

## 298例原位心脏移植受者远期疗效分析

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摘要：

**目的** 分析原位心脏移植受者远期疗效。**方法** 2000年5月至2011年4月，复旦大学附属中山医院298例终末期心脏病患者施行原位心脏移植术。男性235例，女性63例；病因构成：扩张性心肌病占73.2%、缺血性心肌病占8.7%、瓣膜性心脏病占6.4%、原发性心脏恶性肿瘤占2.3%、移植物冠状动脉硬化占0.7%。供心不停搏获取238例、停搏获取60例。采用改良圣托马斯液或结合UW液或单用UW液保存技术,供心冷缺血时间69~600 min, 平均 $(191.0\pm 28.5)$ min。移植方法采用双腔静脉法272例、标准法19例、全心法7例。术后采用环孢素或他克莫司+激素+吗替麦考酚酯三联免疫抑制方案；85%受者采用单克隆抗体免疫诱导治疗。术后定期随访。**结果** 所有存活病例均获完整随访，随访时间1~121个月，平均 $(42.5\pm 9.8)$ 个月。移植后1、3、5、8年受者存活率分别为90.3%、82.8%、73.4%、65.2%。移植物衰竭、急性排斥反应、感染、心脏肿瘤转移、猝死为术后1年内主要死亡原因。远期受者主要死亡原因包括移植物冠状动脉硬化、移植物衰竭、急性排斥反应、感染、肾衰竭等。移植后并发症以感染、急性排斥反应、肾功能不全多见。243例存活受者90%心功能恢复至NYHA I~II级，20%恢复全日工作。**结论** 298例原位心脏移植受者长期疗效良好且稳定。严格规律随访并注意监测和防治感染、急性排斥反应、移植物冠状动脉硬化对提高远期疗效具有重要意义。

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Long-term results of 298 cases of orthotopic heart transplantations: a single center experience

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Abstract (摘要部分的英文抄自文章自身翻译)

**OBJECTIVE:** To summarize the 11 years' heart transplantation results at single center and analyze the risk factors of long term survival.

**METHODS:** From May 2000 to April 2011, 298 patients, including 235 males and 63 females, underwent orthotopic heart transplantation in Zhongshan Hospital of Fudan University. Etiology comprised 73.2% dilated cardiomyopathy, 8.7% ischemic heart disease, 6.4% valvular heart disease, 2.6% primary malignant cardiac tumor and 0.7% cardiac allograft arteriosclerosis. Donor heart grafts were harvested with beating hearts in 238 cases and with fibrillated hearts in 60 cases. Heart grafts were preserved with St. Thomas solution and UW solution, with cold ischemic time ranging from 69-600 min, (191.0+/- 28.5) min on average. The operative procedures included 272 bicaval anastomotic cardiac transplantations, 19 conventional Stanford orthotopic cardiac transplantations, and 7 total heart transplantations. Postoperatively, immunosuppressive therapy strategies included cyclosporine or tacrolimus, corticosteroids, and mycophenolate mofetil. Induction therapy with daclizumab was applied in the latest 85% patients. Regular follow-up was arranged postoperatively.

**RESULTS** All recipients were followed up with duration from 1 to 121 months, (42.5+/- 9.8) months on average. The actuarial survival rate was 90.8% after 1 year, 82.8% after 3 years, 73.4% after 5 years, 65.2% after 8 years. Graft failure, acute rejection, infection, metastasis of primary cardiac tumor, and sudden death contributed to the main causes of death in the 1<sup>st</sup> postoperative year, while graft coronary vasculopathy, graft failure, acute rejection, infection, and renal failure contributed to most of long-term mortality. 90 % of survivors (243 cases) enjoyed heart function of class I-II (NYHA) and 20% of them resumed full time job.

**CONCLUSION** Long-term results of heart transplantation in the 298 patients proved to be promising and stable. Regular follow-up with more attention on surveillance and management of acute rejection, graft coronary vasculopathy and infections should result in a better long-term survival.

**Key Words:** Heart transplantation; Long-term outcomes; End-stage heart failure; Rejection; Infection; Monitor

我国1978年心脏移植成功应用于临床[1], 33年来不断有突破, 移植规模不断扩大且早期疗效已经与国际水平相近[2-3]。然而, 到目前为止, 国内尚无移植受者5年以上存活率及生存质量、监护管理等方面多病例数的经验报道。我国心脏移植受者病因构成、供器官保存技术、种族遗传背景、术后管理等方面与国外存在一定差异, 国际上通行的一些管理措

施并不完全适用。因此总结我国心脏移植术后长期管理经验, 分析受者远期疗效的影响因素很有必要。复旦大学附属中山医院自2000年5月以来共完成298例原位心脏移植, 其中6例受者存活超过10年, 已积累目前国内单中心最大宗的原位心脏移植长期存活病例资料。现将这些病例资料作一回顾性分析, 以期发现一些我国心脏移植受者长期存活的特点, 为进一步研究提供思路。

Since 1978 heart transplantation successfully applied to clinical use in China (Ref 1), during past 33 years, there have been breakthroughs in transplant scale expanding continually and early stage outcome has reached close to international standards (Ref 2-3). However, so far, there is no domestic reports on survival rate of 5-year or longer, and recipients' quality of life after transplantation, follow-up care management, and other aspects of the experiences that are from large number of cases. In the area of heart transplant, China is quite different from overseas in terms of recipients' etiology composition, techniques for donor organ preservation, donor genetic background, and postoperative management. Some internationally accepted management practices are not fully applicable in China. Therefore it is necessary to summarize the experiences of long-term postoperative management of patients with heart transplantation, and to analyze the impact factors that are related to long-term efficacy. Since May 2000, Zhongshan Hospital of Fudan University has performed a total of 298 cases of orthotopic heart transplantation, among them the 6 recipients survived more than 10 years. The hospital has accumulated the largest long-term survival data on orthotopic heart transplantation patients from a single-site domestically. This paper made a retrospective analysis of data in order to discover some characteristics of the long-term survival of heart transplant recipients, and provide ideas for further research.

## 1 对象与方法 Subjects and Methods

### 1.1 受者资料 Recipients information

2000年5月至2011年4月复旦大学附属中山医院共完成原位心脏移植298例 (其中1例恶性肿瘤患者心脏移植3年后复发, 统计为移植物3年死亡, 再次心脏移植时作为新病例), 受者男性235例, 女性63例; 年龄8-75岁, 平均 (43.96 $\pm$ 14.57) 岁。病因构成: 扩张性心肌病218例 (73.2%), 缺血性心肌病26例 (8.7%)、瓣膜性心脏病19例 (6.4%)、肥厚性心肌病9例 (3.0%)、限制性心肌病5例 (1.7%)、先天性心脏病5例 (1.7%)、原发性心脏恶性肿瘤7例 (2.3%)、移植物冠状动脉硬化2例 (0.7%)、其他7例 (2.3%)。术前受者肺动脉收缩压20.3-88.0mmHg (1mmHg=0.133kPa, 下同), 平均 (43.5 $\pm$ 14.3) mmHg, 其中55例患者肺动脉收缩压>60mmHg。所有受者移植术前心功能为纽约心脏协会 (NYHA) III-IV级, 其中57%的患者需静脉应用正性肌力药物或利尿剂维持治疗。

From May 2000 to April 2011, Zhongshan Hospital, affiliated to Fudan University, completed a total of 298 cases of orthotopic heart transplantation (1 case of heart transplant patient with malignant tumor recurrence after 3 years, counted as the 3-year graft death, redo heart transplantation counted as a new case). Among these recipients, 235 cases were male, 63 female; age ranged 8-75 years old (mean 43.96 +/- 14.57). Etiology composition: dilated cardiomyopathy 218 cases (73.2%), ischemic heart disease 26 cases (8.7%), valvular heart disease 19 cases (6.4%), hypertrophic cardiomyopathy 9 cases (3.0%), restriction cardiomyopathy 5 cases (1.7%), congenital heart disease 5 cases (1.7%), primary cardiac malignant tumor in 7 cases (2.3%), graft coronary atherosclerosis 2 cases (0.7%), and others 7 cases (2.3 %). Preoperative recipients' pulmonary artery systolic pressure ranged 20.3-88.0mmHg (1mmHg = 0.133kPa, the same below), average (43.5 +/- 14.3) mmHg, among which 55 patients with pulmonary systolic pressure > 60mmHg. All recipients before transplantation cardiac function classified as grade III-IV based on the New York Heart Association (NYHA) standards, 57% of patients required intravenous inotropic agents or diuretics maintenance therapy.

既往史中瓣膜手术9例（12次）、搭桥手术7例、心血管先天畸形纠治术4例、心脏肿瘤剖胸探查术6例、埋藏式心律转复除颤器植入术13例、心脏再同步化治疗植入术2例。17例（5.7%）患者合并糖尿病或糖耐量异常，合并慢性肾衰竭3例、合并肝衰竭1例。术前检查群体反应性抗体阳性（大于10%）5例，其中2例大于25%；其余阴性。Among patients with past operational history, 9 cases (12 times) had valve surgeries, 7 cases of bypass surgeries, 4 cases of cardiovascular repair of congenital malformations, 6 cases of cardiac tumors exploratory thoracotomy, 13 cases of implantable cardioverter defibrillator implantation, 2 cases of cardiac resynchronization therapy implantation. 17 patients (5.7%) had diabetes or impaired glucose tolerance, 3 had associated with chronic renal failure, 1 had hepatic failure. Preoperative examination of panel reactive antibodies found 5 cases were positive (greater than 10%), including 2 cases that were greater than 25%; the remaining cases were negative.

## 1.2 供者资料与供心保存

尸体供心291例、临床脑死亡供心7例。年龄18-45岁，平均 (26.8+/-4.5) 岁。其中男性283例，女性15例。均无明确心血管疾病或其他重大脏器疾病史。供心获取方法与以前的报道相同[4]。在298例中，自2007年后有60例供心在心室颤动或心搏停止状态下获取，其余在心脏仍搏动时获取。早期的10例供体以改良圣托马斯液停搏并保存，其后131例以改良圣托马斯液500mL停搏加UW液1000-2000mL保存，最近157例供心均以UW液500mL停搏加UW液500-1500mL保存。心脏冷缺血时间大于240min，其中60例大于360min。供心检查发现卵圆孔未闭25例、大室间隔缺损1例、冠状动脉开口异常1例。

## 1.2 Donor Information and donor heart preservation

291 cases of donor heart were cadaveric donors, 7 cases were clinical brain death donors. Age ranged 18-45 years old (mean 26.8 +/- 4.5). 283 cases were male and 15

female. All donors had no definite history of cardiovascular disease or other major organ disease. The method to harvest the donor heart was the same as previously reported (Ref 4). Among 298 cases, since 2007, 60 cases of donor heart were harvested from the state of ventricular fibrillation or cardiac arrest, and the other cases were harvested when heart still beating. During the early stage of practices, 10 cases of donor hearts were placed in modified St. Thomas cardioplegia solution for cardiac arrest as well as preservation. Later 131 cases were in 500ml modified St. Thomas solution for cardiac arrest then addition of 1000-2000ml UW solution for preservation. The recent 157 cases were in 500ml UW solution for cardiac arrest then addition of 500-1500ml UW solution for preservation. In general the heart cold ischemic time was longer than 240min, where in 60 cases the time was longer than 360min. During donor heart examination, 25 cases found foramen ovale not closed, 1 case with large ventricular septal defect, and 1 case of coronary ostium abnormal.

供受者ABO血型相合283例，另15例不相合但相容。除5例Rh阴性受者接受Rh阳性供心外，余均为Rh血型相合移植。术后回顾性HLA配型检查发现，仅有10.1%的患者达到1-2个位点HLA匹配。

In 283 cases donor and recipient ABO blood type were matched and another 15 cases mismatched but compatible. 5 cases of Rh-negative recipients received Rh-positive donor heart, the remainder were Rh blood type matched. Postoperative retrospective examination on HLA typing found only 10.1% of patients who achieved 1-2 loci HLA match.

### 1.3 移植方法 Method of transplantation

所有患者术前置Swan-Ganz漂浮导管，监测肺动脉压、计算肺血管阻力。早期的19例（6.4%）患者采用标准法原位心脏移植手术，其后的272例（91.3%）患者采用双腔静脉技术吻合，操作方法与以前报道的相同[4]。2005年后将传统双腔静脉吻合技术进行改良：先完成左心房、主动脉的吻合，然后开放主动脉阻断钳，心搏恢复后再依次完成下腔静脉、肺动脉、上腔静脉的吻合。这样可使心脏缺血时间减少10-15min。有2例复杂心血管畸形伴右位心的患者在采用供心修剪下的主动脉作为补片衔接供受体下腔静脉后仍采用双腔静脉技术完成心脏移植。7例原发性心脏肿瘤患者均采用全心法心脏吻合技术。

Before operation, all patients were inserted with Swan-Ganz floating catheter, their pulmonary artery pressure monitored, pulmonary vascular resistance calculated. During early stage of practice, 19 cases (6.4%) patients were operated with standard orthotopic heart transplant, later 272 cases (91.3%) were operated with double-lumen venous anastomosis technique. The method of operation was the same as previously reported (Ref 4). After 2005, the traditional double-lumen venous anastomosis technology was modified: complete left atrium and aortic anastomosis first, then open the aortic occlusion clamp, followed by recovery of heartbeat, then complete anastomosis in the order of the inferior vena cava, pulmonary artery, superior vena cava. This approach reduced cardiac ischemia time 10-15min. In the 2 cases that patients had complex

cardiovascular malformations with dextrocardia, the heart transplantations were completed with double-lumen venous anastomosis technique after connecting donor-recipient inferior vena cava using donor heart trimmed aortic as a patch. 7 cases of primary cardiac tumor patients were operated with whole heart anastomosis. therefore, prevention against humoral immune response is another important measure to decrease the patients' forward acute rejections and to improve the survival rate of the recipients.

The coronary artery disease of the transplanted organs is another major factor that affects the recipients' survival rate. The diagnosis for coronary disease currently depends on the angiography. Due to lack of understanding for its etiology mechanism, there is so far no effective treatment for it. It is believed that controlling the lipid and blood pressure and taking mycophenolate mofetil would help to mitigate the coronary artery disease of the transplant organ. However, forward coronary artery disease of transplant organ can only be treated by another heart transplantation. As the heart transplant recipient survives longer, the coronary artery disease will become a very imminent issue for the patient.

### 3.3 Improving the living quality of the organ transplant recipients

The living quality of the long-term surviving recipient depends on factors such as the functionality of the transplant heart, the mental adaptability to the social environment, and whether he/she gets hospitalized again due to adverse events. Biologically speaking, 90 percent of the surviving recipients would regain great functionality of the heart without limitation of activities, and could physically undergo large consumption physiological activities, such as physical sports, hard labor, and sexual activities. Many recipients could climb high mountains after transplantation, according to media reports from both in China and abroad. But it's very common for the recipients to experience neuropsychiatric disorders after the transplant, such as depression and paranoid. In particular, depression would cause more serious consequences. Among the cases cited in this article, one recipient committed suicide due to serious depression. Therefore, once neuropsychiatric disorder is spotted, it has to be intervened and treated as early as possible. About 8 percent of the recipients would be hospitalized because of complications, such as acute rejection, infection, transplant organ failure, kidney dysfunction, etc. Rigorous and careful follow-ups will help to diagnose and treat the above-mentioned complications at the early stage, and accordingly would increase the forward survival rate of the patients.

The patients of restrictive cardiomyopathy discussed in this article suffer from comparatively low surviving rate after surgery, majorly due to multiple organ failures shortly after the procedures. So far there has been very little research on this regard. We believe that many restrictive cardiomyopathy patients may sustain long-term microcirculation perfusion abnormalities, which

cause the dysfunction of other organs like liver and kidney. Such dysfunction could hardly be reversed after the heart transplant. Combined with such factors as surgery trauma and drug toxicity, many patients would be more susceptible to multiple organ failure. The low survival rate of primary cardiac malignant tumor patients after heart transplant is related to the choice of the recipient. Such cardiac malignant tumor patients usually already underwent surgeries to exploit and/or resection of the tumor. Only after the regular surgery failed or when life is endangered by hemodynamic disorder, would the patient consider the heart transplant. So the patient is already at more advanced stage of the tumor. The transplant could just prolong the life. Additionally because the tumor metastasis is very hard to detect at the early stage, many patients would die of tumor metastasis after the transplantation. This reminds us that heart transplant is only a palliative treatment for cardiac malignant tumor patients. Clinically we have to first preclude the tumor metastasis to other organs before conducting the transplant.

In conclusion, the long-term survival rate of orthotopic heart transplant recipients depends on many factors. Aside from the surgery skills and protection of the donor heart, measures such as monitoring and treatment of acute rejection and coronary artery disease of the transplant organ would also play a significant role in improving the survival rate of the recipients.

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