The impact of mechanical circulatory support on outcomes in paediatric heart transplantation†

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INTRODUCTION

There can be little doubt that mechanical circulatory support (MCS) has radically changed, and continues to change, the field of cardiac transplantation. In adults, the results of mechanical destination therapy are rapidly approaching those of transplantation in the short term [1]. Paediatric MCS has, however, not experienced the same rapid evolution in technologies due to the large variation in device size required to support children of different ages and the smaller absolute number of patients requiring support. Where fourth- and fifth-generation devices are now in use in adults, the only widely available paediatric MCS devices for young children are of the first generation, and have a significant incidence of complications. Nevertheless, results of MCS continue to improve, allowing a greater number of children to be successfully bridged to transplantation [2].

METHODS

We assessed the outcomes of paediatric (age ≤16 years) heart transplantation in a single unit in the era of mechanical support (1998–2012) by retrospective cohort study. Outcomes before (1998–2005) and after (2005–2012) the routine use of the Berlin Heart EXCOR device were contrasted.

RESULTS: A total of 167 patients underwent heart transplantation during this period. The diagnosis was dilated cardiomyopathy in 61.7%, two-ventricle CHD in 11.4%, single ventricle CHD in 16.8% and miscellaneous in 10.1%. Sixty-nine (41%) were bridged to transplant by mechanical support, with extracorporeal membrane oxygenation in 19 (28%), ventricular assist device in 40 (58%) and a combination in 10 (14.0%). Post-transplant mortality at 30 days was significantly greater in those supported by MCS than without (7 vs 1%, P < 0.05), and a greater proportion of patients had neurological (23 vs 8%, P < 0.01) and major respiratory sequelae (20 vs 4%, P < 0.001).

CONCLUSION: Along with strategies to increase donor utilization, MCS has allowed an increase in cardiac transplant activity at the expense of a higher early mortality and morbidity.

Keywords: Transplantation—heart • Mechanical circulatory assistance • Congestive heart failure

Abstract

OBJECTIVES: Internationally, the number of donors for cardiac transplantation has remained static, while the number of patients requiring transplantation for congenital heart disease (CHD) has increased. Although the availability of mechanical circulatory support (MCS) may increase the number of transplants performed by reducing deaths while waiting, it may also lead to increased morbidity post-transplantation. We sought to assess the impact of mechanical support on post-transplant outcomes in a single centre.

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The number of cadaveric heart-beating donors has decreased, or at best remained static in most parts of the world over the course of the last decade [3]. Coupled with an increasing use of mechanical support, the number of patients on cardiac transplant waiting lists has increased, with infants and small children being the most severely affected by the resultant shortage of donor organs [4]. Prolonged waiting times on mechanical support leads to the accrual of morbidity. Although the use of mechanical support is intended to allow the restoration and or preservation of end-organ function, the thromboembolic and bleeding complications of MCS may actually worsen functional outcome due to neurological and pulmonary sequelae. We sought to assess the impact that the advent of MCS has had in a supra-regional paediatric cardiac transplantation programme.

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METHODS

Prospective MCS and transplantation databases were amalgamated and interrogated for outcomes of patients ≤16 years of age listed for transplantation between 1998 and 2012. This represents the period in which a bridge-to-transplant MCS programme has existed in our institution. In patients with cardiac failure and clinical deterioration despite inotropic support, MCS was offered as a bridge to transplantation, initially in the form of extracorporeal membrane oxygenation (ECMO). Between 1999 and 2003, we additionally used the Medos ventricular assist device in patients in whom a longer period of support was expected. From 2005, the Berlin Heart EXCOR device was used in these patients predominantly, with the Levitronix Centrimag device being employed in some instances. Over time, a bridge-to-bridge strategy has evolved in the sickest patients, with initial stabilization on ECMO and subsequent implantation of a Berlin Heart EXCOR device if longer-term support was required. ECMO was instituted via neck vessel cannulation in the majority of patients and using a closed circuit and roller pump initially, and the Levitronix Centrimag pump system since 2010. Orthotopic cardiac transplantation was carried out using standard operative techniques and immunosuppressive protocols.

The impact of era (before and after the Berlin Heart EXCOR system entered our routine practice in 2005) was assessed in terms of post-transplantation outcomes, activity and impact on waiting list outcomes. The earlier era comprised patients who underwent transplantation between April 1998 and March 2005, and the recent era, between April 2005 and February 2012. Outcomes analysed included duration on waiting list, removal from waiting list, death while awaiting transplantation, survival after transplantation and major complications. Competing hazards methodology was used to analyse the impact of mechanical support on waiting list outcomes according to the method of Fine and Gray [5]. In this analysis, transplantation with survival to hospital discharge and transplantation leading to death before hospital discharge were considered as competing outcomes. All parametric variables are presented as mean ± standard deviation and non-parametric variables as median with inter-quartile range. Between-group differences in categorical variables were analysed by χ2-test or Fisher’s exact test as appropriate, and continuous variables by Student’s t-test unless non-parametrically distributed. All hypothesis tests used a 0.05 significance level. Analyses were performed using Stata v 11. Our institutional ethics review board approved the study and waived the need for individual patient consent.

RESULTS

Between January 1998 and March 2012, 236 patients ≤16 years of age were accepted onto the active waiting list for heart transplantation. Of these, 64 (26.3%) were infants, 112 (46.1%) were between 1 and 9 years of age, and 67 (27.6%) were ≥9 years of age. Of these listed patients, 167 underwent orthotopic cardiac transplantation, with 69 (41%) of them requiring MCS as a bridge to transplantation. Mechanical support comprised ECMO in 19 (28%), ventricular assist device in 40 (58%)—Berlin Heart EXCOR (31), Levitronix (5) and Medos (4). Ten (14%) required a ‘bridge-to-bridge’ strategy with initial stabilization on ECMO and subsequent conversion to Berlin Heart. The median duration of support was 17 days (1–187). Patient demographics are detailed in Table 1. The mechanically supported group comprised a significantly greater proportion of infants, but the underlying diagnosis was similar between groups, with 28% of children transplanted having congenital heart disease (CHD). Other demographics were similar between groups, apart from a significant preponderance of pre-transplant renal failure requiring replacement therapy and neurological deficits in the mechanical support group.

Median duration on the waiting list for infants increased from 45 (311 days) to 53 (59 days) in the consecutive eras. Children aged 1–9 were similarly affected; 20 (66 days) increased to 61 (86 days) and children 10 years of age and older waited 8.5 (23 days) in the first era and 14 (41 days) in the most recent era. This increase was, however, only statistically significant in the age group 1–9 years (P < 0.01, Mann–Whitney). The proportion of patients requiring MCS prior to transplantation also increased from 16 of 63 (25%) in the early era to 53 of 104 (51%) in the current era.

A greater proportion of patients requiring MCS developed new neurological deficits (28 vs 2%) and required renal replacement therapy (26 vs 2%, P < 0.001), prior to transplantation. Overall survival to discharge was 75% for VAD and 58% for ECMO. Transplant outcomes for patients who did or did not receive MCS are contrasted in Table 2. Survival after transplantation was poorer in patients bridged mechanically to transplantation, with 30-day mortality of 7 vs 1%. Subsequent morbidity was also increased, with 23 vs 8% having new neurological events, and 20 vs 4% requiring tracheostomy after transplantation. Survival in the longer term however was not significantly

<table>
<thead>
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<th>Table 1: Patient demographics</th>
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<td>Age</td>
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<td>0–1</td>
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<td>1–10</td>
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<td>10–16</td>
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<td>Diagnosis</td>
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<tr>
<td>DCM</td>
</tr>
<tr>
<td>CHD–2 ventricle</td>
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<tr>
<td>CHD–1 ventricle</td>
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<tr>
<td>HCM</td>
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<td>RCM</td>
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<td>Other</td>
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<td>Previous cardiac surgery</td>
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<td>Circulatory support</td>
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<td>None</td>
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<td>ECMO–VAD</td>
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<td>BiVAD</td>
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<tr>
<td>Pre-transplant renal support</td>
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<td>Pre-transplant neurological event</td>
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MCS: mechanical circulatory support; DCM: dilated cardiomyopathy; CHD: congenital heart disease; HCM: hypertrophic cardiomyopathy; RCM: restrictive cardiomyopathy; ECMO: extracorporeal membrane oxygenation; VAD: ventricular assist device; LVAD: left ventricular assist device; BiVAD: biventricular assist device.
Impact of pre-transplant mechanical support in univariate analysis (log-rank \( P = \text{NS} \))

The use of MCS as a bridge to transplantation has contributed to an increase in overall cardiac transplantation activity (Fig. 2). Nevertheless, 45 patients died while on the waiting list for cardiac transplantation. Of these, 10 were on VAD support at the time, and 8 on ECMO. Competing hazards analyses for waiting list outcomes in the early and late cohorts are demonstrated in Fig. 3. Competing outcomes curves are virtually superimposable and era of listing is not a significant predictor of death on the waiting list in competing outcomes regression analysis (\( z = -0.98, P = 0.327 \)).

**DISCUSSION**

In the child with cardiac failure, MCS potentially allows for the restoration and/or preservation of end-organ function until such time as myocardial recovery occurs or, in the majority, until a suitable cadaveric donor becomes available for transplantation. Adult MCS devices have undergone a rapid evolution with long-term support using extracorporeal devices now possible with morbidity and mortality rates approaching those of transplantation in some series [1]. The large range of paediatric body sizes and relatively small size of the thoracic cavity limits the possibility of extracorporeal devices in children to very small devices, which remain under development [6–8]. As a result, extracorporeal pumps are the predominant alternative. These systems necessarily impose a larger surface area exposed to device/blood interactions and also multiple/larger percutaneous entry sites. Additionally, extracorporeal devices impose a greater limitation of mobility, delaying rehabilitation. These factors combine to increase the morbidity in children requiring MCS and ultimately limit the duration for which it can be provided safely. The Berlin Heart EXCOR device has become widely used and has been the subject of a recent prospective trial [9]. This demonstrated the comparative efficacy of the device in relation to a matched cohort of patients who received ECMO for MCS, with significantly superior survival. Durable circulatory support is achievable to well over a year, but with these long periods of support, complications will generally intervene to preclude transplantation [10, 11]. We have found shorter durations of support up to 187 days to be generally well tolerated with rates of neurological and respiratory complications of 23 and 20%, respectively, comparable with those of other series [10, 12, 13]. Although very troubling, this represents a significant improvement over what can be achieved with ECMO in the majority of centres [14] and compares favourably with waiting list attrition in this very sick cohort.

**Figure 1:** Kaplan–Meier survival estimates for paediatric patients after transplantation stratified by pre-transplant mechanical support.

**Figure 2:** Paediatric cardiac transplant activity. Bars denote number of transplants per year with grey bars indicating number of transplants without prior mechanical support and black bars those requiring mechanical support prior to transplantation. Only completed years during the study period are graphed.

Ultimately, the availability of suitable donor organs will determine the period of support that is required. The increasing demand for such organs has resulted in a progressive increase in the time spent on the waiting list over the past 14 years, with infants and younger children being the most severely affected. Although this would have resulted in a greater number of deaths on the waiting list, MCS has allowed some of these patients to be bridged to transplant without an increase in waiting list mortality. A continuation of the trend of longer durations of support will, however, lead to the greater accrual of morbidity before transplantation, and possibly worse outcomes following transplantation. We have found that the management of anticoagulation in the infant VAD cohort can be particularly problematic, frequently requiring periods of reduced anticoagulation for bleeding complications or repeated VAD ventricle changes for thrombus/fibrin deposit formation. Despite a relatively aggressive approach to the latter, cerebral vascular events remain persistently high at 20–30%, equivalent to that in most series [10].

The observed increase in transplant activity in the most recent era may be attributed to a number of reasons. Careful scrutiny of donor selection criteria has revealed that many factors previously thought to predict poor graft function have no impact on outcome [15]. As a result, acceptance of donors has been

<table>
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<tr>
<th>30-day mortality</th>
<th>No MCS (n = 98)</th>
<th>MCS (n = 69)</th>
<th>( P )</th>
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<tr>
<td>Renal support</td>
<td>9 (9%)</td>
<td>9 (13%)</td>
<td>NS</td>
</tr>
<tr>
<td>New neurological event</td>
<td>8 (8%)</td>
<td>16 (23%)</td>
<td>0.011</td>
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<tr>
<td>Tracheostomy</td>
<td>4 (4%)</td>
<td>14 (20%)</td>
<td>0.001</td>
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<tr>
<td>Post-transplant MCS</td>
<td>6 (6%)</td>
<td>8 (12%)</td>
<td>NS</td>
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**Table 2:** Short-term outcomes of transplantation after MCS
liberalized, possibly allowing a greater number of transplants than in previous years. The use of organs across ABO, and to some degree, human leucocyte antigen incompatibility boundaries, has possibly also contributed to an increase in the number of donor organs utilized [16, 17]. Almost certainly, mechanical support has itself played a role in allowing the sickest patients to be maintained in a suitable condition for transplantation. Where some of these children may previously have died awaiting a suitable donor, the majority will now survive to transplantation.

Although this is to some extent balanced by an increase in peri-transplant mortality in mechanically supported patients, taking into account the increase in activity, a greater number of successful outcomes have been achieved. Hopefully, improved technologies and greater experience in management will translate into continuing improvement of outcomes of the paediatric population mechanically bridged to transplantation.

**CONCLUSION**

MCS has been an important factor in increasing paediatric cardiac transplant activity. Although a bridge-to-transplant strategy is associated with longer waiting times and an increase in morbidity and early mortality, outcome in the medium term remains good.

Conflict of interest: none declared.

**REFERENCES**


APPENDIX. CONFERENCE DISCUSSION

Dr D. V. Alexi-Meseshkivili (Berlin, Germany): I would like to ask you how you decide during the operation to implant a left ventricular assist device or a biventricular assist device, because according to our experience in Berlin it’s very difficult to decide it before the operation.

Dr Botha: Quite so. I think our strategy is if both ventricles look very poor preoperatively, then we go to the operating room assuming that we’re going to have to implant a BiVAD. If there is any doubt, we’ll implant an LVAD first, see how the heart reacts to trying to come off bypass and then implant an RVAD if it’s necessary. We don’t want to fall back to an RVAD later on, so we make that decision sometimes in the operating room but leaning towards implanting a BiVAD if we’re not certain.

Dr I. Afridi (Rawalpindi, Pakistan): My question is, do these children usually go home after these procedures?

Dr Botha: No, we’ve not been able to discharge children on the Berlin heart as yet. As you may know, the driver is quite a large cumbersome device. We have taken children to the shops within the hospital and out to the park. They are on the normal ward or our high dependency ward. Although we have many adult patients with intracorporeal devices at home, we have not been able to discharge a child home yet with these devices because of the limitations of the driving unit and so forth.

Dr R. Prêtre (Lausanne, Switzerland): Obviously a patient on an assist device is at risk for neurological damage, but you also showed us that those very patients have an additional risk during the procedure, during transplantation, compared to those who had no device. How do you really explain that, is it mobilization of thrombi within the heart?

Dr Botha: Well, we take great care to try and avoid losing any emboli into the circulation. It’s very difficult to discern those, though, in terms of analysis, because some patients may have had a neurological event, for instance, have a scan confirming it while they’re on the VAD and then not have a further scan until after transplantation. I know there are three or four patients such as this within this cohort, where we scan them again after transplant and find a change, then we have to attribute that to a peri-transplant injury. But it may not have happened at the time of transplant, it may have actually happened on the VAD before the transplantation. I believe in our early experience we had air embolism at the time of explant in one patient. But in the majority it’s very difficult to pinpoint the time when these injuries happened.

Dr Prêtre: Another quick question, how many Fontan patients did you have in this series?

Dr Botha: We have, I believe, three completed Fontans. But we have nine patients with the univentricular circulation at some stage of palliation.

Dr B. Maruszewski (Warsaw, Poland): I’d like to ask you (because I know that you have quite a substantial group of patients that you manage to wean from left ventricular support) what your criteria are for trying to wean and how do you test it, to wean patients from left ventricular or biventricular support? And how many of those who you put on the Berlin heart did you manage to wean off?

Dr Botha: Often we don’t have histology to guide us at the time of implantation. But when we do the implant, we obviously send a specimen of the myocardium away from the LV apex. If that shows signs of myocarditis, obviously we’d try to wean much earlier on. Also, with an acute deterioration, we would try to wean them earlier on. But we have a set programme guided by Dr. Kirk, who will, I believe, do the first assessment at four weeks. We’d start moderate-dose inotropes and then reduce the VAD flow and see what the echo looks like and make a decision on that. And we’ll repeat the test, if it looks like it’s getting better, we’ll repeat it sooner rather than later if things look to be improving.

Dr J. Comas (Madrid, Spain): So now a little more about the resources that you need. How many patients could be on mechanical support waiting for transplant in your unit at the same time?

Dr Botha: Well, within the last year we’ve had quite a bad time with small infants particularly. We’ve had four infants on VAD in our centre. And the only other regional transplant centre being in London, I think they also had two or three, all within the same age and weight category, so competing for transplants. So four, I would say, is the maximum that we’ve had.

Dr Comas: So there can be two patients waiting during the same period?

Dr Botha: Oh, yes, absolutely, that is often the case.

Dr Comas: How many people are involved in the follow-up of these patients?

Dr Botha: While they’re inpatients, they remain either on the high dependency unit or in the intensive care unit, and we have to sometimes balance in terms of resources. We can’t have all four, for instance, in the high dependency unit because we only have so many nurses who are skilled and trained. And so a large team, I would say, I couldn’t give you the exact number.

Dr E. Belli (Paris, France): Do you think there is still a margin for LA-aorta, Berlin heart left heart assist device?

Dr Botha: With normal anatomy, I think possibly not. We used the Medos device with less than satisfactory results using left atrial cannulation. We attributed some of the negative results to the atrial cannulation. We have, for anatomical reasons, cannulated the aorta in single ventricles, for instance, and we’re not really sure, but I think the apical ventricular cannulation seems to be the better approach. Our results have been steadily improving with this approach.

Establishing evidence for high-risk medical devices in orphan diseases

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Keywords: Children • Heart transplantation • Left ventricular assist device • Stroke • Orphan medical devices

In this issue, Botha et al. [1] report their clinical experience of using mechanical circulatory support in infants and children awaiting heart transplantation in a single centre between 1998 and 2012. Survival to transplantation was improved by using mechanical support for a median duration of only 17 (range 1–187) days, but at a cost that included neurological complications...