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Non-Heart-Beating Donor Heart Transplantation: Breaking the Taboo

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Roughly 60% of hearts offered for transplantation are rejected because of organ dysfunction. Moreover, hearts from circulatory-dead patients have long been thought to be non-amenable for transplantation, unlike other organs. However, tentative surgical attempts inspired by the knowledge obtained from preclinical research to recover those hearts have been performed, finally culminating in clinically successful transplants. In this review we sought to address the major concerns in non-heart-beating donor heart transplantation and highlight recently introduced developments to overcome them.

MeSH Keywords: Cold Ischemia • Heart Transplantation • Warm Ischemia

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Background

Heart transplantation is the criterion standard therapeutic intervention for patients with end-stage heart failure [1,2]. The first heart transplantation was done in 1967 by Christian Barnard, in which he successfully transplanted the heart of a 25-year-old woman to a 53-year-old man [3]. At that time, before the implementation of cardioplegia and cold preservation, it was necessary to transfer the recipient to the donor's hospital in order to limit the time needed for the procedure, and hence minimize the risk of donor cardiac dysfunction. Due to research and technical advances in organ preservation, we were able to increase the time for transportation, and it is no longer necessary to house both the donor and the recipient in the same hospital.

Challenges in Heart Transplantation

Heart transplantation is notorious for high early mortality rates, caused almost entirely by donor organ failure [4]. Under conventional conditions of donor organ preservation, prolonged cold ischemia is by far the greatest risk factor for primary allograft dysfunction and death [5,6]. Moreover, prolonged ischemia increases other risk factors, such as donor left ventricular hypertrophy (LVH) and pericardial effusion [7,8]. Therefore, organ retrieval, transport, and transplantation procedure should be carefully and optimally organized. The majority of transplantable hearts are being retrieved from the so-called "heart-beating patients". These donors are brain dead, but their hearts are still beating, and therefore it is possible to assess different aspects of cardiac function, such as ejection fraction and cardiac index, and to evaluate them for putative transplantation [9]. However, upon circulatory death of the donor, retrieving the heart for transplantation is no longer an option, unlike other organs such as the kidneys, lungs, and liver [10]. This is due to the extreme sensitivity of the heart to ischemia. Furthermore, hearts from these donors cannot be functionally evaluated, making their transplantation risky [11].

Initiative Attempts

In 2008, Boucek et al. reported 3 successful pediatric heart transplantations from infants with a mean age of 3.7 days [12]. Circulatory death was declared in the donors after an average time of 18.3 minutes from life support withdrawal. Preservation was started by cold fluid infusion in the ascending aorta. Simultaneously, median sternotomy and topical cooling was performed. Venous blood withdrawal was performed while infusing the aorta to prevent cardiac distention. Transplantation of these hearts was successfully performed, showing no mortality after 3.5 years of follow-up [12]. This was an early attempt at transplanting hearts from the so called "non-heart-beating donor" (NHBD).

Surgeons were encouraged to push the limits with NHBD and attempted to retain cardiac functionality by extracorporeal circulation and to race against warm ischemia time. In 2009, Ali et al. reported a successful recovery of an adult heart 23 min after circulatory death [13]. Briefly, sternotomy was performed after 20 min from extubation, including a 5-min stand-off period to ensure the absence of any electrical activity. Right ventricle heparinization was performed, followed by normothermic cardiopulmonary bypass (CPB). Within 5 min of coronary reperfusion, initial fibrillation was observed and spontaneous sinus rhythm was retained at a rate of 90 beats/min. Minimal interventions were required to correct metabolic and pressure abnormalities. Furthermore, cardiac function was normalized, achieving a cardiac output of 4.1 liters/min with a cardiac index of 2.4 liters/min/m^2 [13].

Factors to be Considered in NHBDs

The aforementioned successful attempts have shown great promise for NHBD heart transplantation and spawned further developments aimed at cardiac resuscitation and preservation. In general, 3 main challenges are to be considered in NHBD heart transplantation:

1. The risk of warm ischemia or warm ischemia-induced cardiac dysfunction;
2. Heart preservation until it reaches recipient;
3. The ability to evaluate cardiac function parameters.

The hallmark of NHBDs is circulatory death, a state which is generally defined as an irreversible cessation of mechanical or electrical activity of the heart [14]. At present, it is generally accepted that 3–5 min of cardio-respiratory arrest are sufficient to declare circulatory death, provided there is no subsequent restoration of artificial cerebral circulation [15]. However, circulatory death entails the risk of warm ischemia, which, as previously mentioned, is a major challenge in transplantation from NHBDs. The risk of cardiac dysfunction escalates with the time for which the heart is exposed to warm ischemia. Prolonged warm ischemic time (WIT), defined as the time period between withdrawal of life support and administration of organ preservation solution, puts the heart at a great risk of hypoxia, hypo-perfusion, and cardiac distention [16,17].

Preclinical Research

Attempts to recover hearts after a certain period of warm ischemia have been the subject of pre-clinical studies. A good example is the study published by Iyer et al. in 2014, in which

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they used a pharmacologically conditioned perfusion solution in a porcine asphyxia model [18]. In this study, the perfusion solution was supplemented with erythropoietin, glyceryl trinitrate, and zoniporide, which have been previously shown to mediate ischemic preconditioning and postconditioning by activating intracellular kinases in rat and porcine models [19–21]. The authors reported successful functional, biochemical, and metabolic recovery of the hearts after 30-min WIT, achieving a 10-min superiority to conventional perfusion solution. This clearly highlights the importance of pre-clinical and cell biology-based research in refining the technologies utilized to protect the hearts after circulatory cessation.

These findings encouraged a step forward to challenge cardiac transplantation from non-heart-beating human donors applying novel systems of cardiac preservation.

Clinical Success in Adult Hearts from NHBDs

In 2013 Dithal et al. reported the first NHBD heart transplantation utilizing the newly introduced Organ Care System (OCS) (TransMedics; Andover, MA, USA) [22]. OCS enables both standard and marginal criteria for *ex-vivo* donor hearts to be preserved and enables detection of occult pathology during normothermic *ex-vivo* perfusion [23]. They described 3 successful cases in which OCS enabled long-distance transportation while maintaining cardiac parameters at desirable levels. With increasing perfusion time, lactate levels dropped to the desirable levels (<5 mmol/L), and coronary blood flow and mean aortic pressure remained constant and in the prescribed range.

OCS circuits integrate an oxygenator, a warmer, a reservoir, a pulsatile pump, and a gas exchange unit, permitting coronary perfusion with oxygenated warm blood pumped through the aorta, re-oxygenation of the deoxygenated blood recovered from the pulmonary artery, and reintroduction to the aorta while simultaneously probing for lactate levels (Figure 1) [24].

The main advantages of OCS can be summarized in the following points:

- Competent protection against warm ischemia, minimizing the risk of associated cardiac dysfunction;
- Significant reduction of the cold ischemia (i.e., from cessation of the *ex-vivo* perfusion and cardioplegic arrest to implantation);
- The unprecedented feasibility to extended out-of-body time, allowing for expansion of geographical areas where hearts are transported;
- The ability to evaluate and monitor cardiac functional and metabolic parameters, ensuring their readiness for transplantation.

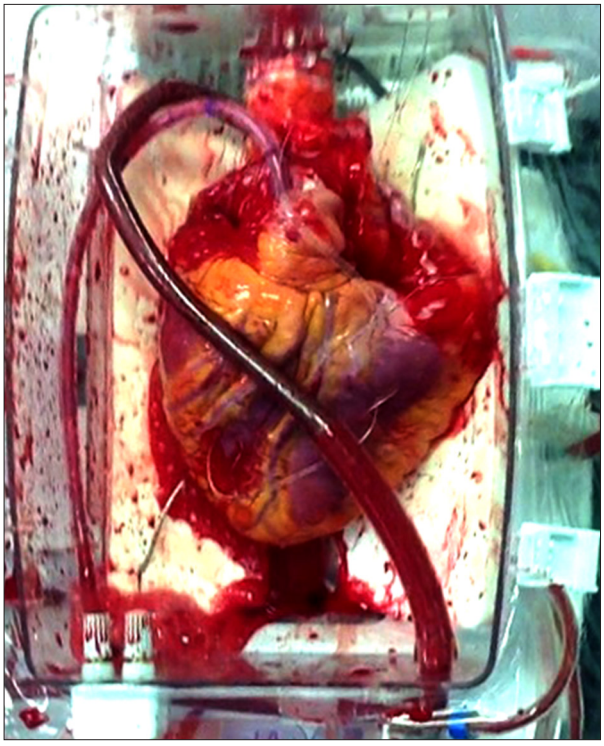

Figure 1. Organ Care System (OCS) – supported heart prior to transplantation.

The clinical effectiveness of OCS has great promise to further expand NHBD heart transplantations, and has been extensively used for orthotopic heart transplantation worldwide.

Final Remarks on Ethical Issues

Ethical issues are of concern in heart transplantation in NHBDs, especially if the patient is to be first weaned from life support. Importantly, the decisions about critical care and termination of life support should be made by the donor's physician and family, not a member of the organ recovery team. The feelings of the family members of the donor have to be considered, and they should be well-informed about the procedure. Termination of life support can, in many cases, be the most humane option to end an unbearable burden on the patient, which might entail prolonged physical and emotional suffering [25]. After withdrawal of life support, we are confronted by the definition of circulatory arrest and/or death, including the stand-off time that precedes the decision to declare it. Guidelines might differ among countries, and more variations are expected if the method is to be widely adopted around the world. Additionally, cultural and religious beliefs should be carefully considered. Lastly, the recipient has to be involved and assured that the organ received was obtained under meticulous ethical standards.

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Conclusions

Transplanting hearts from NHBDs is a major breakthrough in transplantation medicine and cardiac surgery. Thanks to the recently introduced *ex-vivo* perfusion advances, more hearts can be recovered after circulatory death, maximizing the chances for transplantation and overcoming the shortage of suitably transplantable donated hearts [24]. Furthermore, pre-clinical research powered by advances in cell biology and regenerative medicine is indispensible and is expected to offer better solutions to preserve transplantable organ vitality and even regenerate those which have undergone partial damage. We look forward to future advances, and to more lives being saved.

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