Artificial Intelligence-Assisted Strain Echocardiography in an Ex Vivo Heart

Matthew D. Johnson, MD,* Karen G. Zimmerman, BS, ACS,† Takahiro Nakashima, MD,* Kristopher A. Urrea, BA,* Alvaro Rojas-Pena, MD,* Robert H. Bartlett, MD,* and Daniel H. Drake, MD‡

*Department of Surgery, University of Michigan Medical School, Ann Arbor, Michigan
†Department of Cardiology, Henry Ford Health System, Detroit, Michigan
‡Department of Cardiac Surgery, University of Michigan Medical School, Ann Arbor, Michigan

Corresponding Author:
Daniel H. Drake, M.D.
Department of Cardiac Surgery
Michigan Medicine
1150 W. Medical Center Drive
B560 MSRBII/SPC 5686
Ann Arbor, MI 48109
Phone 231-590-1700
Fax 231-941-4321
dhdrake@med.umich.edu

Supplementary Table of Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Title Page</td>
<td>1</td>
</tr>
<tr>
<td>Table of Contents</td>
<td>1</td>
</tr>
<tr>
<td>Clinical Context, Ethical Issues, and Legal Concerns</td>
<td>2</td>
</tr>
<tr>
<td>Surgical Procedure</td>
<td>2</td>
</tr>
<tr>
<td>Cannulation Technique</td>
<td>2</td>
</tr>
<tr>
<td>Ex Vivo Heart Perfusion Circuit</td>
<td>2</td>
</tr>
<tr>
<td>Non-working Mode and Transition to Working Mode</td>
<td>3</td>
</tr>
<tr>
<td>Echocardiographic assessment including Figure S1</td>
<td>3</td>
</tr>
<tr>
<td>Experimental Course including Figures S2 and S3</td>
<td>4</td>
</tr>
<tr>
<td>Supplementary References</td>
<td>5</td>
</tr>
</tbody>
</table>
Clinical Context, Ethical Issues, and Legal Concerns

All declared brain dead (DBD) donor hearts require echocardiographic evaluation while the heart is still in the donor. Because cardiac hemodynamic function is known immediately prior to explantation, direct procurement using hypothermic preservation and transplantation within 4-6 hours achieves excellent short- and long-term results. In contrast, declared circulatory death (DCD) donor hearts must go through the dying process and a mandatory stand-off period of 5 minutes in full cardiac arrest. Therefore, cardiac function is not known immediately prior to direct procurement. There are three options for evaluation of cardiac function following arrest in the DCD donor heart.\(^1\) The first is direct procurement, hypothermic preservation, and implantation into the recipient. This means that the first assessment of cardiac function following DCD occurs after the donor heart is already in the recipient. Because of the uncertainty of myocardial viability following the dying process and cardiac arrest, very restrictive criteria are imposed on the DCD donor. Consequently, the vast majority of DCD donors do not qualify and their hearts are discarded. The second option is resuscitation of the heart while it is still in the DCD donor using normothermic regional perfusion. This practice introduces major ethical and legal concerns. For instance, if the donor is declared dead as a result of irreversible circulatory cessation (DCD), then it should not be possible to resuscitate the donor heart circulatory system following declaration of death. The final option is to resuscitate and evaluate the DCD donor heart ex vivo. This avoids the controversies surrounding resuscitating the heart while in the donor and transplanting a potentially dead heart. For these reasons and the fact that the vast majority of potential donors are DCD, ex vivo hemodynamic and echocardiographic evaluations of DCD donor hearts are ideal and hold great potential for significantly expanding the current heart donor pool.

Surgical Procedure

Details of this procedure and perfusion circuit have been previously described.\(^2\) Endotracheal intubation was performed following the induction of general anesthesia. The neck, chest abdomen and groin were prepped and draped steriley. Vascular access was obtained via the femoral vessels. Intravenous antibiotics and lidocaine 1 mg/kg were administered intravenously prior to a midline sternotomy. Following median sternotomy, the extrapericardial great vessels were isolated and loosely encircled with ligatures. Heparin was used to achieve an activated clotting time >450 seconds. Following documentation of anticoagulation, the left subclavian artery was ligated distally, the superior and inferior vena cava were ligated, the mid descending thoracic aorta was cross-clamped, and the left heart was decompressed by transecting the right inferior pulmonary vein. Careful attention was paid to preserve adequate length of the pulmonary vein for future cannulation. The distal aortic arch vessels were ligated and cold del Nido cardioplegia (CAPS Inc., Detroit, MI) 50 mL/kg was infused through a temporary 18g IV catheter placed in the proximal innominate artery. Concurrently topical sterile iced saline was applied topically. Following cardioplegia administration, the heart was excised with the pericardium intact and placed in an ice bath in preparation for cannula placement. Cold ischemia time was 40 minutes.

Cannulation Technique

The reader is reminded that porcine aortic arch anatomy differs from human. The branch vessels from the aortic arch are typically the innominate and left subclavian. The innominate gives rise to both carotids and the right subclavian artery. A 14-Fr DLP arterial cannula (Medtronic Inc, Dublin, Ireland) was secured within the right inferior pulmonary vein for left heart perfusion in the working heart mode. An 18-Fr DLP venous drainage cannula (Medtronic) was placed in the pulmonary artery. A \(\frac{1}{4}\) x \(\frac{1}{4}\) inch connector with Luer Lock (Medtronic) was secured to proximal descending aorta to initially provide coronary perfusion in beating but non-working mode. The innominate artery was cannulated with a pressure valve that limited systolic pressure 80 mmHg and maintained diastolic coronary perfusion in the working heart mode. A pressure monitoring catheter was introduced through the left subclavian artery and advanced into the ascending aorta.

Ex Vivo Heart Perfusion Circuit

The perfusion circuit has previously been described and illustrated.\(^2,3\) Briefly, it consisted of commercially available components including a reservoir (Terumo, Ann Arbor, MI), a FX05 Baby Capiox Oxygenator (Terumo CVS, Ann Arbor, MI), and roller pump (Stockert, Munich, Germany). The perfusate was platelet- and leukocyte-reduced porcine blood with hemoglobin (Hb) concentration >8 g/dL. Electrolyte and other
metabolic abnormalities were corrected to maintain normal physiological ranges during cardiac perfusion. The priming volume was approximately 300 mL.

**Non-working Mode and Transition to Working Mode**

Heart reperfusion and rewarming were initiated in the non-working heart recovery mode (Figure 1A). Aortic blood flows were slowly increased and adjusted to maintain coronary blood flow at 1.0 mL/min/gram of cardiac tissue, concordant with physiologic coronary blood flow. Perfusate temperature was maintained at 37°C. The sweep gas (50% O₂, 45% N₂, 5% CO₂) was adjusted to maintain pCO₂ 40 ± 5 mmHg. The ECG leads were sewn to the surface of the pericardium in the non-working mode. Following recovery from hypothermic arrest and documentation of a stable rhythm, meticulous de-airing of the left heart was performed. The perfusion circuit was then transitioned into working mode (Figure 1B). Left atrial inflow is initiated and, as soon as the heart begins to eject, retrograde aortic inflow is discontinued while maintaining relatively stable mean aortic pressure. Inflow is increased to achieve left atrial filling pressures within a normal range while fine tuning aortic pressures and cardiac output to insure physiologic coronary perfusion. Myocardial perfusion is further adjusted by continuous monitoring of coronary venous saturation (pulmonary artery catheter) to optimize myocardial oxygen consumption. All pressures are monitored and recorded during this process. The transition from non-working mode to working mode is summarized in Video 2.

**Echocardiographic assessment**

Infection becomes a major issue in open circuit NEVHP and contributes to cardiac decline after 24 hours. Hatami and associates have clearly shown that positioning of the heart affects function. Sterility, cardiac function, and imaging are optimized when the heart is contained within a closed sterile circuit and immersed in a fluid filled sack similar to the in vivo milieu of the pericardium.

Extensive testing was carried out on both rigid and flexible saline containment systems for allowing echocardiographic evaluation of the ex vivo hearts. Numerous factors were considered such as acoustic translucency, unrestricted viewing access, container dimensions, and sufficient wall compliance to allow angulation of the probe but adequate stiffness to prevent the probe from encroaching on the heart. The latter is important for protection of the ex vivo heart.

**Supplementary Figure S1.** A) The ex vivo suspension system was configured to allow initial suspension of the heart with subsequent immersion for imaging. The heart and perfusion tubing were suspended from the top acrylic ring and the immersion container was brought up from the bottom for imaging. Numerous containers were evaluated. B) The example shown demonstrates excellent acoustic translucency but the thin plastic wall was too compliant to provide adequate contact with the probe without encroachment on the heart. C) The optimal immersion container appeared to be a modified 1 liter flexible IV fluid administration container. The wall was reasonably acoustically translucent and thick enough to minimize encroachment.
Following conversion to working mode, the heart was immersed into a warm saline bath to allow echocardiographic evaluation (Epic 7 system with AutoStrain software and X5-1: Philips, Amsterdam, Netherlands). Ex-vivo imaging was challenging as the typical external anatomic landmarks and cardiac stability provided by mediastinal structures were absent. Care must always be taken to avoid compression of probe against the ex vivo heart as ventricular fibrillation is easily induced. Imaging was necessarily limited to avoid disruption of cardiac function or induce arrhythmias and optimize NEVHP survival. The echocardiographic results are demonstrated in Figure 2 and Video 3.

**Experimental Course**

Per protocol, total perfusate exchange was performed after 1 hour on circuit. Hemofiltration was initiated following the exchange (Supplementary Figure S2).

**Supplementary Figure S2.** The experimental timeline is illustrated. EVHP, ex vivo heart perfusion; CIT, cold ischemic time. Reproduced with permission Tchouta L, Drake D, Hoenerhoff M, Rojas-Pena A, Haft J, Owens G et al. Twenty-four-hour normothermic perfusion of isolated ex vivo hearts using plasma exchange. *J Thorac Cardiovasc Surg.* 2022;164(1):128-38.

The heart was continuously maintained in the working mode for 12 hours. New onset ventricular fibrillation occurred at 13 hours. The heart was rapidly transitioned to non-working mode, 500 mg of magnesium was administered, and cardioversion with 6J resulted in sinus rhythm on the first attempt. Despite continuing perfusion in the non-working mode, lactate levels increased substantially (Supplementary Figure S3).
**Supplementary Figure S3.** Perfusate lactate levels are demonstrated as a function of time on the NEVHP circuit. Lactate levels were measured hourly at the inlet and outlet of the hemofilter. The solid line depicts the mean values and error bars reflect the inlet and outlet values respectively.

At hour 19 an attempt was made to return to working mode. Ventricular fibrillation recurred and the heart was again quickly transitioned to non-working mode. Cardioversion at 3J resulted in sinus bradycardia. The heart was atioventricularly paced at 100bpm. Atrial function was observed to be poor. The experiment met termination criteria at hour 23 based on perfusate lactate levels. Necropsy confirmed appropriate cannula placement.

**Supplementary material references**