation centre and the location of the donor hospital in relation to the recipient hospital are typically the causes of a pancreas' CIT. CIT are an independent variable that decreases islet yield and/or function. In our middle, we have tracked down a connection between's drawn out CIT and a lower islet yield in 126 DCD islet detachments. In the current study, the oxygenated HMP-preserved pancreases underwent CIT for an additional six hours [4].

More marginal donors, such as DCD donors, make up an increasing number of organ donors in the Netherlands [5]. Organs obtained from DCD donors are particularly vulnerable to the negative effects of cold ischemia, according to research. When compared to DBD organs, DCD organs are less able to deal with this accumulation of stress factors because of this cold ischemic insult, as well as the inherent injury caused by the agonal phase following life support withdrawal and a period of warm ischemia common in DCD procedures. There were no significant differences in islet yield between DCD and DBD pancreases in three small studies about islet isolation from DCD donors. However, two more recent studies found that DCD pancrease yields were reduced by up to 100,000 IEQ when compared to DBD pancreas yields and that DCD pancrease yields were reduced by 30% when beta-cell number was calculated.

Hypothermic machine perfusion (HMP), according to recent studies, is beneficial for the preservation of DCD kidneys and livers. Six hours of oxygenated HMP with a custom-made, transportable, dual arterial perfusion system at a perfusion pressure of 25 mmHg was technically feasible and safe in a previous study conducted by our group. The splenic and superior mesenteric arteries can be separately perfused by using a dual perfusion system with two centrifugal pumps. As a result, uniform perfusion of the pancreatic tissue was earlier ensured because flow in both systems was continuously monitored and potential perfusion issues could be traced and treated if necessary. The tissue's ATP concentrations significantly increased when oxygen was added to the perfusion system; after 6 h of oxygenated HMP, we observed a 6.8-fold increase in ATP in DCD pancreases and a 2.6-fold increase in DBD pancreases [1].

In this report, we investigated whether the effects of oxygenated HMP remained in diabetic mice's pancreatic islets several days after they were isolated, culturing, and xenotransplanted. During the 6-hour oxygenated HMP period, there was no visible macroscopic or microscopic edema formation, and perfusion flow remained constant.Caspase-3 staining also showed that oxygenated HMP did not increase apoptosis levels. Different frameworks utilizing low perfusion pressures have recorded comparative discoveries of low edema and injury markers in trial HMP of pancreases that were not relocated or utilized for islet disconnection. After 12 and 24 hours, respectively, of HMP in porcine pancreases, a recent study revealed moderate and severe edema. When compared to SCS, histological examination revealed comparable results up to 12 hours of preservation. It was hypothesized in a study of the effect of 24 hours of HMP on isolated porcine islets that HMP-induced edema helped the enzymatic digestion process during isolation. In our hands, perfused pancreatic tissue digested just as well as static-preserved organs. Also, the same number of embedded islets showed that HMP did not seem to help islets separate from the exocrine tissue around them. In that regard, additional factors, such as the age of the donor and the method of enzyme perfusion, may play a larger role. The ability to isolate islets in a normal manner without the inherent risks associated with edema should be viewed as advantageous because it has long been a goal of organ preservation in all its forms to prevent the formation of edema due to its detrimental effects. HMP and SCS islets shared comparable yield, maximum purity, and average purity, according to our findings. Despite prolonged CIT, our groups' islet yields were comparable, indicating that HMP can prevent the detrimental effects of CIT once perfusion has begun. The HMP islets showed a biphasic insulin response to glucose in in vitro tests. During the course of the study, 55% of the diabetic mice's graft function remained adequate (blood glucose levels 10 mmol/L). At day 28, IPGTT revealed that the insulin peak occurred 30 minutes after the normal glucose peak. All of the mice returned to hyperglycemia after the transplant. HMP-preserved DCD islets continue to function normally after recovery in culture, as suggested by these xenotransplantation results, which corroborate the findings of in vitro studies [2].

The current study may have some drawbacks. Islet isolations were carried out in one location. Additionally, only five HMP (DCD) and five SCS (DBD) pancreases were able to be included in this study due to limited access to discarded donor pancreases. DCD pancreases could have been included in a second SCS group to account for differences in cold ischemic injury between DCD and DBD pancreases. Despite this flaw, we hypothesize that comparing our HMP results to theoretically superior DBD donors can shed light on HMP's efficiency. A randomized controlled trial comparing clinical SCS DCD pancreases to HMP DCD pancreases is required to definitively demonstrate the superiority of oxygenated HMP. This study was started to investigate the viability of postprocurement pancreas perfusion in a clinical setting as well as the biological benefits of HMP for islet isolation. Although the presented results indicate that HMP can safely extend CIT without compromising islet yield, function, or viability, the study's methodology—a period of SCS during transportation to the HMP center, followed by a period of HMP during transportation to the islet isolation facility—is challenging. Before it can be used more widely, this difficult undertaking needs to be optimized and, ideally, centralized in dedicated perfusion centers. Direct start of HMP following procurement at the donor centre, which is currently performed for all Dutch kidneys, is one approach that is hypothetically possible: short end-ischemic HMP lasting between 2 and 6 hours following SCS in the recipient hospital, or prolonged end-ischemic HMP lasting between 6 and 12 hours to postpone the isolation procedure for logistical reasons. The study's protocol could theoretically be used with any of the three methods, but because connecting the pancreas to the device requires a lot of time and is a complicated surgical procedure, it probably works best with the last two. In addition, normothermic regional perfusion and end-ischemic normothermic machine perfusion can be used in conjunction with HMP to test the viability or functionality of ECD pancreases. Normothermic local perfusion might be performed for other stomach organs, and islets have been segregated from pancreases after these techniques albeit the outcome of which has not been irrefutable so far. Before isolating the islet, normothermic machine perfusion (NMP) could be carried out following HMP for testing its viability and functionality. However, there has only been one documented case of NMP of the pancreas. Sadly, despite the fact that the endocrine system functioned normally for a brief time during NMP, the perfusion itself may have caused additional necrotic damage to the pancreas [5].

Conclusion

After performing 6 hours of oxygenated HMP, which increased the cold

ischemia time, this study demonstrates that we were able to successfully isolate functional islets from discarded human DCD pancreases.

Acknowledgement

None.

Conflict of Interest

None.

References

1. Scaglione, Steven, Stephanie Kliethermes, Guichan Cao and David Shoham, et al. "The epidemiology of cirrhosis in the United States." *J Clin Gastroenterol* 49 (2015): 690-696.
2. Cartwright, Emily J., Christopher Rentsch and David Rimland. "Hepatitis C virus screening practices and seropositivity among US veterans born during 1945–1965." *BMC Res Notes* 7 (2014): 1-5.
3. Rustgi, Vinod K., Gary L. Davis, Steven K. Herrine and Arthur J. McCullough, et al. "Future trends in hepatology: Challenges and opportunities." *Hepatology* 48 (2008): 655-661.
4. Wise, Matthew, Stephanie Bialek, Lyn Finelli and Beth P. Bell, et al. "Changing trends in hepatitis C–related mortality in the United States, 1995-2004." *Hepatology* 47 (2008): 1128-1135.
5. Mitchell, Tarissa, Gregory L. Armstrong, Dale J. Hu and Annemarie Wasley, et al. "The increasing burden of imported chronic hepatitis B—United States, 1974–2008." *PloS One* 6 (2011): e27717.

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