Description of a Novel Set-up for Functional Echocardiographic Assessment of Left Ventricular Performance During Ex Vivo Heart Perfusion

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A new set-up for functional echocardiographic assessment of left ventricular performance during ex vivo heart perfusion

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GMR: Performed all studies, collected and analyzed all experimental data. Participated in creating the outline, wrote the first draft of the manuscript and subsequent revised versions.

JQH: Designed and produced the image acquisition setup and helped with data collection. He also reviewed the final manuscript.

EP: Performed statistical analysis and reviewed the final manuscript

AM, RVPR, LX and MB: Reviewed the final manuscript

FB and BT: provided quality control for data analysis and reviewed the final manuscript

MM: Conceived this study and the experimental setup, supervised experimental measurements and data collection. Created the outline, reviewed the data quality and analysis and edited the original manuscript.

Abstract

Ex-vivo heart perfusion (EVHP) is a new technology aimed at decreasing cold ischemia time and evaluate cardiac function before transplant. In an experimental EVHP swine model, we tested a custom-made setup to perform surface echocardiography on an isolated beating heart during left ventricular loading. The views obtained at any time point were comparable with corresponding standard transesophageal and transthoracic for all measurements. Echocardiographic measurements were compared with those derived from invasive pressure-volume (P-V) loops catheters. The absolute values recorded with the P-V loop catheter were lower despite a comparable trend.

Introduction

Heart transplantation remains the definitive therapeutic option to improve survival and quality of life in patients with end-stage heart failure. However, organs availability is still its main limiting factor. Despite a good long term outcome with an overall survival rate of 50% at ten years, early graft failure (EGF) after heart transplant still accounts for 31-42% of mortality in the first 30 days after transplantation(1). The current standard method for heart preservation is cold storage to minimize, yet not eliminate, anaerobic metabolism. While it allows organ transportation, still invariably results in a time-dependent degree of organ damage that may play a key role in EGF (2). Ex Vivo Heart Perfusion (EVHP) (3,4) is an emerging alternative strategy for prolonged and better heart preservation. Commercially available EVHP systems provide normothermic oxygenated perfusion to a beating heart from the time of retrieval to its transplantation. Maintenance of persistent aerobic metabolism during transport also allows a functional evaluation, and potentially recovery of marginal organs thus expand the donor pool. (5) The available platform relies on venous lactate concentration as an indicator of myocardial performance (3,4) as direct assessment of myocardial contractility would require ventricular loading, which is not currently available.

Echocardiography has become the standard tool for non-invasive assessment of heart function in clinical practice. It is used for the assessment of potential heart donors, for the intra-operative evaluation of cardiac function post reperfusion in the heart recipients and for long-term heart transplant recipients follow-up. This makes it an ideal tool to assess cardiac function during EVHP. Several groups have reported the use of echocardiography during EVHP (6,7), but a standardized echocardiographic setup in this unique setting is currently lacking. In fact, the isolated heart poses a number of technical challenges. For echocardiographic assessment during EVHP, the heart chambers must be progressively loaded. The probe must have access to the heart from different angles in order to obtain echocardiographic views comparable to the standard ones, while maintaining sterility and minimizing heart manipulation. A support system is necessary to maintain contact between the probe and the heart, and to obtain a stable echocardiographic plane of cut with minimal external compression. Finally, transition between views should be easy and allow an efficient scanning workflow.

To fulfill these requirements, we built a custom-made setup to allow the execution of epicardial echocardiographic examination during a porcine experimental EVHP model with left ventricular loading. The primary objective of our study was to assess the system's feasibility in acquiring echocardiographic views comparable to standard transesophageal (TEE) and transthoracic (TTE) for the assessment of LV function. The secondary objective was to compare the echocardiographic measurements of LV function with those derived from invasive pressure-volume (PV) conductance catheters. (8)

Methods

After Institutional Ethics Board approval, we conducted 6 experiments on male Yorkshire swines (53±5 Kg). All animals received humane care in compliance with the Canadian Council on Animal Care guidelines. This manuscript adheres to the ARRIVE guidelines.

In all animals, general anesthesia was inducted with intramuscular injection of 30 mg/Kg Ketamine and maintained with 2% inspiratory fraction of Isoflurane. Standard anesthesia monitoring included: electrocardiogram, pulse-oximetry and non-invasive blood pressure. After midline sternotomy, a comprehensive baseline epicardial echocardiographic examination was performed using a 3D TEE probe (Z6Ms Siemens, Acuson SC2000, Siemens, Mountainview, CA, USA). After administration of 1000 mL of Celsior cardioplegic solution in the aortic root, the hearts were excised and the animals sacrificed after exsanguination for pump priming. Each heart was then rested in ice for 60 minutes of cold ischemia. During this period, aorta, pulmonary artery and left atrium were cannulated, the inferior and superior vena cava were oversawn. The hearts were then placed on the EVHP circuit on a Langendorff mode (LM) for four hours with retrograde oxygenated blood perfusion into the ascending aorta and venous drainage from the pulmonary artery. During LM the ventricles were left unloaded. At the first and fourth hour of EVHP perfusion, working mode (9) was established by progressively loading the left atrium (LA) to a pressure of 12 mmHg while maintaining anterograde flow into the ascending aorta at a pressure above 90 mmHg. The right ventricle was not loaded in this protocol and therefore its function not assessed.

A custom-made and 3D printed system was developed to support the cannulas and the TEE probe while maintaining the heart in an orientation mimicking the in vivo anatomical relationship between heart and esophagus (Fig. 1 A). The system was designed using a parametric 3D computer aided design software (FreeCAD v.0.16) and fabricated with a fused deposition modelling (FDM)

Lultzbolt TAZ 6 3D printer (Aleph objects Inc. Loveland CO, USA) using a thermoplastic elastomer. It consisted of 3 parts: a bucket-like cubic holder with a curved posterior wall that was anteriorly open; a flexible probe track fitted in the middle of the posterior wall; a cannulas support with four grooves and fastening system for each EVHP cannula at the top of the holder. A custom-made spacer was designed and 3D printed with a flexible thermoplastic elastomer fitted to the 3D TEE probe tip. A standard sterile plastic ultrasound probe cover was positioned around the spacer, unrolled to the probe handle and was filled with warm saline solution. The echocardiographic scanning protocol included: two trans-gastric (LV short and long axis: Fig. 1E) and three apical views (four and two chambers and LV 3D volume) comparable to standard TTE and TEE images (Fig. 1 B-C-D). To move between trans-gastric and apical views, the transducer was advanced along the track behind the heart from mid papillary level to the LV apex and anteflexed. Echocardiographic functional assessment was performed during WM at one and four hours of EVHP and LV systolic function was quantified by measuring ejection fraction (EF) on 2D and 3D images using Simpson Biplane method of the Disks (MOD).

A SPC-571 conductance catheter (Millar Inc, Houston, TX, USA) was inserted through the LV apex after placing a purse string on a tourniquet and PV loops acquired in vivo and during WM. Echocardiographic measurements of LV function using 2D and 3D methods were compared with PV loop.

Continuous variables data are reported as mean and standard deviation (SD). Agreement between 2D end 3D methods for measuring EF was assessed with Bland-Altman plot (JM Bland and DG Altman, 1986) and T test for paired measures was used for evaluating mean difference between methods (by using Stata 13, StatCorp). A p-value < 0.05 indicates statistical significance.

Results

For all experiments and at all timing (in vivo, 1 and 4 hours after EVHP), we were able to obtain all of the five LV views. The images were reliably obtained by two different operators (MM and GMR). The Bland-Altman plot showed a 6.2% mean difference in estimating EF (95% confidence interval 1-11.3) between 2D and 3D method with two separate clusters, for low and high average values of 2D and 3D measures (between -14.6% and 0% EF and between 0% and 26.9% EF, respectively).

A significant decrease in the LV systolic function was observed over time regardless of the method used to quantify the EF (Tab. 1). Although the absolute values recorded with the PV loop catheter were lower compared to 2D and 3D echocardiography, these two methods did not show significant difference between them except for evaluation performed 1 hour after the beginning of EVHP.

Discussion

Our report showed the feasibility of echocardiographic assessment of LV function during EVHP using a custom-made 3D printed system. The echo-probe was left in place during WM and allowed continuous LV visualization during the experiments. The system's modular design allows for replacement or re-deign of single parts as necessary. The TEE probe can be manipulated to complete the scanning protocol without affecting the position and movements of the heart and without interfering with access to the organ by the surgical team. The views acquired were comparable with their corresponding standard TEE and TTE ones (10,11) and the imaging quality adequate for functional LV assessment. The good agreement between measurements obtained with 2D and 3D echocardiography, suggests that the echocardiographic methods may be considered a reliable way for estimating EF. The differences found in comparison with invasive conductance catheter as a gold standard (8), despite a similar trend, highlight the need of further studies to confirm these preliminary results and better understand the agreement between echocardiographic to the PV loop measurements in the EVHP setting.

References

1. Lund LH, Edwards LB, Dipchand AI, Goldfarb S, Kucheryavaya AY, Levvey BJ, Meiser B, Rossano JW, Yusen RD, Stehlik J, International Society for H, Lung T. The Registry of the International Society for Heart and Lung Transplantation: Thirty-third Adult Heart Transplantation Report-2016; Focus Theme: Primary Diagnostic Indications for Transplant. J Heart Lung Transplant 2016;35:1158-69.
2. Collins MJ, Moainie SL, Griffith BP, Poston RS. Preserving and evaluating hearts with ex vivo machine perfusion: an avenue to improve early graft performance and expand the donor pool. Eur J Cardiothorac Surg 2008;34:318-25.
3. Ardehali A, Esmailian F, Deng M, Soltesz E, Hsich E, Naka Y, Mancini D, Camacho M, Zucker M, Leprince P, Padera R, Kobashigawa J. Ex-vivo perfusion of donor hearts for human heart transplantation (PROCEED II): a prospective, open-label, multicentre, randomised non-inferiority trial. The Lancet 2015;385:2577-84.
4. Ardehali A, Esmailian F, Deng M, Soltesz E, Hsich E, Naka Y, Mancini D, Camacho M, Zucker M, Leprince P, Padera R, Kobashigawa J, investigators PIt. Ex-vivo perfusion of donor hearts for human heart transplantation (PROCEED II): a prospective, open-label, multicentre, randomised non-inferiority trial. Lancet 2015;385:2577-84.
5. Colah S, Freed DH, Mundt P, Germscheid S, White P, Ali A, Tian G, Large S, Falter F. Ex vivo perfusion of the swine heart as a method for pre-transplant assessment. Perfusion 2012;27:408-13.
6. Lowalekar SK, Cao H, Lu XG, Treanor PR, Thatte HS. Subnormothermic preservation in somah: a novel approach for enhanced functional resuscitation of donor hearts for transplant. Am J Transplant 2014;14:2253-62.

7. Abicht JM, Mayr TA, Jauch J, Guethoff S, Buchholz S, Reichart B, Bauer A. Large-Animal Biventricular Working Heart Perfusion System with Low Priming Volume-Comparison between in vivo and ex vivo Cardiac Function. Thorac Cardiovasc Surg 2016.

8. Burkhoff D, Mirsky I, Suga H. Assessment of systolic and diastolic ventricular properties via pressure-volume analysis: a guide for clinical, translational, and basic researchers. Am J Physiol Heart Circ Physiol 2005;289:H501-12.

9. Kohn MA, Carpenter CR, Newman TB. Understanding the direction of bias in studies of diagnostic test accuracy. Acad Emerg Med 2013;20:1194-206.

10. Hahn RT, Abraham T, Adams MS, Bruce CJ, Glas KE, Lang RM, Reeves ST, Shanewise JS, Siu SC, Stewart W, Picard MH. Guidelines for performing a comprehensive transesophageal echocardiographic examination: recommendations from the American Society of Echocardiography and the Society of Cardiovascular Anesthesiologists. J Am Soc Echocardiogr 2013;26:921-64.

11. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2015;16:233-70.

Figure Legend

Figure 1

The custom made setup for surface echocardiography during ex vivo heart perfusion (A). It allows short axis (at mid papillary muscle level) (D) and long axis (2D and 3D) (at the apical level) views of the left ventricle.

Table Legend

Table 1

Mean Ejection fraction (EF) estimated by PV loop catheter and 2D and 3D echocardiographic methods in vivo and after 1 and 4 hours of ex vivo heart perfusion. Comparison was performed using t test for paired data: #$p>0.05$ between 2D and 3D EF estimates; * $p<0.05$ between 2D and 3D EF estimates