Applied Cardiopulmonary Pathophysiology 15: 207-212, 2011

Organ preservation with the organ care system

Ruhi Yeter, Michael Hübler, Miralem Pasic, Roland Hetzer, Christoph Knosalla

Department of Cardiothoracic and Vascular Surgery, Deutsches Herzzentrum Berlin

Abstract

Clinical heart transplantation is limited by the shortage of donor organs. The recent development of new donor organ maintenance systems may help to increase the utilization of available organs. This article reviews current experience with the Organ Care system for heart preservation.

Key words: organ preservation, warm preservation, heart donor, heart transplantation

Introduction

Heart transplantation presents the most efficient therapy for end stage heart disease.

Until today orthotopic heart transplantation has been performed in 89,000 patients worldwide (1). With the success of heart transplantation the criteria for acceptance of donor hearts have been continuously expanded. Nevertheless, transplantation is limited by the shortage of suitable donor organs. Especially donor age and length of ischemic time are limiting factors (1). Utilization of marginal donor hearts that reveal significantly impaired function as a consequence of the brain dead environment are currently not used due to the lack of a reliable method to predict the functional recovery of the graft after procurement.

In order to circumvent these limitations, recent efforts have led to the development of donor organ maintenance systems that minimize the cold ischemia time and enable cardiac function to be assessed ex vivo.

Cold hypostatic organ preservation

The standard method of organ preservation in this context is cold hypothermic static preservation. The heart is perfused with a cold preservative solution, then explanted and stored at 4°C in a solution for transportation to the recipient hospital. There are two main groups of preservation solutions: intracellular solutions such as Bretschneider solution, University of Wisconsin (UW), Euro-Collins and Stanford solution and the extracellular solutions Celsior, St. Thomas Hospital, Lyon Preservation and modified University of Wisconsin solution (2). The preference for a specific cardioplegia solution often depends on the individual experience of each transplant center. A whole arsenal of different preservation solutions are used today and this fact may suggest that there is no "superior" one available. Despite the large number of different solutions there are limitations for cold preservation. The generally accepted ischemic time for cold preservation lies within 4 hours. Data from the ISHLT registry sug-

gest that ischemia times exceeding 6 hours are associated with primary graft dysfunction and acute right heart failure, both of which contribute substantially to postoperative morbidity and mortality. Even the etiology of hemodynamic failure is multifactorial; indubitably suboptimal graft preservation and subsequent ischemia-reperfusion injury play a critical role (3). Goldsmith et al. showed by a proportional hazard regression analysis that overall the recipient had 1.16 times the hazard with each hour of increase in ischemia time (95% confidence interval 1.07 to 1.25) (4). A further limitation of static preservation is the inability to assess the graft during storage. While cold storage aims to minimize ischemia injury it does not allow resuscitation of the graft. These aspects gain even more importance considering the recent development in donor age. During the period of 2002 to 2009 donor age increased significantly up to 33 years, whereas between 1992 and 2001 the corresponding value was 31 years. Additionally, donors in Europe are more than 6 years older on average compared to those in North America (1). In this context Russo et al. demonstrated that the effect of ischemic time on survival after heart transplantation is essentially dependent on donor age (5). Supportively Gupta et al. observed a considerable reduction in survival among patients who were allocated donor hearts from patients of at least 50 years of age (6).

Warm blood perfusion

In order to address the shortcomings of cold hypostatic preservation, approaches using warm blood preservation have been developed. The advantages lie in the fact that blood has an excellent capacity for oxygen delivery, and is a potent antioxidant free radical scavenger and an efficient buffer. Furthermore, blood revealed the potential to protect the endothelial function and reduce injury.

Based on the early research by Hassanein et al. (7) on building a portable perfusion apparatus for use in donor heart preservation, TransMedics, Inc. (Andover, MA, USA) succeeded in developing the Organ Care System (OCS), the first commercial, portable warm blood perfusion system for donor organs. The OCS is a sophisticated device that allows the heart to be maintained in a warm, beating state ex-vivo to optimize its function and enables its analysis and monitoring during transportation. Monitoring of the heart comprises measurement of aortic pressure and flow, coronary flow, blood temperature, saturation and hematocrit.

The first clinical evaluation of the system took place in two phase I trials, one in Europe and one in the United States that were started in 2007.

In Europe the PROTECT trial (Prospective Multicenter European Trial to evaluate the Safety and Performance of the Organ Care System for Heart Transplants) was performed to evaluate the safety and effectiveness of the OCS for the preservation of donor hearts. In its context 20 heart failure patients received cardiac transplantation using donor hearts that were maintained and transported using OCS. The main result of the study was a 30-day patient and graft survival of 100 percent; the percentage of cardiac related complications was 23% (8).

In the United States, the PROCEED trial (Prospective Multicenter Safety and Effectiveness Evaluation of the Organ Care System Device for Heart Use) was performed as a 15 patient, single arm, non-randomized, FDA approved safety and performance study. Consenting patients who met the inclusion criteria received a donated heart that was maintained and transported using the OCS (9). Perfusion and cardiac metabolic and function parameters were continuously monitored and stored from the device. For this purpose blood samples were taken from the arterial and venous port to measure the serum lactate levels using a portable analyzer. The analysis by Hamed A et al. showed that serum lactate is a powerful predictor of graft failure subsequent to heart transplantation with high sensitivity and specificity (10). Pa-

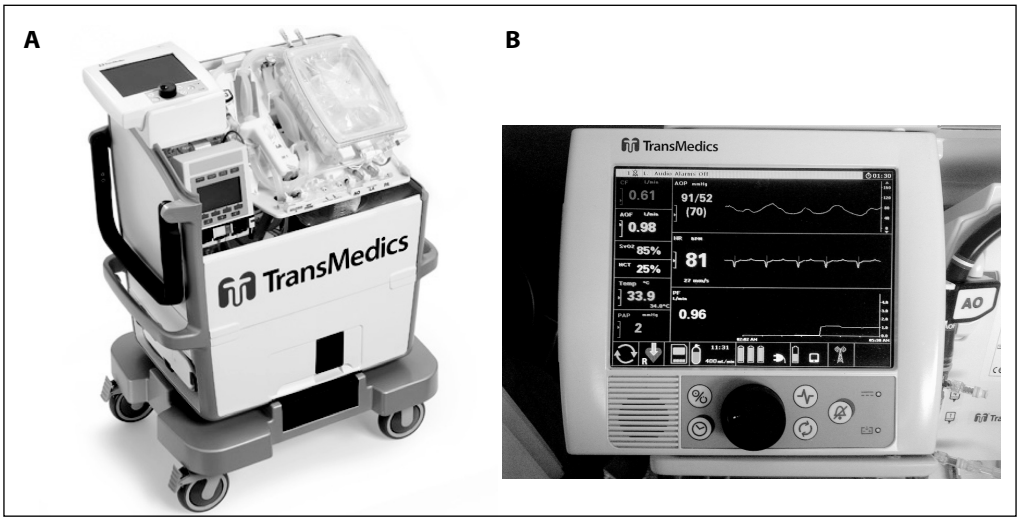

Figure 1: A)The Transmedics Organ Care System (OCS) after removal of the cover. B) Wireless monitor of the Organ Care System that enables monitoring of several vital parameters: Aortic pressure (AOP), aortic blood flow (AOF), coronary blood flow (CF), pulmonary artery pressure (PAP), pump flow (PF), electrocardiogram (ECG), heart rate (HR), blood temperature, hematocrit and coronary sinus saturation.

tients were followed for 30 days post transplantation. Thirty-day patient survival was 93% and the percentage of cardiac complications was 33%. These results compare favorably to those of the Celsior cold solution perfusion trials, demonstrating a lower incidence of cardiac related adverse effects and higher 30-day patient survival (11).

In both OCS trials, the cold ischemia time could be significantly reduced to approximately 60 to 80 minutes. In addition, the OCS allows the surgeon to survey both the maintenance condition and the graft function in a way that is not possible during cold static preservation.

Limitations

A certain limitation of the OCS is the much more complex management than with simple cold storage. Each perfusion module of the OCS requires 1.5 l of donor blood with a minimal hematocrit of 30% to allow adequate maintenance perfusion of the donor heart in the system. The blood is usually obtained through an aortic cannula that permits 1.5 l to be obtained within 40 seconds just prior to aortic clamping and thereby does not interfere with the retrieval of any other organs. Although the OCS requires more resources than the standard storage technique it allows continuous monitoring and treatment of the heart.

Our own experience

We have used the Organ Care System in cases of extended organ transportation time of >180 minutes to bridge the time gap of ischemia and in cases of marginal donor hearts, fractional hypertrophic hearts with an interventricular septal thickness ≥13 mm and hearts with undifferentiated coronary heart disease. Our current single center experience of more than 20 graft procurements with the OCS has shown that even hearts that were turned down by up to seven other centers for various reasons, as well as hearts transported over long distances with perfusion times of up to 7 hours and 32 min, can be transplant-

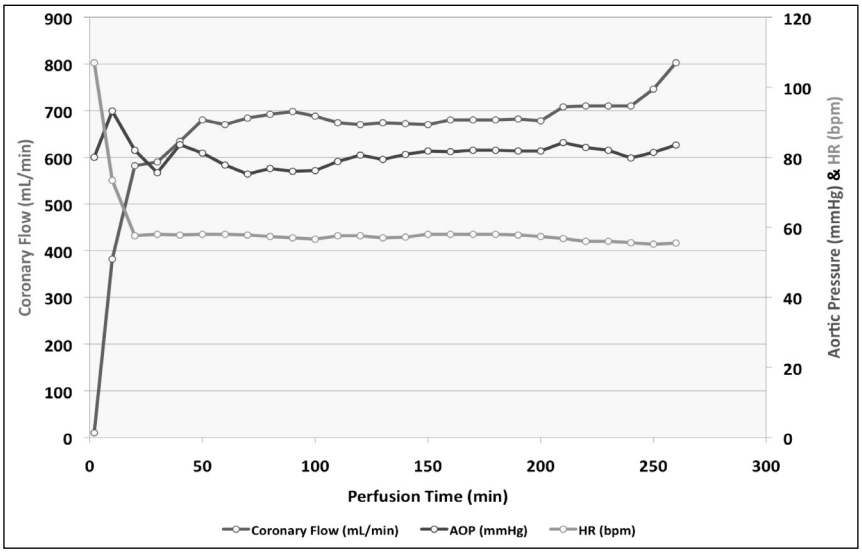

Figure 2: OCS perfusion parameters of a donor heart during transportation from Thessaloniki (Greece) to Berlin (Germany). The graph shows, after initial adjustment, stable parameters for coronary flow (dark grey), aortic pressure (black), heart rate (HR, light grey).

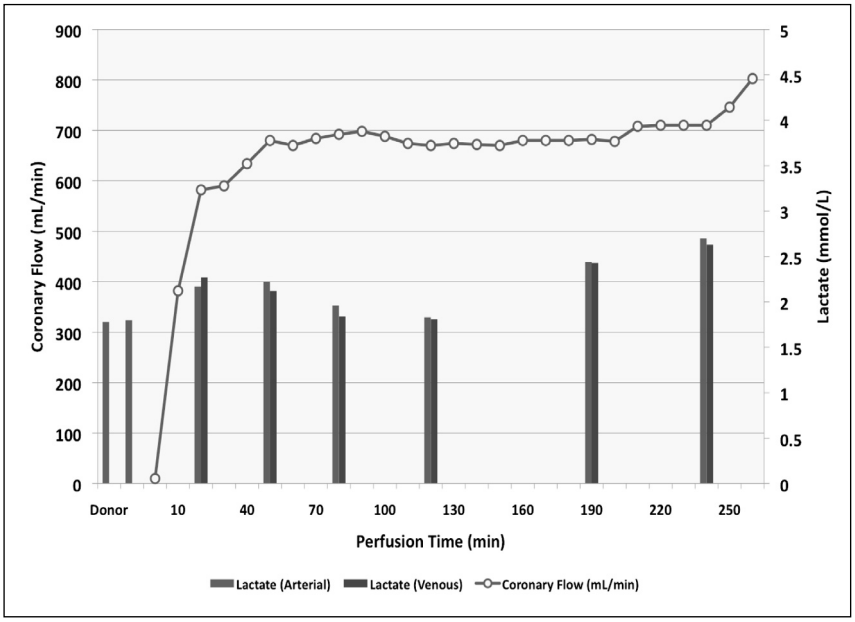

Figure 3: Time course of coronary blood flow and of lactate levels taken during heart perfusion. After initial stabilization lactate levels from the postcapillary site reveal lower levels than those taken from the precapillary site, indicating lactate metabolism by the heart.

ed with excellent primary graft function. Furthermore, as shown by our center, both experimentally and clinically the OCS allows coronary angiographic assessment prior to transplantation (Yeter R, et al., manuscript in preparation).

Future directions

Prolonged safe preservation may allow better histocompatibility cross-matching and may enable heart transplantation to be performed as an elective procedure. Long-term follow-up will show whether the lessening of ischemia reperfusion injury translates into a decrease of the incidence of cardiac vasculopathy, which is still the leading cause of late graft failure (12). As already demonstrated for ex-vivo lung perfusion the OCS may also provide a platform to treat the heart by gene therapy in order to decrease the inflammation and/or antigenicity of the heart (13)

Conclusion

Cold static storage has been the gold standard in clinical heart transplantation, used in more than 89,000 cases worldwide. The criteria for acceptance of organs that are currently applied have been developed on the basis of experience with standard preservation solutions. Based on our own experience we believe that growing use of new perfusion devices such as the OCS will lead to an expansion of the organ acceptance criteria and thereby increase the size of the donor organ pool.

Acknowledgement

We thank Anne M. Gale for editorial assistance.

References

1. Stehlik J, Edwards LB, Kucheryavaya AY, Aurora P, Christie JD, Kirk R et al. (2010) The Registry of the International Society for Heart and Lung Transplantation: twenty-seventh official adult heart transplant report – 2010. J Heart Lung Transplant 29 (10): 1089-103
2. Michel P, Vial R, Rodriguez C, Ferrera R (2002) A comparative study of the most widely used solutions for cardiac graft preservation during hypothermia. J Heart Lung Transplant 21 (9): 1030-9
3. Chandraker A (1999) Ischemia-reperfusion injury in experimental models of organ transplantation. Transplant Proc 31 (5): 2073
4. Goldsmith KA, Demiris N, Gooi JH, Sharples LD, Jenkins DP, Dhital KK et al. (2009) Life-years gained by reducing donor heart ischemic times. Transplantation 87 (2): 243-8
5. Russo MJ, Chen JM, Sorabella RA, Martens TP, Garrido M, Davies RR et al. (2007) The effect of ischemic time on survival after heart transplantation varies by donor age: an analysis of the United Network for Organ Sharing database. J Thorac Cardiovasc Surg 133 (2): 554-9
6. Gupta D, Piacentino V, 3rd, Macha M, Singhal AK, Gaughan JP, McClurken JB et al. (2004) Effect of older donor age on risk for mortality after heart transplantation. Ann Thorac Surg 78 (3): 890-9
7. Hassanein WH, Zellos L, Tyrrell TA, Healey NA, Crittenden MD, Birjiniuk V et al. (1998) Continuous perfusion of donor hearts in the beating state extends preservation time and improves recovery of function. J Thorac Cardiovasc Surg 116 (5): 821-30
8. Tenderich G TS, El_Banayosy A et al. (2008) The 1-year follow-up of the Protect patient population using the Organ Care System. J Heart Lung Transplant 27 (2): S166
9. McCurry KR, Jeevanandam V, Mihaljevic T et al. (2008) Prospective multi-center safety and effectiveness evaluation of the Organ Care System Device for cardiac use (PROCEED). J Heart Lung Transplant 27 (2): S166
10. Hamed A TS, Huber J, Lin R, Pogglo EC, Ardehalt A (2009) Serum lactate is a highly sensitive and specific predictor of post cardiac transplant outcomes using the organ

care system. J Heart Lung Transplant 28 (2): S71
11. Vega JD, Ochsner JL, Jeevanandam V, McGiffin DC, McCurry KR, Mentzer RM, Jr. et al. (2001) A multicenter, randomized, controlled trial of Celsior for flush and hypothermic storage of cardiac allografts. Ann Thorac Surg 71 (5): 1442-7
12. Hiemann NE, Wellnhofer E, Knosalla C, Lehmkuhl HB, Stein J, Hetzer R et al. (2007) Prognostic impact of microvasculopathy on survival after heart transplantation: evidence from 9713 endomyocardial biopsies. Circulation 116 (11): 1274-82
13. Cypel M, Liu M, Rubacha M, Yeung JC, Hirayama S, Anraku M et al. (2009) Functional repair of human donor lungs by IL-10 gene therapy. Sci Transl Med 1 (4): 4ra9

Correspondence address
Christoph Knosalla, MD, PhD
Department of Cardiothoracic and Vascular Surgery
Deutsches Herzzentrum Berlin,
Augustenburger Platz 1
13353 Berlin
knosalla@dhzb.de