Effects of Antegrade and Retrograde Machine Perfusion Preservation on Cardiac Function After Transplantation in Canines

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ABSTRACT

Introduction. Most studies investigating machine perfusion preservation for heart transplantation perfuse through the aortic root (antegrade), but the coronary sinus (retrograde) is a potential option. We hypothesized that retrograde machine perfusion provides better functional protection than static storage, while avoiding the potential irregular perfusion seen when aortic insufficiency occurs with antegrade perfusion.

Materials and Methods. Eighteen canine donor hearts were arrested, procured, and stored in modified Celsior solution for 4 hours by using either static storage at 0°C to 4°C (n = 6) or machine perfusion preservation at 5°C via the aortic root (antegrade, n = 6) or coronary sinus (retrograde, n = 6). Lactate and myocardial oxygen consumption were measured in perfused hearts. Hearts were reimplanted and reperfused for 6 hours with hourly function calculated by using the preload recruitable stroke work (PRSW) relation. Myocardial water content was determined at the end of the experiment.

Results. Storage lactate levels and myocardial oxygen consumption were comparable in both perfused groups. The PRSW was increased immediately after bypass in the antegrade group (120.6 ± 19.1 mm Hg) compared with the retrograde (75.0 ± 11.3 mm Hg) and static (78.1 ± 10.5 mm Hg) storage groups ($P < .05$). At the end of reperfusion, PRSW was higher in the retrograde group (69.8 ± 7.4 mm Hg) compared with the antegrade (40.1 ± 6.8 mm Hg) and static (39.9 ± 10.9 mm Hg) storage groups ($P < .05$). Myocardial water content was similar among groups.

Conclusions. Both antegrade and retrograde perfusion demonstrated excellent functional preservation, at least equivalent to static storage. Initial function was superior in the antegrade group, but the retrograde hearts displayed better function late after reperfusion. Neither perfused group developed significant edema. Machine perfusion preservation is a promising technique for improving results of cardiac transplantation.

MACHINE perfusion for the preservation of donor organs has already been established clinically as superior for early graft function and long-term graft survival in kidney transplantation compared with static cold storage [1,2]. This method has also been evaluated for >50 years for cardiac transplantation [3] but has not yet been applied to clinical practice. The current standard remains hypothermic static storage, which limits safe ischemic times to <6 hours. However, review of registry data suggests that although results are acceptable at ischemic times up to 6 hours, there is an increase in the relative risk of recipient mortality, both 1-year and long-term, when the ischemic times are extended beyond 3 to 4 hours [4]. The potential benefits of machine perfusion preservation in cardiac transplantation include improved immediate and long-term graft function, tolerance of longer ischemic times, better donor–recipient matching, resuscitation of injured or circulatory death hearts, and improved results

The perfusion device prototype, LifeCradle, was provided by Organ Transport Systems Inc, Frisco, Texas. The only support received for this study was for this prototype perfusion device.

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from extended criteria donors. Studies in small- and large-animal models in our laboratory and by others for both short- and long-term preservation have shown improved functional results, higher ATP stores, and improved lactate-to-alanine ratios in the cardiac tissue with cold machine perfusion preservation compared with static storage [5–7].

Most studies examining machine perfusion preservation for hearts use antegrade perfusion through the coronary arteries via the aortic root. Although this technique has been shown in previous studies to be superior to standard cold storage [6,7], there is the potential for aortic valve incompetence, resulting in inconsistent perfusion and nonnutrient flow [8]. Under hypothermic conditions, at standard ischemic intervals, the heart would essentially undergo static cold storage; however, for longer ischemic times, normothermic perfusion, and procurement of extended criteria hearts, nonnutrient flow could have significant implications for graft function. We previously demonstrated that the use of an initially high loading flow rate, followed by normal flow rates of perfusion solution, may result in better apposition of the aortic valve leaflets and potentially avoid this problem [8]. However, it is difficult to assess and verify adequate leaflet closure during machine perfusion. In addition, unlike the controlled, stable laboratory setting, during transport of donor hearts, intermittent distraction of the aortic valve leaflets could occur, resulting in inadequate perfusion.

A potential alternative to antegrade perfusion is retrograde perfusion through the coronary venous system via a catheter inserted in the coronary sinus. Retrograde cardioplegia is already frequently used during cardiac surgery for myocardial protection [9–11]. Using this technique, the issue of aortic valve incompetence, especially in relation to potential movement during transport, would be avoided. An additional benefit to this technique is that the heart could continue to be perfused with oxygenated blood cardioplegia during implantation, essentially eliminating the warm ischemic interval [12–14]. One concern with retrograde perfusion is decreased perfusion to certain regions of the heart, especially the right ventricle [15,16]. We previously reported some decrease in the perfusion of the right ventricle; however, the implications of this finding on reperfusion graft function have not been completely investigated [17].

The purpose of the present study was to compare hypothermic retrograde machine perfusion with both hypothermic antegrade machine perfusion and conventional hypothermic static storage over a clinically relevant ischemic interval in a large animal model. We hypothesized that retrograde machine perfusion would provide better functional protection at standard storage intervals than static storage, while avoiding the potential irregular perfusion seen when aortic insufficiency occurs with antegrade perfusion.

MATERIALS AND METHODS

Experimental Protocol

The protocol used in this study was approved by the Institutional Animal Care and Use Committee at the University of Texas Southwestern Medical Center. All animals were treated in accordance with guidelines set forth in the Guide for the Care and Use of Laboratory Animals (National Institutes of Health Publication No. 86-23, revised 1996).

Thirty-six adult mongrel dogs between 24 and 39 kg were used, divided into 18 donor–recipient pairs. The first 12 pairs were part of a previously published study comparing hypothermic static preservation versus hypothermic antegrade perfusion preservation using a perfusion device (LifeCradle, Organ Transport Systems Inc, Frisco, Tex, United States) [7]. The functional data from these experiments were reanalyzed by using updated software and improved filtering techniques for use in this study. For further comparison, 6 additional pairs were then subjected to hypothermic retrograde perfusion preservation using the same device with an adaptable coronary sinus catheter (Medtronic, Inc, Minneapolis, Minn, United States) and using the same perfusion solution. The functional data from these animals were analyzed by using the same updated techniques.

All hearts were stored for 4 hours, then reimplanted into recipient animals and reperfused for 6 hours. Celsior organ preservation solution (Genzyme Corporation, Cambridge, Mass, United States) supplemented with 1 g/L (5.5 mmol/L) of glucose was used in all the storage techniques.

Anesthetic Protocol

The animals were premedicated with atropine (0.07 mg/kg intramuscularly) and Telazol (tiletamine/zolazepam) (4.4 mg/kg intramuscularly) and then intubated and ventilated with 100% oxygen at a rate of 10/min, a tidal volume of 10 mL/kg, and positive end-expiratory pressure of 5 cm H_2O. Isoflurane at 1% to 4% was used to maintain anesthesia. Electrocardiograms and arterial pressure were continuously monitored. Arterial blood gas measurements were obtained and used to adjust the ventilator settings to maintain a pH of 7.35 to 7.45, partial pressure of carbon dioxide of 35 to 45 mm Hg, and oxygen saturation >95%.

Donor Protocol

After induction of anesthesia, a sternotomy was performed and the heart exposed. Each animal was given intravenous heparin (300 U/kg), and a cardioplegia catheter was inserted into the ascending aorta. The hearts were instrumented with a left ventricular (LV) pressure catheter and sonomicrometry crystals, and baseline cardiac function was measured. After application of an aortic cross-clamp, the heart was arrested with 1 L of cold modified Celsior solution, and the donor cardiectomy was completed.

Donor hearts randomized to static preservation were stored in an ice chest, in a container of 1 L of modified Celsior. Donor hearts randomized to antegrade perfusion preservation were attached to the perfusion device by a connector in the ascending aorta. This provided continuous antegrade flow of oxygenated, modified Celsior solution at a flow rate of 10 mL/100 g myocardium/minute at a temperature of $5 \pm 2^{\circ}C$. For the antegrade perfusion group, a small polyethylene catheter was secured in the coronary sinus to allow for serial measurements of oxygen tension, lactate, and pH. Donor hearts in the retrograde perfusion preservation group were attached to the perfusion device with a catheter in the coronary sinus. In this group, the polyethylene catheter used for serial measurements was placed in the aortic root to capture coronary effluent.

Recipient Protocol

Each recipient was placed on cardiopulmonary bypass (CPB) after induction of anesthesia and sternotomy. Excision of the heart was