Abstract

Heterotopic heart transplantation was initially developed in the laboratory for experimental transplantation. While it was more widely utilized in the pre-cyclosporine era to provide adjunct circulatory support in combination with the native heart, associated complications as well as improved long-term graft survival have now established orthotopic transplantation as the procedure of choice. Heterotopic heart transplantation is currently reserved for highly selected patients. The technique is only performed at selected transplantation centers, and indications include significant donor recipient size mismatch or irreversible recipient pulmonary hypertension. The foreseeable introduction of clinical porcine xenotransplantation may lead to renewed interest in the technique of heterotopic heart transplantation as a bridge to potential native heart recovery or allotransplantation in selected patients.

Keywords: Heart; Transplantation; Heterotopic; Xenotransplantation; Pig

1. Introduction

Orthotopic positioning is an established and commonly utilized technique for cardiac transplantation. Nevertheless, heterotopic positioning may be a useful approach in some selected cases. There are currently two accepted indications for heterotopic heart transplantation: (i) preoperative irreversible high pulmonary vascular resistance in the recipient; (ii) significant donor–recipient size mismatch. There may soon be a third indication for heterotopic heart transplantation: xenotranplant bridging. Recent advances in immunology have moved the field of xenotransplantation closer to clinical trials and it is possible that the first porcine xeno-graft will be heterotopically positioned to bridge a patient to allotransplantation or to myocardial recovery.

This article will first review the experimental development and research application of heterotopic heart transplantation. We will then discuss present clinical application of the technique. We will conclude with a discussion of the future application of heterotopic cardiac transplantation, especially its potential use in clinical trials with cardiac xenografts.

2. Experimental development of heterotopic heart transplantation

The phrase ‘heterotopic’ describes placing the heart in an ectopic position without removing the native heart. The heterotopic technique has been used in experimental transplantation and can be categorized into ‘working’ and ‘non-working’ models. In non-working models the donor heart is perfused but does not support the recipient’s circulation. Non-working models have been applied in animal experiments studying anastomotic techniques, immunosuppressive therapies, and immunopathology of graft rejection. The non-working heterotopic approach offers several advantages over orthotopic graft positioning in research applications, including technical simplicity, better accessibility for biopsies, and survival of the recipient even in case of graft rejection.

Non-working heterotopic implantation of the donor heart has been described in different anatomic positions. Following the development of vascular surgery by Alexis Carrel, he and Guthrie performed the first heterotopic heart transplantation. In 1905 they placed the heart of a puppy into the neck of an adult dog by anastomosing the external jugular vein and common carotid artery of the recipient to the aorta, pulmonary artery, vena cava, and one of the pulmonary veins of the donor heart. The donor heart survived for 2 h failing from thrombus formation in both cavities of the heart.
In 1933, Mann et al. simplified this technique by anastomosing the aorta end-to-side to the host’s common carotid artery establishing coronary circulation. The pulmonary artery was connected to the external jugular vein permitting emptying of the venous return of the coronary sinus. The venae cavae and the pulmonary veins were ligated [2]. In the following years several subsequent investigators have used Mann’s technique successfully, mostly in canine models for heart transplantation [3–8]. In 1985, Michler et al. described the heterotopic transplantation of pig hearts into the neck’s of baboons [9]. However, due to space limitation the cervical placement of cardiac grafts is not always possible. Therefore, especially in the setting of small primates, Minanov et al. positioned primate hearts into the iliac fossa of primate recipients [10]. The abdominal positioning of a heterotopic transplanted heart was originally described by Ono and Lindsey [11] and recently employed for transplantation of porcine hearts into baboons [12] (Fig. 1). The abdominal aorta was used as the arterial supply and the inferior vena cava as the venous return of the recipient’s heart. The venae cavae and pulmonary veins were ligated as already described by Mann et al. [2]. Demikov and Sinskiy were the first to attempt the intra-thoracic creation of a working model of heterotopic heart transplantation (i.e. the transplanted heart contributes to the cardiac output of the recipient). Among 20 different techniques of intrathoracic heterotopic heart and lung placement in dogs, Demikov developed a working model and demonstrated in a singular case that the auxiliary heart could maintain adequate circulation in the recipient for 15.5 h [13]. The dog died because of thrombosis of the superior vena cava anastomosis [14].

In 1967, the era of clinical heart transplantation started with the first successful orthotopic cardiac transplantation by Barnard [15]. However, primary graft failure was common and mortality was high. In addition, frequent acute right ventricular failure was a major complication during the first years of human orthotopic heart transplantation. It was realized that orthotopic graft placement could

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**Fig. 1.** Technique for abdominal placement of a non-working model of heterotopic heart transplantation. (A) The superior and inferior venae cavae, hemiazygos and pulmonary veins are identified and vascular inlets are ligated with silk sutures. (B) The pulmonary artery is sutured end-to-side to the inferior vena cava, while the ascending aorta is sutured in a similar fashion to the abdominal aorta. (Reprinted from Adams et al., Ann Thorac Surg 1999; 68: 265–268, with permission [12]).
not be applied to patients with elevated pulmonary vascular resistance.

To overcome these problems Barnard and colleagues expanded on the work of Demikov to developed a working model of heterotopic heart transplantation which is still valid today (Fig. 2). In order to create a working heterotopic cardiac graft it is necessary to establish an atrial connection. Either uni-ventricular or bi-ventricular support is possible with ‘parallel’ placement of the heart. For left ventricular support the heart is placed in the right chest. The donor’s and recipient’s left atria are anastomosed and the donor’s aorta is connected end-to-side to the native aorta. A shunt is established for coronary sinus return by suturing the pulmonary artery to the recipient’s right atrium. In order to create bi-ventricular support a right atrial anastomoses is also performed. The pulmonary arteries are anastomosed, usually by employing a prosthetic end-to-side conduit. After establishment of a working heterotopic heart by parallel positioning, graft atrial and ventricular filling is determined predominately by native heart ventricular end-diastolic pressure. Thus the relative contribution of donor’s and recipient’s hearts to ventricular cardiac output is determined by intracardiac resistances.

Prior to its clinical application Barnard et al. performed extensive experiments in a primate model to evaluate the function of this working heterotopic model [16]. Fifty baboons underwent heterotopic heart transplantation whereby acute cardiac failure of the recipient heart was induced by coarctation of the aorta and ligation of the left anterior descending coronary artery. The experimental results demonstrated that this working model had a low mortality, good donor heart function, and the capability to sustain a normal circulation in the recipient despite acute cardiac failure of the native heart.

3. Clinical experience

Clinical heterotopic heart transplantation was introduced by Barnard and colleagues at the Groote Schuur Hospital, Cape Town, South Africa in 1974 [17]. Based on their experimental surgery in primates, summarized above, they applied the technique in two patients requiring heart transplantation for acute left heart failure. In both cases the donor heart functioned only as a left ventricular assist device using the technique previously described. Both patients suffered from severe left ventricular failure with pulmonary hypertension and moderate elevated pulmonary vascular resist-

Fig. 2. Technique of a working model of heterotopic heart transplantation. The procedure is begun by placing the donor heart in the right chest. Following, the recipient’s left pulmonary vein cuff is anastomosed in a continuous fashion to an opening made on the donor left atrium just behind the interatrial groove (a). Now a longitudinal incision is made on the recipient right atrium anterior to the interatrial groove, and the incision is extended superiorly into the SVC. After the donor right atrium is similarly incised, the donor–recipient anastomosis is performed in a diamond shape (b). Therefore a continuous suture is started at the most caudal point of the donor atrium incision and at the middle point of the incised donor right atrium to accomplish a diamond shaped opening of the atrium. The donor pulmonary artery and aorta are anastomosed in an end-to-side fashion to the recipient pulmonary artery and ascending aorta, respectively (c). Before connecting both aortas, the donor’s aorta is shortened just before the origin of the brancheocephalic trunk to form a 90° angle between the graft and native heart. This allows the widest possible opening and prevents kinking of the right atrial anastomosis. Because of the length limitation, vascular grafts are often necessary to bridge the vessels. Thus, the donor heart is connected in parallel with the recipient functioning as a bi-ventricular assist device. (Reprinted from Chen et al., Graft 1999;2:119–122, with permission of Graft and Landes Bioscience [56].)
tance (PVR). Despite postoperative problems with dysrhythmias leading to several episodes of right sided heart failure, the initial results were encouraging. Both patients survived this new approach to cardiac transplantation. It was concluded that this procedure would offer several advantages over conventional orthotopic heart transplantation.

First, the technique could be used as a temporary device to bridge a patient in reversible cardiac failure to myocardial recovery. Second, as previously demonstrated in earlier experimental work, mortality from acute rejection or infection could be reduced. The circulation of a patient could be maintained in case of rejection by the native heart. In addition, the graft could be removed by side-clamping the three anastomotic areas without the use of cardiopulmonary bypass in the setting of rejection or recovery.

However, these first two cases were complicated by intermittent episodes of ventricular fibrillation of the native heart, leading to acute right-sided failure [18]. Consequently, the technique was modified to allow bi-ventricular circulatory support of the patient’s heart. From 1974 to 1981 38 heterotopic heart transplantations were performed by the Cape Town group. The results of these cases compared favorably with the best orthotopic heart transplantation results of these years. One-year survival was 60% and 4-year survival 50% compared to patients undergoing orthotopic transplants at Stanford University, where 1-year survival was 63% and 4-year survival 44% [19]. A summary of published ‘larger’ clinical series (number of patients > 10) of heterotopic heart transplantation is shown in Table 1.

With the introduction of the immunosuppressive agent cyclosporine the incidence of sudden graft failure due to acute rejection decreased, thus eliminating one of the major advantages of heterotopic heart transplantation (Fig. 3) [20]. Consequently, over the following years orthotopic heart transplantation became the procedure of choice in end-stage heart disease and heterotopic transplantation with its increased morbidity and mortality rate was only performed in a few transplantation centers for specific indications.

Currently, indications for heterotopic transplantation include: (i) the presence of irreversible, high PVR and (ii) significant donor recipient size mismatch. Heterotopic heart transplantation has been reported to be advantageous for recipients with irreversible elevated PVR. Patients with a PVR index greater than 6 Wood units are considered appropriate candidates [21]. This depends on the assumption that the recipient’s right ventricle will support the pulmonary circulation until the graft undergoes a hypertrophic process. Although a combined heart–lung transplantation is an alternative to a heterotopic graft placement, the severe shortage of suitable donor lungs has limited this approach. In all patients with an elevated PVR, preoperative catheterization should be performed in an attempt to decrease the PVR by using multiple drugs such as oxygen, nitroprusside, prostaglandin, isoproterenol, and inhaled nitric oxide. Patients where the PVR can be decreased to less than 6 Wood units by these means should not undergo a heterotopic graft placement, since conventional orthotopic transplantation can provide better outcome [22]. It was once argued that heterotopic heart transplantation should not be performed in pediatric patients with elevated PVR due to their small thoracic cavities. In order to overcome the space limitation, opening of both pleural cavities was suggested [23]. Cochrane and colleagues demonstrated that the hetero-

### Table 1

Clinical experiences in heterotopic heart transplantation

<table>
<thead>
<tr>
<th>Years</th>
<th>No. of patients</th>
<th>Age range (years)</th>
<th>1-year survival</th>
<th>5-year survival</th>
<th>Immunosuppression</th>
<th>Hospital</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1978–1985</td>
<td>22</td>
<td>N/A</td>
<td>N/A</td>
<td>N/R</td>
<td>C.H.U., Nice</td>
<td>Texas Heart, Houston</td>
<td>[54]</td>
</tr>
<tr>
<td>1985–1988</td>
<td>42</td>
<td>24–65</td>
<td>43%</td>
<td>63%</td>
<td>AZ, S, ATG, CS</td>
<td>Groote Schuur, Cape Town</td>
<td>[27,31]</td>
</tr>
<tr>
<td>1986–1987</td>
<td>10</td>
<td>36–65</td>
<td>N/R</td>
<td>N/R</td>
<td>AZ, CS</td>
<td>University of Kiel, Kiel</td>
<td>[53]</td>
</tr>
<tr>
<td>1991–1996</td>
<td>12</td>
<td>1–15</td>
<td>83%</td>
<td>N/A</td>
<td>AZ, CS</td>
<td>Harefield</td>
<td>[55]</td>
</tr>
</tbody>
</table>

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A, azathioprine; ATG, antithymocyte globuline; S, corticosteroids; CS, cyclosporine; N/A, not available; N/R, not reported.
topic technique can be safely applied to this group of patients [24].

Poor outcomes in orthotopic cardiac transplantation have been observed in cases of weight and height donor–recipient mismatch [25,26]. Several studies, however, have reported successful heterotopic transplantation in this setting [27–29]. For example, a study by Reichenspurner et al. suggests heterotopic transplantation in case of a donor recipient weight mismatch of more than 20% [30]. Kawaguchi and colleagues demonstrated that heterotopic graft positioning for severe donor recipient mismatch (donor recipient weight ratio <66%), however, resulted in increased morbidity and mortality when compared to orthotopic heart transplantation [31]. Thus heterotopic heart transplantation should be considered cautiously, in cases of severe donor recipient size mismatch.

Another advantage offered by heterotopic heart transplantation is the possible preservation of the native heart. The residual myocardial function of the remaining native heart may be life-saving in cases of acute failure of the heterotopic graft. Studies of patients suffering from ventricular arrhythmias demonstrated that the heterotopic graft sustains adequately systemic hemodynamics during malignant ventricular dysrhythmias of the native heart. The results of these studies suggest that heterotopic heart transplantation is not absolutely contraindicated in the face of severe ventricular dysrhythmias, as was previously suggested [32,33]. Housmans et al. identified dysrhythmias following heterotopic heart transplantation by selectively obtained precordial ECG recordings from the right and the left chest, respectively [34]. However, conventional ECG skin leads cannot be used as effectively to distinguish between the QRS complex of each heart, to identify the heart rate of each heart, or to detect arrhythmias. Therefore, Nakatani et al. devised a method of monitoring separately the electrical activity of each heart with temporary pacing wires that are placed in the right ventricle of each heart during the operation [28] (Fig. 4).

An additional challenge to postoperative follow-up presents the assessment of graft viability and function requiring invasive techniques like right heart catheterization, endomyocardial biopsies and coronary angiography. By performing more than 300 right and left heterotopic heart catheterization and endomyocardial biopsy procedures and in two-thirds of patients successful angiography, Lowry et al. demonstrated that routine follow-up can be performed safely and reliably in patients following heterotopic heart transplantation. This study does not report any mortality or any other resulting significant morbidity associated with these procedures [35].

There are several recognized complications of heterotopic graft placement. An early postoperative complication is the compression of the right middle and right lower lobes of the lungs by the donor heart, leading to infection and impaired ventilation. Nakatani et al. reports an aggressive approach to prevent atelectasis and used bronchoscopy to clear secretions in eight of 11 patients following heterotopic heart transplantation [27]. Due to the impaired assessment of the opacity of chest X-rays by the presence of the accessory heart in the right chest, computed tomography was found to be useful in detecting and localizing fluid collections, atelectasis, and consolidations. Furthermore a premature deterioration of the recipient heart is often observed after heterotopic transplantation [36,37]. Theoretically,
heterotopic heart transplantation should result in two hearts acting in parallel, each contributing to antegrade blood flow. However, in practice, the recipient heart often fails to eject, with infrequent opening of the aortic valve. The worst scenario shows a retrograde flow due to almost continuous aortic and mitral regurgitation [37,38]. The mechanism of this deterioration is unknown, although possible factors include prolonged ischemia, progression of the underlying heart disease, or asynchronous and competitive contractions of the recipient and donor hearts. Morris-Thurgood et al. demonstrated that paced counterpulsation of the donor’s and recipient’s hearts results in improved hemodynamics, confirming that coupling the systole of a supporting device with the cardiac diastole is hemodynamically preferable to a synchronous setting [41]. Further investigations will be necessary to investigate the influence of long-term counterpulsation pacing on heterotopic heart transplantation recipients.

Due to frequent dysrhythmias and different flow conditions between the two hearts the incidence of thrombus formation is increased in heterotopic heart transplantation. In 1984 a study by Hassoulas et al. showed the incidence of thromobembolism was about 20% in a series of 40 heterotopic heart transplantations [42]. Eight cerebral or peripheral embolic episodes were encountered in six patients. One death occurred after pulmonary embolus. Thus, long-term anticoagulation therapy with warfarin is necessary in patients following heterotopic heart transplantation.

The inclusion of a prosthetic conduit into an immunosuppressed patient following heterotopic heart transplantation is a potential risk for bacterial endocarditis. Subsequently, Cooper et al. regards the presence of a prosthetic valve in the recipient heart as an absolute contraindication to heterotopic transplantation, as the risk of thrombus formation and the potential risk for infection must be higher [20]. Novitzky et al. suggest the removal of a prosthetic valve in order to minimize this potential risk and experienced no infectious complications related to the presence of the prosthetic conduit in 46 cases following heterotopic heart transplantation [44].

Another potential complication in adult recipients following heterotopic heart transplantation is the possible ischemic disease of the native heart which may result of the recurrence of angina. Myocardial revascularization should be performed at the time of transplantation to avoid recurrent angina [43]. A problem of heterotopic heart transplantation isolated to pediatric patients was reported by Reichart. The so-called ‘big heart syndrome’ followed the use of large donor hearts in small recipients, whose brain was not accustomed to higher perfusion pressures. Ensuing cerebral vasoconstriction led to convulsion and coma of the recipient [23]. Careful size matching and close hemodynamic management is essential in the pediatric age group.

4. Future heterotopic heart transplantation: pig xenotransplantation

The shortage in the availability of suitable donor hearts will increase in the future. It is estimated that tens of thousands of patients per year would benefit from heart transplantation, yet less than 3500 cardiac transplants worldwide are performed annually [45]. These limitations on organ availability have increased the interest in potential clinical xenotransplantation.

In the search for a suitable donor species, pigs have emerged as the most likely source for human replacement organs. There are several reasons for this: (i) they grow to human size in a short period of time, (ii) they are easy to raise in large numbers and their short generation time is ideal for genetic manipulation, (iii) the likelihood of endogenous virus transmission is decreased compared to the risk associated with other proposed xenograft donors (i.e. primates), and (iv) there is less ethical controversy about the use of pigs as organ donors.

Several groups have now reported that genetically modified pig cardiac xenografts expressing human complement regulatory proteins are capable of surviving up to several months following transplantation into primates. Recently, Schmoeckel et al. performed orthotopic cardiac xenotransplantations into baboons by using genetically modified porcine hearts. The donor hearts survived up to 9 days [46]. Results from non-working heterotopic models report porcine xenograft survival between 4 days to up to 3 months in a baboon model [47–49]. We believe that prior to initial clinical attempts, consistent long-term survival of working porcine xenografts supporting the circulation must be achieved in the primate models. Further, the immunosuppressive regimen required to achieve this survival must be clinically tolerable, without evidence of primate recipient compromise.

Eventually remaining scientific and ethical barriers will be overcome and clinical trials will be likely initiated in selected transplant centers. The first application of cardiac xenografts could involve attempted bridging of patients in cardiogenic shock to potential recovery or allotransplantation. This xenograft bridging concept was originally introduced by Barnard and colleagues in 1977 when they performed heterotopic transplants from primate donors into two patients in postcardiotomy shock who could not be weaned from cardiopulmonary bypass [50]. In the first case a heart from a 30-kg baboon was transplanted heterotopically into a 25-year-old woman who could not be weaned after reoperative aortic valve replacement. After 5.5 h, the native heart fibrillated and the heterotopic xenograft could not sustain adequate systemic perfusion on its own. Barnard later performed a second heterotopic heart transplant of a chimpanzee heart into a 60-year-old man.
who would not wean from cardiopulmonary bypass following aortic valve replacement. The graft functioned well early on and the patient was taken to the intensive care unit in stable condition. Despite ‘high-dose’ immunosuppression, the function of the transplanted heart deteriorated over 4 days, as did the native heart function. Rose et al. later performed histopathological examination, which revealed rejection of both xenografts [51].

The most significant contribution from this experience was the demonstration that heterotopically placed xenografts could support the circulation of the recipient from hours to days. Barnard concluded that ‘evidence that the patient’s own heart’s function will recover rapidly’ might be one indication for heterotopic xenotransplantation, linking the ‘bridge’ concept to xenotransplantation. Advantages of heterotopic xenotransplantation would include preservation of the recipient’s heart, which might provide lifelong sustaining support in the event of acute xenograft failure, and allow a window for re-replacement of a failed graft [52]. The first candidates for future cardiac xenotransplantation will likely have relative contraindications to conventional mechanical assistance, such as small body surface area or previous mechanical valve replacement. Analysis of the outcome of early cases of heterotopic porcine cardiac xenotransplants will likely determine whether orthotopic placement with hopes for permanent replacement should be attempted.

5. Summary

Heterotopic heart transplantation has been investigated for many years. Currently, indications for a heterotopic graft placement are a significant donor recipient size mismatch and the presence of irreversible, high PVR in recipients. This technique is actively performed only in a few centers as an adjunct procedure in these highly selected patients due to the complexity of the operation, the difficult postoperative care and the potential disadvantages including arrhythmias, thromboembolism, recurrence of angina and bacterial endocarditis. A future application of heterotopic porcine cardiac xenotransplants may occur in the setting of transgenic porcine xenografts bridging patients with cardiogenic shock towards recovery or allotransplantation.

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References


