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Review

Continuous donor perfusion for heart preservation

Richard Kirk[a,*], Anne I. Dipchand[b,1]

[a] University of Texas Southwestern Medical Center, Dallas, USA
[b] The Hospital for Sick Children, University of Toronto, Toronto, Canada

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ABSTRACT

One of the keys to successful cardiac transplantation is preservation of the heart during explantation, transport and implantation. To date the most commonly used method has been cold static storage and this currently remains the only method available for pediatric recipients. However, there has long been interest in continuous perfusion of the donor organ during the ex vivo period to mitigate the effects of ischemia and this is now becoming a clinical reality for adult recipients with good short and early midterm results. Data to date however suggests that the greatest benefit lies in preserving marginal organs, especially those following circulatory death, or when a prolonged ischemic time can be predicted.

1. Introduction

Cold static storage (CSS) aims to reduce the ischemic-reperfusion injury (IRI) that occurs during retrieval of a donor organ by inducing asystole with cardioplegia and then cooling. These strategies reduce cell metabolism to < 10% [1] and thus minimize the effect of absent myocardial blood flow – absence of oxygen, nutrients and removal of waste product. They do not however reduce cell metabolism to zero and so the longer CSS continues, the more severe becomes the IRI, which ultimately results in primary graft dysfunction and reduced graft survival [2,3]. Continuous perfusion of the organ aims to minimize the IRI by providing nutrients, removing products of metabolism and with some techniques, adding supplemental oxygen. This has the potential benefit of reducing primary graft dysfunction and improving outcomes. Additionally, it may allow for longer ischemic times, enabling access to organs that are too far away for CSS to be used safely. Finally, it provides an opportunity to assess graft function prior to the decision to implant and may allow for therapeutic maneuvers to improve the donor organ function. This review aims to discuss the physiologic changes that lead to IRI, outline the different methods of continuous donor perfusion that are available, their clinical applicability and the potential benefits of such techniques to cardiac transplantation.

2. Review

2.1. Graft dysfunction & IRI

The effect of primary graft dysfunction (PGD) on outcomes is well known and it is the commonest cause of death within the first 30 days [3]. PGD may be the result of the donor, procurement and recipient factors [2]. It is outside the scope of this review to discuss the factors relating to donor and recipient factors however an understanding of the role procurement plays in PGD is pertinent.

All donor hearts undergo a period of warm and cold ischemia during the explant and implant process in addition to ischemic injury during transportation and reperfusion injury upon implantation. No donor organ is therefore immune from the effects of IRI however minimizing the severity of IRI is clearly important. Much work has been done on understanding the mechanism of IRI, which has been reviewed in detail and is summarized below [4,5].

With the onset of ischemia, oxygen and nutrients are depleted as cell metabolism switches from aerobic to anaerobic and the mitochondria can no longer generate adenosine triphosphate (ATP) efficiently. ATP delivers the energy required for ionic pump exchanges and myocyte contraction. The myocyte is not the only cell disrupted as endothelial cells are also compromised. The switch to anaerobic metabolism leads to a rise in lactate and acidosis. As hydrogen ions (H^+) accumulate, the sodium-hydrogen pump exchanger attempts to restore pH by extruding H^+ at the expense of drawing excess sodium (Na^+) into the cell. The excess Na^+ in turn activates the sodium-calcium pump exchanger and so intracellular calcium (Ca^{++}) also increases. The mitochondria have some protection from these cytoplasm ionic fluxes as acidosis closes the mitochondrial permeability transition pore (mPTP) preventing Ca^{++} from entering mitochondria. However anaerobic metabolism in the mitochondria and lack of ATP leads to the production of adenine nucleotide metabolites such as adenosine, inosine, hypoxanthine and

* Corresponding author at: Children's Medical Center B3440, 1935 Medical District Drive, Dallas, TX 75235, USA.
E-mail addresses: Richard.kirk@utsouthwestern.edu (R. Kirk), Anne.dipchand@sickids.ca (A.I. Dipchand).
[1] Labatt Family Heart Centre, Hospital for Sick Children, 555 University Avenue, Toronto M5G 1X8 Canada

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xanthine in addition to inorganic phosphate (Pi) and reactive oxygen species (ROS). All these metabolites are detrimental to cell integrity and are also important in the reperfusion phase.

During reperfusion, the cell receives oxygen and nutrients which leads to decreasing lactate and increased pH as aerobic metabolism returns. Unfortunately, the oxygen allows hypoxanthine and xanthine levels to increase further causing inflammation. As the pH normalizes the mPTP opens allowing the excess H^+, Na^+, Ca^{++} and water into the mitochondria. This causes yet more ROS to form, further disrupting the mitochondrial enzyme cascade and preventing ATP production. The mitochondria cannot therefore produce enough ATP to service the cell. This causes the membrane receptor, enzymes and ion channels to malfunction. This lack of membrane integrity allows an influx of fluid and brings about myocyte and endothelial cell death. The excess hypoxanthine and xanthine produced by ischemia react with oxygen and are converted to uric acid leading to inflammation in the vascular cells and edema. The lumen size is thus reduced and perfusion impaired once again.

2.2. Preservation techniques

The standard method of preserving the donor heart during transport to date has been cold static storage (CSS). The heart is arrested using cardioplegia and then cooled to reduce metabolism; however anaerobic metabolism still continues at a low level and metabolites accumulate [1]. Whilst CSS remains the current standard, considerable research has gone into finding alternatives. These include continuous myocardial perfusion (CMP) either with hypothermia (HCMP) or normothermia (NCMP). This is not a new concept; Oskar Langendorff demonstrated in 1895 a heart would continue to beat outside the body if perfused but it has taken over a century for this concept to be developed for transporting donor hearts.

CMP enables oxygen and nutrients to be supplied to the myocardium and for metabolites to be removed. The principle of the technique is to infuse the perfusate through the aortic root into the coronary arteries. In the HCMP technique the perfusate is usually crystalloid and in the NCMP technique it is leukocyte depleted blood. Whether the heart is arrested or not also depends upon which technique is utilized (Table 1). Many issues remain to be resolved – the optimal constitution of the perfusate, the pressure at which it should be infused (too much and myocardial edema occurs, too little and not enough oxygen and nutrients are delivered), whether continuous or pulsatile flow is preferable [6]. In addition to these issues manufacturing a continuous myocardial perfusion machine which is portable and simple to use remains challenging.

2.2.1. Kidney, liver and lung experience of continuous perfusion

Hypothermic machine perfusion in renal transplantation was first performed in man in 1968 and was initially used extensively until CSS became the preferred technique due to simplicity and cost effectiveness. Over the last decade however, the renal community have increasingly used extended criteria donors (marginal donors) and those from donation after circulatory death (DCD) and turned again to the use of hypothermic machine perfusion. In the US now almost 45% of renal transplants occur using this method with the predominant machine being the LifePort Kidney Transporter which is lightweight and portable allowing an organ to be perfused from time of recovery until transplantation. It is designed to travel unaccompanied by land or air, safely transporting the kidney across town or between countries. Whilst the kidney is being perfused at a temperature of 4 °C the LifePort Kidney Transporter records data on temperature, flow rate, vascular resistance and pressure every 10 s. The first trial published in man using marginal donors comparing outcomes from ex vivo normothermic perfusion (EVNP) to CSS demonstrated no difference in graft or patient survival at 12 months; however there was a significant improvement in early graft function in the EVNP cohort [7]. A recent review of continuous perfusion methods in renal transplantation has confirmed these results [8]. Organ preservation in liver transplantation continues to utilize CSS however some preliminary experience with continuous perfusion in Europe and North America is encouraging [9–11]. The use of normothermic ex vivo lung perfusion (EVLP) in lung transplantation is being extensively investigated and as in the renal field, appears to show most benefit in marginal organs. The current methodologies allow the assessment of marginal organs and by discarding those that are deemed unusable, outcomes comparable with acceptable lungs (by conventional criteria) can be achieved [12–14]. This technique would also be useful in pediatric lung transplantation but implementation has yet to be reported due to practical issues [15].

Table 1
Continuous myocardial perfusion: hypothermia vs normothermia.

	Hypothermia	Normothermia
Temperature	4–10 °C	35–37 °C
Metabolic demand	Much reduced	Reduced (↓ workload)
Oxygen added	Yes	Yes
Perfusate	Crystalloid	Leukocyte depleted donor blood
Cardiac rhythm	Arrested	Beating
Commercially available	Kidneys, liver	Kidney & heart

2.2.2. Cardiac continuous myocardial perfusion

Whilst there is active research in hypothermic CMP and indeed this was the technique utilized by Dr. Barnard in the first human heart transplant in 1967, it has yet to re-enter the clinical arena, unlike normothermic CMP which has been brought to clinical practice by Transmedics, Inc. with the Organ Care System® (OCS) which is currently the only available system on the market. It has yet to be used in the pediatric population due to the logistics of large cannula sizes. The OCS is primed using 1200–1500 ml of donor blood passed through a leukocyte filter and added to the pump reservoir together with 500 ml of a proprietary priming solution containing a variety of metabolic nutrients [16]. The donor heart is arrested by injecting cardioplegia solution into the aortic root and kept cool whilst removed from the donor and attached to the OCS. Warm, oxygenated blood is infused into the aortic root and through the coronary circulation. As it returns through the coronary sinus it flows into the right atrium (the superior and inferior origins of the vena cava are sutured closed), right ventricle and thence to the pulmonary arterial cannula and returned to the reservoir (Fig. 1). It should be noted that the heart, whilst on the OCS, is mainly volume “unloaded” as coronary flow rates are approximately 10% of a normal cardiac output. The heart can be paced if necessary, and undergo echocardiography or coronary angiography if necessary. The efficacy of the perfusion (which can be adjusted) is measured by the difference between arterial and venous lactate and the overall recovery of the heart can be assessed by a general reduction in lactate levels. On arrival at the transplant center the donor heart is again arrested, removed from the OCS and implanted. Thus the heart undergoes two periods of ischemia during the explant and implant procedure although this is less than that of CSS retrieval [16]. The first clinical trial of the OCS system (Proceed II Trial) was a multicenter, randomized non-inferiority trial comparing OCS with CSS outcomes reported in 2015 [16]. 67 patients in the OCS arm were compared to 63% in the CSS arm. There was no difference in 30 day graft survival, rejection or serious adverse cardiac events. The mean preservation time was significantly longer in the OCS group than in the CSS group (324 min vs 195 min) but the total cold ischemia time was significantly shorter in the OCS cohort compared to the CSS cohort (113 min vs 195 min). Five hearts retrieved using the OCS technique were not implanted. Four had rising lactates whilst on the OCS system and one had an aorta too friable to attach to the OCS. Intermediate outcomes have been reported from one of the participating centers (Cedar-Sinai) and demonstrated that the 2 year outcomes were the same in their 38 patients [17]. There