Transplantation of a Beating Heart: A First in Human

Yin Shengli,‡, Rong Jian,‡, Chen Yinghua, Cao Lu, Liu Yunqi, Mo Shaoyan, Li Hanzhao, Jiang Nan, Xiong Mai, Shi Han, Wang Tielong, Shi Yongxu, Zhu Yanlin, Liang Mengya, Xiong Wei, Chen Yili, Xu Guixing, Chen Xiaoxiang, Chen Xiaojun, Yin Meixian, Tang Baiyun, Gong Fengqiu, Huang Wenqi, Dong Yugang, Björn Nashan, Stefan G Tullius, Guo Zhiyong, Wu Zhongkai, He Xiaoshun

1Department of Cardiac Surgery, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou 510080, China
2Department of Extracorporeal Circulation, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou 510080, China
3Organ Transplant Center, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou 510080, China
4Guangdong Provincial International Cooperation Base of Science and Technology (Organ Transplantation), Guangzhou 510080, China
5Guangdong Provincial Key Laboratory of Organ Donation and Transplant Immunology, Guangzhou 510080, China
6Department of Anesthesiology, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou 510080, China
7Department of Cardiology, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou 510080, China
8Department of Neurosurgery, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou 510080, China
9Operating Room and Anesthesia Center, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou 510080, China
10Cardiac Surgery Intensive Care Unit, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou 510080, China
11Organ Transplantation Center, The First Affiliated Hospital of the University of Science and Technology of China, Hefei 230001, China
12Division of Transplant Surgery, Brigham and Women's Hospital, Harvard Medical School,
Boston, MA, USA

†The first three authors contributed equally to this work and should be considered as co-first authors

*Corresponding authors:
He Xiaoshun, Organ Transplant Center, The First Affiliated Hospital, Sun Yat-sen University, NO.58 Zhongshan Er Road, Guangzhou 510080, China; E-mail: gdtrc@163.com

Wu Zhongkai, Department of Cardiac Surgery, The First Affiliated Hospital, Sun Yat-sen University, NO.58 Zhongshan Er Road, Guangzhou 510080, China; E-mail: wuzhk@mail.sysu.edu.cn

Guo Zhiyong, Organ Transplant Center, The First Affiliated Hospital, Sun Yat-sen University, NO.58 Zhongshan Er Road, Guangzhou 510080, China; E-mail: rockyucsf1981@126.com
SUMMARY

Ischemia and reperfusion injury (IRI), an inevitable component in organ transplantation, contributes to inferior graft survival, compromised organ quality and limitations in organ availability. The heart is most vulnerable to IRI and tolerated ischemic times are very short. We present an entire novel heart transplant procedure during which the donor heart was continuously perfused, oxygenated at normothermia and transplanted while beating. The dynamic electrocardiogram and echocardiogram indicated an absence of ischemic injury and excellent function of the donor heart during the entire procedure. This ischemia-free beating heart transplantation (IFBHT) avoids graft IRI. The approach has thus the potential to improve transplant outcome while improving organ utilization.
Heart transplantation is the gold standard treatment for patients with end-stage heart failure\textsuperscript{1}. Organ shortage is the limiting factor to apply the procedure to all in need and waitlisted patients are frequently complex\textsuperscript{2,3,4}. In the current practice, all heart transplants will experience a period of ischemia during procurement, preservation and implantation\textsuperscript{5}. Ischemia and reperfusion Injury (IRI) is a well-known significant risk factor for primary graft dysfunction, thus contributing to early graft loss, the most frequent cause of death within the first month post-heart transplantation\textsuperscript{6}. Donor hearts with an ischemic time over 6 hours are considered marginal and frequently discarded. Furthermore, IRI is one of the three leading causes for cardiac allograft vasculopathy (CAV) accounting for an estimated one in eight deaths in heart transplant recipients surviving the first year\textsuperscript{7}. According to the 2019 International Society for Heart and Lung Transplantation (ISHLT) registry data report, the 1-, 5- and 10-year prevalence of CAV are 8%, 29% and 47%, respectively\textsuperscript{8}.

To ameliorate the consequences of ischemia, efforts have been made in developing protection and preservation methods. The normothermic machine perfusion (NMP) technique has been applied clinically\textsuperscript{9}. This approach allows preservation and transportation of a beating, normothermic, oxygenated, and perfused heart and has the capacity to ameliorate the consequences of IRI. Nevertheless, this approach still entails a period of ischemia during the procurement of the heart after cold cardioplegic arrest and while being implanted under hypothermic and hypoxic conditions. In this scenario, the donor heart might even suffer a “double-hit” of IRI, limiting the potential of NMP.

We have taken an entirely novel approach avoiding ischemia during heart transplantation and have developed an ischemia-free beating heart transplantation (IFBHT) procedure. This approach is based on extensive pre-clinical work in large animals. Herein we present the first IFBHT in man.

**CASE REPORT**

A 67-year-old male patient, presented with chest tightness and shortness of breath for 4 months. The echocardiogram (ECHO) study showed enlargement of the left and right atrium, and the left ventricle, with a left ventricle ejection fraction (LVEF) of 27%, and a pulmonary artery systolic pressure (PASP) of 56 mmHg. The contrast enhanced cardiac magnetic
resonance (MR) study showed enlargement of the heart with extensive myocardial fibrosis; based on morphological changes together with a LVEF of 16%, the patient was diagnosed with a non-ischemic dilated cardiomyopathy. Therefore, the patient was listed for a heart transplant. Preoperatively, the patient needed to undergo a surgical placement of an intra-aortic balloon pump (IABP) through the femoral artery. The patient was also receiving non-invasive ventilation for respiratory support.

On June 26th, 2021, a donor heart from our hospital was allocated to this patient through the China Organ Transplant Response System (COTRS). The donor was a 29-year-old man who died of a head trauma. Brain death was confirmed after intensive care treatment for 10 days. There was no history of cardiopulmonary resuscitation prior to organ donation. The pre-procurement creatine kinase MB (CK-MB) isoenzyme, and cardiac troponin I (cTnI) were 56 unit per liter and 0.012 ng per milliliter. The electrocardiogram (ECG) findings were within normal range. An ECHO could not been done due to the presence of pneumomediastinum. The family members of the donor provided informed consent of donating the heart, liver and two kidneys. Therefore, the liver and kidneys were also procured and transplanted, while the lungs and pancreas were not procured.

During organ procurement, the donor was managed according to international standards. Additional monitoring included a transesophageal echocardiography (TEE), revealing a PASP of 49 mmHg and LVEF of 70%. Around 600 ml of donor blood were collected and passed through a leucocyte filter in preparation of the machine perfusion perfusate. The heart machine perfusion was performed with a heart-lung machine (S5, LivaNova, Germany). The perfusion system was primed with 300 ml of donor blood, and 100 ml of priming solution containing buffered electrolytes, mannitol, vitamins, and steroids (Table 1).

Figure 1 and Video 1 show the details of the IFBHT technique. The donor heart was procured in a continuous beating state. A median sternotomy was performed using a sternum saw. The aorta, superior vena cava, and inferior vena cava were dissected and umbilical tapes were positioned circumferentially. The aortic root and right atrium were sutured in a purse-string manner. After the donor was fully heparinized, the aortic root (for perfusion), right atrium and left ventricular apex (for drainage) were cannulated and connected to the heart-lung machine. The superior and inferior vena caval veins were clamped. The distal
ascending aorta was cross-clamped and retrograde coronary perfusion was started through the proximal ascending aorta directly from the heart-lung machine. The pulmonary artery and left atrium were cut open to vent the heart and maintain it in a decongested state. The pump flow was adjusted to maintain the mean aortic pressure between 60-100 mm Hg (Figure 2A). Both the superior vena cava and inferior vena cava were ligated and divided. The donor heart maintained sinus rhythm and the ECG showed no ischemic ST-T changes. Subsequently, the heart was harvested and moved to the organ reservoir.

The heart graft was perfused with an oxygenated blood-based solution in a normothermic state \textit{ex situ}. A maintenance solution containing isotonic electrolytes, aminoacids, and nicorandil was infused at a rate of 0-30 ml per hour. Nicorandil and adrenaline, as well as an adjustable circuit pump flow, were used to assure a coronary vascular flow of greater than 500 ml per min (Figure 2B) and keep the sinus rhythm rate of around 60-100 beat per min. The venous PH values were within normal range (Figure 2C). The arterial and venous lactate were 2.8-4.9 and 3.1-4.9 mmol per liter, respectively, with a downward trend after 30-min of NMP (Figure 2D). The arteriovenous gradient showed a substantial consumption of oxygen and production of carbon dioxide (Figure 2E and 2F). In addition, the heart exhibited adequate right ventricular contraction without obvious evidence of wall motion abnormality, although the visual assessment of left ventricular contraction is inherently limited in a resting mode configuration. These parameters collectively suggest a good graft viability. During \textit{ex situ} NMP, the integrity of the superior vena cava, inferior vena cava, aorta, pulmonary artery, atria and ventricles was confirmed. The left atrial cuff was created by incisions between each of the four pulmonary veins to create a smooth continuous edge. The mitral valve was working normally.

The extracorporeal circulation and excision of the diseased heart of the recipient were conducted using a standard method. The beating donor heart was placed \textit{in situ} in the recipient without discontinuation of normothermic perfusion. The donor left atria cuff was anastomosed end-to-end to the recipient left atria with running sutures using 3-0 Prolene. The right superior pulmonary vein vent was inserted into the left ventricle through the mitral valve. The donor and recipient aortas were anastomosed with running suture using 4-0 Prolene. 400 ml washed red blood cells were used to rinse the donor heart. In the meanwhile,
Air-evacuating maneuvers were performed in the aorta and left ventricle. The recipient received 500 mg Methylprednisone prior to the discontinuing the NMP of the donor heart. The cross clamp was gently released, and the recipient blood perfusion of the donor heart was restored. The heart rate, rhythm and blood pressure were stable. The ECG showed no abnormality of the ST segments. An intraoperative TEE showed an immediate graft function with a LVEF of 70%. The donor inferior vena cava, superior vena cava, and pulmonary artery were anastomosed end-to-end to the recipient counterparts. Hemodynamics and blood gas analysis were stable, while vasoactive drugs were reduced and a sufficient urine volume was observed. Extracorporeal circulation was thus weaned off and the use of IABP was resumed. Drainage tubes were placed in the pericardium and mediastinum. The operation was completed, and the patient was admitted to the ICU for close monitoring.

The recipient received a routine immunosuppression (induction treatment with IL-2α receptor blocker and maintenance tacrolimus and mycophenolate) and antibiotics therapy in our center. The patient was extubated by day 2. The use of vasoactive drugs and IABP were discontinued on day 3. Daily ECG showed no change of the ST segments. Daily ECHO demonstrated normal cardiac function with LVEF greater than 75%; PASP dropped to 16 mm Hg post-transplantation. The patient had an acute kidney injury which recovered without the requirement for hemodialysis. Acute rejection, vascular complications and lung infection did not occur. The patient was discharged on post-operative day 20.

**DISCUSSION**

Although advances have been made in most aspects of heart transplantation, donor hearts are still preserved with a cardioplegic static cold storage. IRI is considered as an inherent component of all solid organ transplants including heart transplantation, contributing to early graft dysfunction and patient death. Importantly, IRI also contributes to allograft rejection and CAV, which are the major reasons for long-term graft loss and patient death in heart transplantation. Therefore, a reduction or even complete avoidance of ischemia is key in improving cardiac transplant outcomes while increasing the utilization of available organs.

To the best of our knowledge, this case represents the first ischemia-free, normothermic, oxygenated, beating heart transplantation. During NMP, we confirmed the excellent quality of
the cardiac graft by measuring perfusion pressure and flow; we also observed a downward trend of the lactate profile after 30-min NMP, as well as the normal sinus rhythm and myocardial contractility. Importantly, the ECG suggested the absence of ischemic injury and intraoperative TEE monitoring indicated continuous excellent cardiac function during the whole procedure. Therefore, IFBHT might be able to optimally preserve graft function and largely prevent the IRI-mediated complications.

There are at least two *ex situ* heart machine perfusion strategies. The organ care system (OCS) is to perfuse the heart in a normothermic, oxygenated, beating state\(^9,14\). In contrast, the XVIVO system perfuses the heart under hypothermic, oxygenated, cardioplegic conditions\(^15\). A direct comparison of these techniques has not been performed. Of note, continuous machine perfusion has thus far only been used during heart preservation. The cardiac allograft will therefore still undergo a period of ischemia during procurement and implantation. In contrast, the IFBHT technique has been designed to completely avoid graft ischemia during the entire procedure of heart procurement, preservation and implantation.

There are certain limitations concerning IFBHT that require further innovation. Firstly, there is no commercially available heart machine perfusion device in our country, which limits the procurement of distant donor hearts. However, the concept of ischemia-free (beating or non-beating) heart transplantation can be applied with the use of both OCS and XVIVO systems, after modification of the cannulation systems as shown in our case. Secondly, the success of the IFBHT requires an excellent cooperation between the surgeons and perfusionists to avoid accidental warm ischemia of the heart allograft or air embolism of the coronary artery. The whole team has practiced the technique in pigs for about half year prior to moving forward with the first case in man. In addition, the whole multi-organ procurement team should be well organized to make sure that the extra-cardiac organs are procured with minimal warm ischemia time when IFBHT is performed. Finally, the criteria of transplantability of the donor heart under *ex situ* NMP is yet to be defined, particularly when using organs from marginal donors.

In summary, this first case report shows the feasibility of IFBHT. This novel approach has potentially broad applications. From a clinical perspective, the technique may offer the opportunity to expand the donor pool to donors that are currently considered marginal. The
approach may furthermore allow to reduce rates of primary non-function, acute rejection and CAV, thus improving transplant outcomes. From a research perspective, our approach is expected to significantly contribute to an improved understanding of the complex interaction between IRI and alloimmunity.

**Authors’ contributions**

HXS is the conceptor of IFBHT; he organized the animal experiments and clinical trial, and critically revised the report. YSL, RJ, CYH, GZY, WZK and HXS designed the procedure and study protocol. YSL, RJ, and GZY analyzed the data and wrote the report. CL, MSY, SH, SYX and ZYL assisted design of NMP protocol and the preclinical preparation, as well as collected NMP parameters. LYQ, CYH, WTL, LHZ, XM and LMY assisted the design of the procedure, preclinical preparation and the operation. JN, XW, CYL, CXX, CXJ, GFQ, HWQ, and DYG assisted the design of the protocol and preclinical preparation. WZK, YSL, TBY, and XM were in charge of peri-operative care of the patient. BN and SGT critically revised the manuscript.

**Disclosure**

The authors of this manuscript have no conflicts of interest to disclose as described by *The New England Journal of Medicine*.

**Acknowledgement**

We thank Professor Peter Macdonald from St. Vincent’s Hospital, Sydney, New South Wales, Australia, for critical review and providing insightful comments on this study.

This study was supported by grants as follows: the National Natural Science Foundation of China (82070670 and 81970564), the Guangdong Provincial Key Laboratory Construction Projection on Organ Donation and Transplant Immunology (2013A061401007, 2017B030314018), Guangdong Provincial international Cooperation Base of Science and Technology (Organ Transplantation) (2015B050501002), Science and Technology Program of Guangzhou (201704020150), Science and Technology Program of Guangdong
REFERENCE

1. Stehlik J, Kobashigawa J, Hunt SA, Reichenspurner H, Kirklin JK. Honoring 50 Years of Clinical Heart Transplantation in Circulation In-Depth State-of-the-Art Review. Circulation 2018;137:71-87.
2. Fuchs M, Schibilsky D, Zeh W, Berchtold-Herz M, Beyersdorf F, Siepe M. Does the heart transplant have a future? Eur J Cardiothorac 2019;55:i38-i48.
3. Benck L, Kransdorf EP, Emerson DA, et al. Recipient and surgical factors trigger severe primary graft dysfunction after heart transplant. J Heart Lung Transplant 2021. (Online ahead of print)
4. Khush KK, Potena L, Cherikh WS, et al. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: 37th adult heart transplantation report-2020; focus on deceased donor characteristics. J Heart Lung Transplant 2020;39:1003-15.
5. Fernandez AR, Sanchez-Tarjuelo R, Cravedi P, Ochando J, Lopez-Hoyos M. Review: Ischemia Reperfusion Injury-A Translational Perspective in Organ Transplantation. Int J Mol Sci 2020;21:8549
6. Lund LH, Khush KK, Cherikh WS, et al. The Registry of the International Society for Heart and Lung Transplantation: Thirty-fourth Adult Heart Transplantation Report-2017; Focus Theme: Allograft ischemic time. J Heart Lung Transplant 2017;36:1037-46.
7. Lund LH, Edwards LB, Kucheryavaya AY, et al. The Registry of the International Society for Heart and Lung Transplantation: Thirty-second Official Adult Heart Transplantation Report--2015; Focus Theme: Early Graft Failure. J Heart Lung Transplant 2015;34:1244-54.
8. Khush KK, Cherikh WS, Chambers DC, et al. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Thirty-sixth adult heart transplantation report - 2019; focus theme: Donor and recipient size match. J Heart Lung Transplant 2019;38:1056-66.
9. Ardehali A, Esmailian F, Deng M, et al. 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.
10. Souter MJ, Eidbo E, Findlay JY, et al. Organ Donor Management: Part 1. Toward a Consensus to Guide Anesthesia Services During Donation After Brain Death. Semin Cardiothorac Vasc Anesth 2018;22:211-22.
11. Eltzschig HK, Eckle T. Ischemia and reperfusion--from mechanism to translation. Nat Med 2011;17:1391-401.
12. Mehra MR, Crespo-Leiro MG, Dipchand A, et al. International Society for Heart and Lung Transplantation working formulation of a standardized nomenclature for cardiac
allograft vasculopathy-2010. J Heart Lung Transpl 2010;29:717-27.

13. Monteagudo Vela M, García Sáez D, Simon AR. Current approaches in retrieval and heart preservation. Ann Cardiothorac Surg 2018;7:67-74.

14. Chew HC, Iyer A, Connellan M, et al. Outcomes of Donation After Circulatory Death Heart Transplantation in Australia. J Am Coll Cardiol 2019;73:1447-59.

15. Nilsson J, Jernryd V, Qin G, et al. A nonrandomized open-label phase 2 trial of nonischemic heart preservation for human heart transplantation. Nat Commun 2020;11:2976.
Figure 1. The ischemia-free beating heart transplantation procedure. The aortic root (for perfusion), right atrium and the left ventricular apex (for drainage) were cannulated and connected to the heart-lung machine. The donor heart is procured after the in situ normothermic machine perfusion (NMP) circuit is established, was then moved to the organ reservoir and underwent continuous ex situ NMP. The donor heart is implanted under in situ NMP. The donor left atrium and aorta were firstly anastomosed to the recipient counterparts. Subsequently, the donor heart is reperfused with the recipient’s blood. Finally, the donor inferior vena cava, superior vena cava, and pulmonary artery are anastomosed end-to-end to the recipient counterparts.
Figure 2. The normothermic machine perfusion (NMP) of donor heart. Panel A and B show the perfusion pressure (mm Hg) and flow (ml per min) of the coronary artery. Panel C and D show the pH value and lactate level (mmol per liter) of the arterial and venous perfusate. Panel E and F show the oxygen (PO$_2$, mmHg) and carbon dioxide (PCO$_2$, mmHg) tension of the arterial and venous perfusate.
**Table 1. The components of the perfusate solution**

| Components | Priming Solution (per 500 ml) | Heart Maintenance Solution (per 500 ml) | Catecholamine Maintenance Solution |
|------------|-------------------------------|----------------------------------------|-----------------------------------|
|            |                               | Calcium Chloride 1.2 g                  | Epinephrine 1 mg in 50 ml of 0.9% Normal Saline 0.6-18 ug per min |
| Mannitol   | 12.5 g                        | Magnesium Sulfate 0.2 g                 |                                   |
| Sodium Chloride | 2.63 g                | Potassium Chloride 0.01 g               |                                   |
| Potassium Chloride | 185 mg                  | Sodium Chloride 0.825 g                 |                                   |
| Sodium Gluconate     | 251 mg                   | Nicorandil 12 mg                       |                                   |
| Sodium Acetate       | 184 mg                    | Amino Acids 3%                         |                                   |
| Magnesium Chloride   | 150 mg                    |                                       |                                   |
| Sodium Bicarbonate   | 20 mEq                    |                                       |                                   |
| Myethylprednisolone  | 200 mg                    |                                       |                                   |
| Multivitamins       | 5 ml                      |                                       |                                   |
| Heparin             | 2500 IU                    |                                       |                                   |
| Ceftriaxone Sodium and Tazobactam Sodium | 1.5 g |                                       |                                   |
| 25% Albumin         | 100 ml                     |                                       |                                   |