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Continuous improvement in outcome after heart transplantation — Long-term follow-up after three decades of experience

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ABSTRACT

Aims: Heart transplantation (HTx) has become the standard treatment for patients with end-stage heart disease. We report on the long-term outcome after HTx at our centre and investigate trends in outcome over time.
Methods: During the period, between 1984 and 2014, a total of 610 HTx procedures were performed in 595 patients (median 48 years; IQR 31–57 years; range 24 days-71 years; mean 43 years; 75% male) in our institution. Long-term outcome was investigated in the whole cohort, among children ($n = 76$), bridged with mechanical circulatory support (MCS, $n = 131$), re-transplanted ($n = 17$), and concomitant kidney transplantation ($n = 12$).
Results: Long-term survival was at 1, 5, 10, 15 and 20 years: 86% (95CI 0.83–0.89); 77% (95CI 0.73–0.80); 63% (95CI 0.59–0.68); 48% (95CI 0.43–0.54) and 30% (95CI 0.25–0.36), respectively. The median survival for the whole cohort was 14.1 years. Patients transplanted during the most recent time period (2010–2014) had a better survival compared to previous eras, with a 1- and 3-year survival of 94% (95CI 0.89–0.97) and 93% (95CI 0.88–0.96), respectively ($p < 0.001$). However, when survival was analysed for long-term MCS ($n = 80$) versus short term MCS ($n = 35$), there was a significantly poorer survival for the short-term MCS group ($p = 0.001$). Independent predictors of long-term mortality included recipient age ($p = 0.041$); previous smoking ($p = 0.034$); ischemic heart disease ($p = 0.002$); and preoperative ventilator therapy ($p = 0.004$).
Conclusions: We have shown that continuous improvement in outcome after HTx still occurs. In the last time era, direct transplantation from short-term MCS was abandoned, which may have inflicted outcome during the last time era.

1. Introduction

The first successful heart transplantation (HTx) was performed in South Africa in the late 1960s [1]. At our centre HTx was initiated in 1984 [2]. In this report we review our three decades of experience with HTx with focus on differences in outcome over time.

2. Material and methods

2.1. Patient demographics

At the Sahlgrenska University Hospital in Gothenburg, Sweden, 610 HTx procedures were performed in 595 patients (median 48 years; IQR 32–57 years; range 24 days–71 years; mean 43 years) between 22nd of June 1984 and 31st of December 2014. Patients that underwent heart-lung transplantation during the same time interval ($n = 38$) were excluded from this study. Indications and contraindications for HTx evolved over time in general in agreement with international guidelines. Patients with heart failure according to New York Heart Association (NYHA) class IIIb or IV, without contraindications, were assessed and worked up for HTx wait listing. Absolute contraindications in the early era, such as pulmonary hypertension and kidney failure, have in the late era been successfully managed with assist devices, concomitant kidney transplantation and kidney sparing immunosuppressive protocols, and therefore converted to relative contraindications.

The present analysis is based on prospectively collected registry information along with data from patient charts gathered retrospectively. The national registration (of births and deaths) in Sweden allows complete tracking of patients, even if they move out of the area of the transplant centre and are followed elsewhere. Consequently, no patient that underwent HTx in this series was lost to follow-up regarding mortality and follow-up was 100% complete. In order to achieve a minimum of 9 months follow-up ending at 30th August 2015 in all surviving patients, the closing interval was chosen between 1st of August and 15th of September 2015. The whole cohort had a median follow-up time of 6.5 years (2383 days) (IQR 2.2–12.7 years (807–4622 days); interval 0–27.6 years; mean 8.2 years).

Patient characteristics for the total HTx cohort are given in Table 1. Median waiting time for HTx was 55 days (IQR 52–140, range 0–769, mean 105 days). Median donor age was 39 years (IQR 24–50), for further donor characteristics see Table 2.

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2.2. Surgical procedure

All patients were operated through median sternotomy and with extra-corporeal circulation. Biatrial technique was initially used but this was slowly changed to bicaval technique during the 1990ths and has been previously described [3]. Over time the complexity of surgery has increased with a higher number of patients having undergone previous thoracic surgery, not least due to bridging with mechanical circulatory support (MCS, $n = 131$). MCS has been used as bridge to HTx in, particular, left ventricular assist devices (LVAD) and extra corporeal membrane oxygenation (ECMO) (Table 1). Short-term MCS has been used as bridge-to-HTx ($n = 35$) and the first cases were managed with the Biomedicus system ($n = 13$: as ECMO ($n = 8$); LVAD ($n = 4$); or right ventricular assist device (RVAD, $n = 1$)) starting in 1988, and continuing through 1997. In 1999 the Abiomed BVS 5000 system ($n = 2$) was used for short-term MCS bridge (as LVAD ($n = 1$) and BVAD ($n = 1$)). From 2007 the Centrimag Levitronix system ($n = 10$) has been used (as ECMO ($n = 6$); LVAD ($n = 2$); or BVAD ($= 2$)), and since 2008, in parallel, the Rotaflow system ($n = 10$) has been used (as ECMO ($n = 8$); BVAD ($n = 1$); or LVAD ($n = 1$)). The last short-term MCS bridge-to-HTx was in 2012 and none thereafter. Different long-term LVAD devices ($n = 57$) have been explanted over time in conjunction with HTx (1994–1999 Novacor ($n = 3$); 1997–2004 Heart Mate I ($n = 15$); 2005–2007 DeBakey ($n = 7$); 2007–2009 Ventrassist ($n = 4$); 2009–2010 Berlin Excor ($n = 3$); 2009–2014 Heart Mate II ($n = 22$); and 2013–2014 HeartWear ($n = 3$)). The Berlin Excor device has also been used for long-term RVAD support ($n = 1$). Finally, long-term BVAD support ($n = 23$) has been achieved with: the total artificial heart (TAH, $n = 2$) between 2008 and 2009; the Berlin Excor ($n = 19$) between 2010 and 2014; and in rare occasions a mixture of devices (Heart Mate II with either Berlin Excor RVAD ($n = 1$) or Centrimag RVAD ($n = 1$)).

Indications for LVAD as bridge-to-HTx were largely in agreement with international guidelines [4]. However, in patients with very poor right ventricular function, those with multi-organ failure, or on-going short-term MCS (INTERMACS class 1) we have preferred a BVAD, instead of a direct HTx, as mostly performed before 2011.

A small number of patients have in addition to a heart transplant also concomitantly received a kidney transplant ($n = 12$), and mostly young patients with mGFR <25 ml/kg/min or on hemodialysis.

Table 1
Patient characteristics.

	Number or Mean ± SD	% or range
Patients	595	
Heart transplantation (HTx) procedures	610	
Age	43 ± 17	24 days–71 years
<18	76	12
18–29	65	11
30–39	70	11
40–49	123	20
50–59	190	31
60–69	83	14
≥70	3	<1
Gender		
Men	458	78
Women	152	22
Smoking		
Never	307	50
Previous, stopped <6 months before HTx	57	10
Previous, stopped >6 months before HTx	213	35
Not known	33	5
Hypertension	63	10
Diabetes Mellitus	62	10
Dietary treatment	12	
Oral medication	18	
Insulin medication	28	
Oral and insulin medication	4	
Neurological insults	76	12
Minor stroke	63	
Transitory ischemic attacks (TIA)	13	
Previous history of malignancy	22	4
Diagnoses		
Dilated cardiomyopathy	324	53
Idiopathic	304	
Adriamycin	4	
Myocarditis (biopsy proven)	16	
Restrictive cardiomyopathy	15	2
Amyloid	7	
Restrictive pericarditis	2	
Other	6	
Hypertrophic cardiomyopathy	20	3
Ischemic cardiomyopathy	146	24
Valvular heart disease	11	2
Congenital heart disease	62	10
Re-transplantation	17	3
ARVD	15	3
Preoperative mechanical circulatory support (MCS)		
No MCS	478	78
MCS	131	22
Short-term MCS, mostly ECMO	35	
Long-term LVAD	57	
Long-term RVAD	1	
Long-term BVAD or TAH	22	
Intra aortic balloon pump	16	
Previous cardiac operation (only first counted, if several)	255	42
Preoperative mechanical ventilation	46	8
Preoperative dialysis	15	2

ARVD = arrhythmogenic right ventricular dysplasia, MCS = mechanical circulatory support, LVAD = left ventricular assist device, BVAD = biventricular assist device, TAH = total artificial heart, ECMO = extra corporeal membrane oxygenation.

2.3. Immunosuppression

All patients have received triple treatment with a calcineurin inhibitor (cyclosporine or tacrolimus), an antimetabolite (azathioprine or mycophenolate mofetil) and a corticosteroid. However, there has been some minor diversity in how immunosuppressive therapy has been managed over time. We have used induction therapy ($n = 510$), mainly *anti*-thymocyte globulin, with some exception ($n = 105$, some of these in the early 1980s and some others as a deliberate decision to withhold). Most patients have been managed with cyclosporine; however, tacrolimus has been used in children or when change in therapy has been required for different reasons from early 2000. In January 2012 we altered the calcineurin inhibitor mainstay therapy changed though from cyclosporine to tacrolimus. Another mainstay therapy change, from azathioprine towards mycophenolate mofetil occurred between 2000 and 2001, and since 2002 nearly all patients have been discharged on mycophenolate mofetil. We participated in the SCHEDULE trial in 2010 and 2011, and have since then consistently used a renal sparing protocol in patients with postoperative kidney failure with everolimus, as described in the study [5]. We have used percutaneous trans venous myocardial biopsies for rejection monitoring, initially 14 biopsies during the first postoperative year, which we have now reduced to 10–11 biopsies. Finally, although not an immunosuppressive treatment, lipid-lowering therapy with statins has been consistently used since the late 1990s.

2.4. Re-transplantation

Re-transplantation has only been offered in selected cases ($n = 17$). Indication for re-transplantation has mostly been late graft failure due to cardiac allograft vasculopathy (CAV, $n = 11$) in patients otherwise without contraindications. A few patients ($n = 6$) underwent early acute re-transplantation (at day 1, 4, 30, 54, 59, 132) due to early graft failure.

Table 2
Donor characteristics.

	Number or Mean ± SD	% or range
Ischemic time donor hearts (min)	190 ± 64	44–399
Donor age	41 ± 16	0–73
Donor length	176 ± 18	55–203
Donor weight	77 ± 19	4–175
Donor gender	190 ± 64	44–399
Male	381	62
Female	229	38
Donor causes of death		
Donation brain dead (DBD)	610	100
Intracranial bleeding	294	48
Thromboembolic stroke	18	3
Trauma	190	31
Other	98	16
Missing data	10	2
Donor blood group		
A	265	43
B	66	11
AB	9	2
0	264	43
Missing data	6	1