Heterotopic heart transplantation: where do we stand?

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Summary

Orthotopic heart transplantation (OHT) is a well established and commonly utilized procedure for end-stage heart failure patients. Heterotopic heart transplantation (HHT) is a surgical procedure that allows the graft to be connected to the native heart in a parallel fashion. The main advantage of HHT is to assist the patient’s native heart and to maintain circulation in the cases of severe acute rejection. HHT has also been proposed to overcome pulmonary hypertension, to increase the size of the donor pool and to decrease waiting times without increasing morbidity caused by the procedure. However, only a few papers have reported the short- or long-term results of HHT, and most of these studies have included <30 cases. OHT remains the standard technique and is preferable whenever the patient meets the current criteria and a suitable organ is available. HHT is far less useful than in the past because of the major advances in immunosuppression therapy and the development of long-term mechanical circulatory support. This study reviews the origin of HHT and discusses clinical developments, including their advantages and disadvantages.

Keywords: HHT • Orthotopic • Transplantation

INTRODUCTION

Orthotopic heart transplantation (OHT) is a well established and commonly utilized procedure for patients with end-stage heart failure. Heterotopic heart transplantation (HHT) is a surgical procedure that allows the graft to be connected to the native heart in a parallel fashion to provide a kind of biological biventricular support. Performed first in a human being by Barnard in 1974 [1, 2], this surgical technique was a useful approach during the precyclosporin era as it reduced early patient death caused by the high rate of graft failure. However, this indication is no longer relevant, and HHT is most used in rare and selected cases, such as patients with fixed pulmonary hypertension (PH; to avoid heart-lung transplantation) or for patients with a major donor-recipient body-size mismatch.

This study reviews the origins of HHT, describes the surgical procedures and discusses the clinical developments, including their advantages and disadvantages.

THE ORIGINS OF HETEROTOPIC HEART TRANSPLANTATION

HHT can be described as a ‘working’ or ‘non-working model’. In a non-working model, the cardiac graft is perfused, but does not support the patient’s circulation. This model was mainly used to establish the feasibility of the procedure, for studying surgical sutures and anastomosis and, later, immunosuppressive therapy and to help prevent graft rejection.

Although suddenly emerging into the world’s consciousness in December 1967, heart transplantation evolved through much earlier experimental development. HHT has been investigated for many years. Alexis Carrel (Nobel Prize in Physiology and Medicine 1912) and Charles Guthrie first reported an experimental HHT, where they placed the heart in an ectopic position without removing the native heart [3].

In the 1930s, Franck Mann at the Mayo Clinic interested by Carrel’s experiments, concentrated on heart transplantation [4] and recognized rejection of the heterotopic dog-heart transplant to the neck: ‘the failure of the homotransplanted heart to survive is not due to the technique of transplantation but to some biological factor’.

In the mid-1940s in the Soviet Union, Demikhov and Sinitsyn began a number of ingenious experiments that showed the feasibility of intrathoracic heart transplantation (as a working model). Demikhov reported a total of 24 anatomical variants of intrathoracic HHTs by performing a series of 250 canine experiments between the years 1940 and 1960; he succeeded in keeping a cardiac graft beating at 32 days after a successful implantation in 1956 [5]. Although this work was not well known in Europe or the USA until 1962, Demikhov clearly achieved some remarkable firsts (among them was the first experimental heart-lung transplant with the longest survival time of an animal for 6 days). His influence is unquestionable in developing human thoracic transplantation [6]. Demikhov influenced other pioneers...
too: Norman Shumway and Richard Lower were well aware of his achievements, and Christian Barnard even visited him.

Additional experiments of HHT were performed during the 1950s and, subsequently, heterotopic cerebral and inguinal-heart transplantation became tools for studying immunological and rejection problems. Indeed, due to obvious space limitations, the cervical placement of a cardiac graft is not always possible (particularly in primates); Minanov et al. [7] described positioning it into the iliac fossa of primate recipients. The abdominal positioning of a heterotopic transplanted heart was originally reported by Ono and Lindsey when they transplanted porcine hearts into baboons [8, 9].

In 1967, the era of clinical heart transplantation started with the first successful orthotopic cardiac transplantation by Barnard [10] in his patient Louis Washkansky. In 1973, after a transplant patient died on the table, Barnard thought that if the patient’s own heart had been left in place, and the cardiac graft inserted as a ventricular support, the failure of the donor’s heart may not have resulted in the patient’s death. Thus, Barnard set Jaques Losman, a junior surgeon in his team, to work on establishing a surgical procedure where the second heart is placed in the chest and the two hearts can work in parallel. Two techniques were described: in the first, the donor’s heart worked as a left ventricular assist device (LVAD; only a few cases were performed using this technique) and, in the second technique, the donor’s heart provided biventricular support.

Prior to its clinical application, Barnard and his team performed extensive experiments in primates (56 baboons underwent HHT) to evaluate this procedure [11]. Clinical HHT was first introduced by Barnard at the Groote Schuur Hospital, Cape Town, South Africa in November 1974 [1].

SURGICAL TECHNIQUES

To create a working model with the cardiac graft, a connection between the atria is mandatory. Either univentricular or biventricular support is possible depending on the selected technique; however, most of the HHTs are performed using the biventricular model. The complete surgical techniques have been described elsewhere; here, we will outline the main steps of the biventricular model [12].

**Donor cardiectomy**

This procedure is similar to that used in orthotopic transplantation with minor changes, such as increased length of the superior vena cava (obtained by ligating and dividing the azygos vein), and extensive dissection of the ascending aorta and pulmonary arteries. Excision from the donor is then similar to that of orthotopic transplantation.

**Donor heart preparation**

This is performed in a bowl of cold saline solution. The inferior vena cava and right pulmonary veins are over-sewn with a running 4-0 monofilament suture, with care being taken to ensure that coronary sinus drainage is not occluded during closure of the inferior vena cava. The segment of tissue between the left pulmonary veins is excised to create one large orifice into the left atrium (required diameter is ~4 cm). The main pulmonary artery is divided at its bifurcation. A linear incision of 6 cm is made in the posterior wall of the superior vena cava (SVC) with an extension into the right atrium to create an adequate right atrial orifice; at least, half the length of this incision must involve the right atrial wall (Fig. 1).

**Surgery on the recipient**

Although heterotopic transplantation has been conducted through a right-sided thoracotomy, a median full sternotomy is obviously the main approach [13]. Preparations for skin incision are similar for both orthotopic and heterotopic transplantations. Once the sternotomy is performed, a right-sided pleuroperticardial flap is created, extending this incision over the diaphragm. Care should be taken to stay 2 cm above the phrenic nerve, and haemostasis should be obtained along the cut edges of the flap at that time. A similar reflection is made superiorly, extending the pleuroperticardial flap towards the SVC, again taking care not to injure the phrenic nerve. The flap will fall back to the right lung creating a single right pleuroperticardial space. Cannulation of the recipient for a cardiopulmonary bypass is then similar to the orthotopic procedure. According to the surgeon’s preference, one may directly cannulate the SVC or it may be performed through the right appendage. Snares are used and, after the recipient’s aorta is cross-clamped, a cardioplegic solution is administered. Further increments of cold cardioplegic solution can be infused later during the operation to both the donor’s and recipient’s hearts according to the surgeon’s preference. The surgery may also be performed with the recipient heart simply fibrillated, allowing continuous coronary perfusion.
Left atrial connection or anastomosis is first performed

An incision is made, as performed in mitral-valve surgery, into the recipient's left atrium, starting at the right superior pulmonary vein and extending inferiorly to the interatrial groove. The donor's heart is placed into the right thoracic cavity, to lie alongside the recipient's heart. Anastomosis is initiated at the posterior portion of both left atria using a double-ended 4-0 polypropylene running suture, with both sutures terminating on the anterior edges (Fig. 2). Surgeons should be aware that the complete anastomosis will be inaccessible at the end of the operation (covered by the right atrial anastomosis); thus, it is essential to sew with caution to prevent any further bleeding. It is also important to make this connection between both left atria as large as possible to prevent any restriction or stasis in blood flow. The objective at this point is to obtain a common atrium from which blood can enter either via the donor's or recipient's left ventricles.

A second anastomosis connects both right atria

A 5- to 6-cm longitudinal incision is made into the lateral aspect of the recipient's SVC and is extended inferiorly to the lateral wall of the right atrium (3 cm above the junction of the vena cava in the right atrium and 3 cm below). The anastomosis forms a diamond shape, so that the midpoint of the posterior lip of the incision in the recipient's atrium is sutured to the most caudal point of the incision in the atrium, using a double-ended 4-0 polypropylene suture (Fig. 3). The diamond shape of the connection between both right atria should ensure that this anastomosis remains wide open to ensure good blood drainage. The donor's SVC and azygos vein are tied. Some authors recommend adding a few metal clips, which can be used after surgery as a fluoroscopic reference for the passage of the endomyocardial biopsy forceps.

A third anastomosis connects both aortas

The proper length of the donor's ascending aorta is determined by temporary inflation of the lungs. An end-to-side anastomosis is performed using a side-biting clamp applied to the right side of the recipient's ascending aorta and a continuous suture using 4-0 polypropylene. Because of the limitation in length, a vascular graft may be necessary to bridge the vessel; however, keeping the donor aorta short helps to rotate the donor heart to the anterior part of the right chest, reducing compression of the right lung.

The pulmonary artery connection is completed

The donor's main artery is often not long enough, and a 22-mm Dacron graft may be needed to avoid any tension or distortion (Fig. 4).

The rest of the operation is similar to that for orthotopic transplantation: rewarming, release of both snares, cautious and long de-airing manoeuvres with a patient placed in the Trendelenburg position and discontinuation of the cardiopulmonary bypass.

Before closure of the chest, it is recommended to fully ventilate both lungs to ensure the expansion of the right lung and its lower lobe, which has been compressed by the donor's heart during the operation.

For left-ventricular support alone, the heart is similarly placed in the right chest, and both left atria are first connected as described above. The aorta is then connected to the recipient's ascending aorta. Both vena cava are tied and, in order to create a shunt for the coronary sinus, the pulmonary artery is sutured end-to-side to the recipient's atrium.

CLINICAL DEVELOPMENTS

Only a few papers have been published on the short- or long-term results of HHT, and most of the studies include <30 cases. Indeed, most of the studies are case reports and no major series have been published.
published within the last 5 years. This may explain the currently reduced and decreasing role of HHT for end-stage heart disease.

It is also difficult to compare HHT with OHT because of the high level of variability between published studies. Boffini et al. [14] reported a survival rate for HHT that was comparable with OHT in 12 patients (701 OHTs performed during the same period). However, the mean ischaemic time for the donor’s heart was surprisingly low (149 min), which suggests that the donor was in the same area as the recipients, which may have impacted on their results. In their report, 4 patients developed arrhythmic episodes, which have been also described elsewhere [15]. Immunological follow-up was found to be more difficult, and postoperative right-heart catheterization was only completed in 6 (50%) patients. Due to the dilated native heart being kept in place, all patients received anticoagulation therapy with an International Normalized Ratio target of \(\approx 3\) (1 patient had a cerebral haematoma and 1 had a gastric bleed that required temporary suspension of anticoagulation therapy).

Beasley et al. [16] reported on 42 consecutive adult patients who had similar survival rates to that seen in patients after OHT, if the procedure was performed using a size-matched graft. Indeed, they found HHT with an undersized graft resulted in significantly decreased survival. Kaplan–Meier survival analysis of HHT vs OHT showed a 30-day survival of 76 vs 87\%, respectively. One-year survival was 59 vs 74\%, and 3-year survival was 56 vs 69\%. In these analyses, HHT was not an independent predictor of survival. However, if donor–recipient-size mismatch was excluded from the multivariate model, HHT re-emerged as a predictor, indicating a confounding effect between HHT and size mismatch. This was well known for OHT and, before this study, one may have expected that HHT would abrogate this effect; however, this report did not confirm this opinion. Kawaguchi et al. [17] reported a similar finding using a cardiac graft to perform an HHT in severe donor–recipient mismatches, and these authors already warned to cautiously considering HHT in these cases.

Newcomb et al. [18] retrospectively analysed 20 HHTs performed on 151 patients who underwent heart transplantation at their institutions between August 1997 and September 2003. There were 2 deaths in the HHT group (\(n = 20\)) within 30 days, including one after an endomyocardial cardiac biopsy. Eight deaths occurred within 30 days in the 131 OHTs. The authors noted that 4 of the heterotopic cardiac allograft did not function adequately immediately after implantation, mainly due to ischaemic times being >7 h and high pulmonary-arterial pressures. There were 7 later deaths in the HHT group (mean follow-up was 25 months), and Kaplan–Meier survival curves in this series were statistically different from the OHT group. It is important to note that, at 2 years post-implantation, only 6 recipients in the HHT group were considered to fulfil these statistics. When comparing the subgroups of patients who had a high pulmonary gradient, this difference was diminished (\(P = 0.54\)). In this series, a lower survival time was associated more with HHT compared with OHT patients over the same time period. This survival benefit was lost when subgroup analysis was performed for those patients with a high pulmonary pressure.

Taegtmeyer et al. [19] reported an interesting finding in 2004: HHT patients were found to have lower systolic blood pressure than OHT patients. The authors hypothesized that because HHT leaves the native heart intact, its use may be associated with less hypertension than OHT. This series compared 233 OHT with 38 HHT patients between 1991 and 1999. Despite the lower blood pressure in the HHT patients, survival beyond 3 months and up to 5 years was found to be significantly better than in OHT patients (\(P = 0.044\)).

**DISCUSSION: ADVANTAGES AND DISADVANTAGES**

HHT has many theoretical advantages, these include the following.

(i) The main advantage of HHT is the assistance given by the cases [17]. Heart in the cases of severe acute rejection where it may maintain circulation. Indeed, the residual myocardial function of the remaining native heart may be lifesaving in the cases of acute failure of the heterotopic graft. However, the availability of cyclosporine in 1983 resulted in its decreased utility, and OHT became the configuration of choice. Nowadays, major improvements in mechanical circulatory support, including extracorporeal life support, allow us to deal with early acute graft failure as a bridge to recovery or a bridge to decision.

(ii) HHT has been reported to be advantageous for recipients with irreversible elevated pulmonary resistance [20]. Indeed, HHT may overcome PH, although one should also consider heart-lung transplantation or implantation of an LVAD [21, 22]. Obviously in patients with elevated PH, which decreases significantly after medical treatment (nitroprusside, prostaglandin, dobutamine, inhaled nitric oxide . . .) or implantation of an LVAD, one should instead consider conventional orthotopic transplantation.

(iii) The waiting time until a suitable organ has been found has increased in most of the countries. HHT has been proposed to increase the size of donor pools and to decrease waiting times without increasing morbidity [23]. HHT may be considered in the cases of a significant donor–recipient-size

Figure 4: Final aspect after anastomosis of both aorta and pulmonary arteries.
mismatch. HHT also allows the use of marginal donor hearts that may otherwise be wasted.

(iv) Cardiac transplantation is a life-saving procedure in infants and children with advanced cardiomyopathy. However, it is greatly limited by the shortage of paediatric donors and the complications of very long-term immunosuppression. HHT has the potential to reduce waiting periods for such young patients. Most importantly, this procedure may enable prolonged offloading of the left ventricle and could result in functional recovery of the recipient’s heart [24].

(v) More recently, it has been shown that HHT patients have a reduced incidence of hypertension when compared with those with an OHT, with both groups receiving the same immunosuppression protocols in the same centre [19].

(vi) HHT is extensively used in animal models (especially in the rat and mouse) in order to test various experimental hypotheses from the immunology field to drug monitoring. Most of these models are in the non-working mode, but it can also be used for functional assessment [25].

However, there are several recognized complications of heterotopic graft placement: these include the following.

(a) An early postoperative complication is compression of the right middle and right lower lobes of the lung by the donor’s heart, leading to atelectasis, infection and impaired ventilation. An aggressive approach to prevent atelectasis using bronchoscopy to clear secretions has been proposed [26].

(b) Ventricular arrhythmias have been reported in HHT, although its actual incidence is unknown. Both native and heterotopic hearts may show tachyarrhythmias in the same patient, which can be easily overlooked because the patient’s other heart is acting as a backup biventricular support and may be temporarily asymptomatic [15]. Reduced exercise capacity has been also observed in HHT recipients compared with patients after orthotopic transplantation, possibly due to the competitive contraction of the two hearts. Indeed, the donor’s left ventricle may generate a high afterload to the failing recipient’s left ventricle. However, counter-pulsation of the two hearts is possible by linking them with a pacemaker, which can improve overall haemodynamics in the immediate postoperative period [27, 28].

(c) In patients with ischaemic cardiomyopathy, recurrence of angina in the post-transplantation period can be disconcerting. Although concomitant coronary artery bypass grafting can be performed, the persistence of angina remains a potential long-term problem that affects the recipients’ quality of life. Similarly, progression of native valve disease may occur in the follow-up period.

(d) By leaving the often dilated native heart in place, thromboembolic events may occur at an increased rate [29]. Long-term anticoagulation is then recommended with its own morbidity risk to the transplant recipient.

(e) Another disadvantage of using the heterotopic configuration is the added complexity and prolonged duration of the operation; although it may be discussed, some centres even consider previous cardiac surgery as a contraindication for this procedure [18].

(f) It has been suggested that endomyocardial biopsies in heterotopic patients are much more difficult to realize. This has to be considered for the follow-up, though a modified technique via the femoral vein has been described by Boffa et al. [30].

(g) The main advantage of HHT (assistance of the patient’s native heart in the cases of severe acute rejection to maintain circulation) disappeared with the introduction of cyclosporine in the 1980s. In addition, better options are now available to deal with recipients who have high pulmonary-arterial pressure, especially the implantation of an LVAD. Indeed, adequate left-ventricular decompression, achieved using a continuous-flow LVAD support, despite the partial LV unloading, can reverse significant PH in patients with end-stage heart failure, making them eligible for a heart transplant. Moreover, pulmonary haemodynamics remain within normal limits in the post-transplant period, even in patients with prior severe PH. Thus, the many advantages of the smaller continuous-flow LVADs (e.g., improved durability and reliability, and reduced incidence of adverse complications) can be safely offered as a bridge to transplant to patients with heart failure and PH instead of considering HHT [21, 22, 31]. Recent data suggest that, 6 months after LVAD implantation, an important reduction of PH is observed, and longer support does not add any effect on PH reduction [32]. Relative roles of heart transplantation (HHT or even OHT) and LVAD therapy should be investigated. Indeed, the 1-year survival in LVAD continuous-flow pumps is over 80% and therefore reaching similar intermediate-term outcomes as heart transplantation [33]. The balance comparing both strategies (HHT for HP rather than LVAD then OHT) appears now clearly in favour of mechanical support. However, implantation of the LVAD is not possible in biventricular heart failure, which is often the case for patients on waiting lists. Therefore, implantation of the LVAD is useful for a few specific patients, but will not respond and solve all the problems of PH in this population.

Moreover, long-term mechanical circulatory support with a good quality of life is not yet attainable for patients with biventricular heart failure. By facilitating the utilization of small and marginal donor hearts, HHT increases the donor pool and decreases waiting times. In addition, transplant candidates with a large body size, who often wait considerably longer than other patients to obtain a size-matched graft, may also benefit. This option remains currently one of the best available today; however, new devices dedicated to long-term biventricular support are being developed that may change this approach over the next few years [34].

CONCLUSIONS

OHT is the standard technique and is preferable whenever a patient meets the criteria and a suitable organ is available. HHT is far less useful than in the past due to the major progress in immunosuppression therapy and the development of long-term mechanical circulatory support. The use of HHT may still be considered under special circumstances, but this decision needs to be made in the light of the patient’s expected prognosis and depends on the therapeutic options available.

Conflict of interest: none declared.

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