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ORIGINAL ARTICLE

Mechanical circulatory support after heart transplantation†

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Abstract

OBJECTIVE: Mechanical circulatory support (MCS) may be used for severe graft failure after heart transplantation, but the degree to which it is lifesaving is uncertain.

METHODS: Between June 1990 and December 2009, 53 patients after 1417 heart transplants (3.7%) required post-transplant MCS for acute rejection ($n = 17$), biventricular failure ($n = 16$), right ventricular failure ($n = 16$), left ventricular failure ($n = 1$), or respiratory failure ($n = 3$). Although support was occasionally instituted remotely post-transplant (5 > 1 year), in 39 (73%) instances it was required within 1 week. Initial mode of support was extracorporeal membrane oxygenation in 43 patients (81%), biventricular assist device in 4 (7.5%), and right ventricular assist device in 6 (11%).

RESULTS: Risk of requiring respiratory support was highest in those with restrictive cardiomyopathy as indication for transplant, women, and those with elevated pulmonary pressure or renal failure. Complications of support, which increased progressively with its duration, included stroke in two patients (3.8%), infection in two (3.8%), and reoperation for bleeding (seven instances) in four (7.0%). Nineteen patients (36%) recovered and were removed from support, five (9.4%) underwent retransplantation (four after biventricular failure and one after acute rejection), and 29 died while on support (55%). Overall survival after initiating support was 94%, 83%, 66%, and 43% at 1, 3, 7, and 30 days, respectively. Patients requiring support for biventricular failure had better survival than those having acute rejection or other indications ($P = 0.03$). Survival after retransplantation or removal from support following recovery was 88% at 1 year and 61% at 10 years.

CONCLUSION: Severe refractory heart failure after transplantation is a rare catastrophic event for which MCS offers the possibility of recovery or bridge to retransplantation, particularly for patients with biventricular failure in the absence of rejection. Early retransplantation should be considered in patients who show no evidence of graft recovery on MCS.

Keywords: Heart transplantation • Graft failure • Mechanical circulatory support

INTRODUCTION

Primary graft failure is a catastrophic complication and the most common cause of early death after heart transplantation [1]. Graft failure can be caused by poor myocardial preservation of the donor heart, prolonged ischemic time, right ventricular failure caused by high pulmonary vascular resistance of the recipient, and rejection [1–3]. Initial pharmacologic measures of support most commonly include a combination of inotropic agents (e.g., milrinone, dobutamine, and epinephrine) and pulmonary vasodilators (nitric oxide). Mechanical circulatory support (MCS) is indicated for patients whose graft function remains poor despite optimal medical therapy [4–9]. Commonly used forms of MCS include extracorporeal membrane oxygenation (ECMO) and right and biventricular assist devices. Although instituting MCS following primary graft failure results in immediate hemodynamic improvement, long-term outcome is not well known. The purpose of this study was to examine effectiveness of MCS on survival of patients after heart transplantation.

PATIENTS AND METHODS

Patient demographics

Between 1 January 1990 and 1 January 2010, 1417 heart transplants were performed in 1387 patients at Cleveland Clinic. MCS was instituted for primary graft failure after 53 transplants (3.7%). The most common indications for transplantation were dilated cardiomyopathy ($n = 23$ (43%)) and

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ischemic cardiomyopathy ($n = 21$ (40%)) (Table 1). Age at transplantation ranged from 7.5 to 66 years (mean 48 ± 14 years). Weight (mean 73 ± 21 kg) and body mass index (25 ± 5.1 kg m^{-2}) were similar to those of other heart transplant recipients, as was total ischemic time (160 ± 73 vs 160 ± 70 min) (Table 1). Preoperative patient characteristics and intraoperative data were retrieved from the Electronic Data Interface for Transplantation (EDIT), a database maintained concurrently with patient care and approved for use in research by the Cleveland Clinic's Institutional Review Board, with patient consent waived. Incomplete information was supplemented by reviewing patient medical records.

Mean follow-up of survivors was 6.5 ± 4.1 years, with 25% followed more than 9.7 years and 10% more than 12.3 years. A total of 142 patient-years of data was available for analyses.

Table 1: Recipient and donor characteristics

Characteristic	MCS (total $n = 53$)		Non-MCS (total $n = 1364$)	
	n[a]	No. (%) or mean ± SD	n[a]	No. (%) or mean ± SD
Recipient				
Demographics				
Age (years)	53	48 ± 14	1361	49 ± 16
Female	53	21 (40)	1364	313 (23)
Race	53		1360	
Caucasian		40 (75)		1162 (85)
African-American		9 (17)		158 (12)
Other		4 (7)		40 (3)
Height (cm)	53	170 ± 12.0	1307	170 ± 19.0
Weight (kg)	53	73 ± 21	1311	74 ± 21
Body mass index (kg m^{-2})	53	25 ± 5.1	1303	25 ± 4.9
Body surface area (m^2)	53	1.9 ± 0.32	1303	1.9 ± 0.36
Indication for transplant				
Coronary artery disease	53	21 (40)	1364	587 (43)
Dilated cardiomyopathy	53	23 (43)	1364	516 (38)
Restrictive cardiomyopathy	53	7 (13)	1364	69 (5.1)
Valvular heart disease	53	1 (1.9)	1364	38 (2.9)
Congenital heart defect	53	1 (1.9)	1364	58 (4.4)
Comorbidity				
Diabetes	53	6 (11)	1364	220 (16)
Hypertension	53	12 (23)	1364	259 (19)
Dialysis	53	2 (4)	1364	50 (4.0)
COPD	53	2 (4)	1364	47 (3.4)
BUN (mg dl^{-1})	49	31 ± 23	1186	26 ± 14
Serum creatinine (mg dl^{-1})	49	1.3 ± 0.49	1192	1.3 ± 0.94
Surgical				
Total ischemic time (min)[b]	53	160 ± 73	1317	160 ± 70
Hemodynamics				
Diastolic blood pressure	27	64 ± 10	594	63 ± 12
Systolic blood pressure	27	00 ± 16	597	100 ± 19
Cardiac index	30	2.2 ± 0.69	723	2.0 ± 0.60
Cardiac output	34	4 ± 1.4	774	3.9 ± 1.9
Diastolic PPA	41	27 ± 9.8	1064	24 ± 9.0
Systolic PPA	41	51 ± 18	1063	47 ± 16
Donor				
Age (years)	52	35 ± 15	1256	34 ± 14
Female	52	26 (50)	1296	508 (39)
Race	52		1264	
Caucasian		43 (83)		1062 (84)
African-American		4 (7.7)		177 (14)
Other		5 (9.6)		25 (2)
Height (cm)	51	170 ± 20	1258	170 ± 18
Weight (kg)	51	70 ± 17	1271	75 ± 27
Body mass index (kg m^{-2})	51	27 ± 19	1257	27 ± 9.2
Body surface area (m^2)	51	1.8 ± 0.28	1257	1.9 ± 0.37
Recipient–donor mismatch				
Gender mismatch	52	19 (37)	1296	468 (36)
Race mismatch	52	9 (17)	1264	252 (20)
Recipient–donor ratios				
Weight	51	1.0 ± 0.2	1253	1.0 ± 0.23

Key: BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary disease; MCS, mechanical circulator support; PPA, pulmonary artery pressure.
[a]Patients with data available.
[b]Includes pump time.

MCS: definitions, indications, timing, and modalities

Primary graft failure was defined as a need for MCS for hemodynamic failure of the transplanted heart regardless of etiology, despite maximal pharmacologic therapy. Milrinone, dobutamine, and epinephrine were the most common inotropic agents used in the early postoperative period. Vasopressin and norepinephrine were used to treat hypotension in patients with low systemic vascular resistance.

The etiology of graft failure is unknown in most patients at its onset. We have therefore characterized primary graft failure according to mode of presentation into (1) biventricular failure (in the absence of acute rejection), (2) right heart failure (secondary to increased pulmonary resistance or suboptimal myocardial protection), and (3) acute rejection (documented by myocardial biopsy). Diagnosis of right or biventricular failure was based on hemodynamic measurements and clinical presentation, along with echocardiographic findings. Our analysis also included patients who required MCS after heart transplantation due to isolated respiratory failure.

Indications for MCS included acute rejection in 17 patients (32%), biventricular failure in 16 (30%), right ventricular failure in 16 (30%), and respiratory failure in 3 (6%). Isolated left ventricular failure was an indication for MCS in 1 patient (2%).

Timing of MCS depended on etiology and severity of primary graft dysfunction. Of the 53 patients, 23 had support initiated on the day of transplant, 8 at 1 day after transplant, and 5 at more than 1 year post-transplant.

Modality of MCS was determined by the operating surgeon and depended on extent and severity of myocardial dysfunction and presence or absence of associated pulmonary dysfunction. ECMO was used in 43 patients with right or biventricular failure accompanied by respiratory insufficiency. Right ventricular assist devices (RVADs) were used for patients with isolated right ventricular failure and preserved pulmonary function ($n = 6$). Biventricular assist devices (BiVAD) were implanted in four patients with preserved pulmonary function and biventricular graft failure. Seven patients required more than one type of device, and one patient required three different devices (Fig. 1).

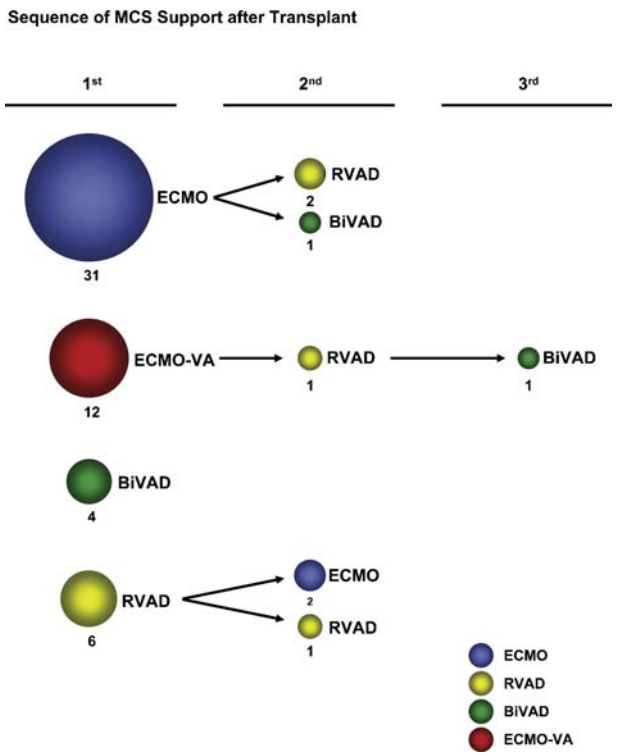

Figure 1: Sequence of mechanical circulatory support. The volume of each sphere is proportional to the number of patients who received that support device.

Surgical technique

Organ procurement was performed in standard fashion from brain-dead, beating-heart donors (Table 1). All patients underwent orthotopic heart transplantation using bicaval anastomoses. Neither harvesting nor implanting technique changed during the course of the study.

Data analysis

Risk of MCS. Logistic regression analysis was used to identify risk factors for MCS after the 1417 heart transplants using the following variables (italicized variables were associated with at least five deaths and thus were used in the death model described subsequently):

(i) Recipient variables: *gender*, age, *race, body mass index*, *body surface area*, *coronary artery disease*, *dilated cardiomyopathy*, restrictive cardiomyopathy, coronary artery bypass grafting, stroke, *myocardial infarction*, open heart surgery, sternotomy, diabetes, hypertension, *smoking*, blood type (A, AB, B, O), Rh+, *pulmonary arterial pressure* (diastolic and systolic), *albumin*, *blood urea nitrogen*, *creatinine*, *hemoglobin*, *total bilirubin*, *ischemic time*, *years from 1/1/1990 to transplant*.

(ii) Donor variables: *gender*, *age*, *race*, *body mass index*, *body surface area*, *blood type*, *cause of death*.

(iii) Recipient–donor: *gender mismatch*, *race mismatch*, *weight ratio*.

Variable selection used bagging, whereby 500 bootstrap samples were drawn from the data set and automatically analyzed for variables significant at $P = 0.05$ [10]. Thereafter, these results were aggregated. We generally consider risk factors reliable if they enter 50% or more of analyses.

Complications of MCS. Cumulative incidence estimates of complications were estimated by the repeated-events method of Nelson [11].

Competing outcomes on MCS. Three mutually exclusive outcome states were considered: (1) retransplant, (2) MCS removal for recovery, and (3) death before either retransplant or MCS removal. These end states were defined by the earliest transition from 'alive on MCS' to one of these outcome states, or 15 June 2010, for those subjects still alive who had not experienced any of these outcomes.

Freedom from each outcome was estimated by the nonparametric product limit method, and variances of the estimates were based on the Andersen formula [12]. The instantaneous risk (hazard function) for each competing event was estimated by a parametric method [13]. Consequences of the independent,

simultaneously operative transition rates (hazard functions) from the category 'alive on MCS' into each of the outcome states were calculated by integrating the parametric equations [13].

Survival after initiating MCS. Survival estimates were obtained nonparametrically by the Kaplan–Meier method and parametrically by multiphase hazard analysis [13]. The parametric model was used to resolve the number of phases of instantaneous risk of events (hazard function) and to estimate shaping parameters for each. Survival was estimated while on MCS, overall, and after retransplant or device removal.

Risk factors for all-cause mortality after initiating MCS were identified for each of two hazard phases using bagging as described above and variables that were associated with at least five deaths, listed in preceding text under Section 'Risk of MCS'.

Presentation. Continuous variables are summarized by mean ± standard deviation. Categorical variables are summarized by frequencies and percentages. Uncertainty is expressed by 68% confidence limits, comparable to ±1 standard error. Statistical analysis used SAS version 9.1 software (SAS Institute, Inc., Cary, NC, USA).

RESULTS

Risk of MCS

Patients at highest risk of primary graft failure requiring MCS were those with restrictive cardiomyopathy (7/53 (13%) MCS patients vs 69/1364 (5.1%) non-MCS patients) and women (21/53 (40%) MCS patients vs 313/1364 (23%) non-MCS patients) (Table 2). Patients with elevated pulmonary artery pressure and renal insufficiency were also at higher risk.

Complications of MCS

Complications of MCS included stroke in two patients (3.7%), device infection in two (3.7%), and reoperation for bleeding in four (7%). Cumulative number of events increased nearly linearly with duration of MCS at the rate of 0.34 events/patient per week.

Table 2: Risk factors for mechanical circulatory support after heart transplant

Factor	Point estimate ± SE	*P*	Reliability (%)[a]
Restrictive cardiomyopathy	2.6 ± 0.43	0.02	61
Female	2.2 ± 0.29	0.006	59
Diastolic PPA	1.03 ± 0.015	0.04	43
BUN (mg dl^{-1})	1.02 ± 0.011	0.02	56

Key: BUN, blood urea nitrogen; PPA, pulmonary artery pressure; SE, standard error.
[a]Percent of times factor appeared in 500 bootstrap samples.

Competing risks

During the course of the study, 19 patients (36%) were removed from MCS for recovery, with the highest rate on days 2 and 3 of support; five (9.4%) underwent retransplantation (four after biventricular failure and one after acute rejection), at a nearly constant rate during MCS; and 29 died while on MCS (55%), at an increasing rate as duration of MCS was prolonged (Fig. 2).

Survival after MCS

Survival of patients requiring MCS at 1 day, 3 days, 1 week, 1 month, 1 year, 5 years, and 10 years was 94%, 83%, 66%, 43%, 40%, 37%, and 29%, respectively (Fig. 3). Probable risk factors for death after MCS included indications for MCS other than biventricular failure (acute rejection or right ventricular failure) (Fig. 4), renal insufficiency, and larger recipient–donor weight ratio (Table 3). Type of device did not appear to affect survival ($P = 0.6$). Nonparametric estimate of survival after removal of MCS in 24 patients at 1 month, 6 months, 1 year, 5 years, and 10 years was 92%, 88%, 88%, 83%, and 61% (Fig. 5).

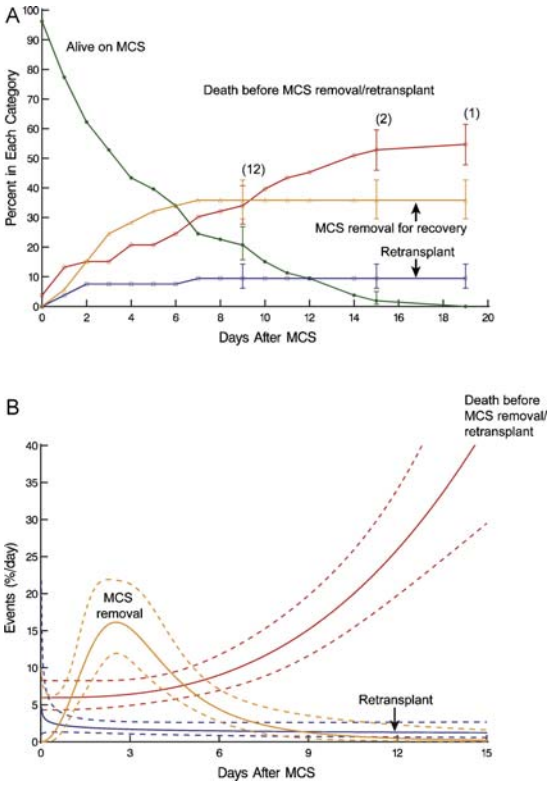

Figure 2: Competing risks during mechanical circulatory support (MCS): death before MCS removal/retransplant (red), MCS removal for recovery (yellow), and retransplant (blue). Green line represents patients alive on MCS at any given time. (A) Percent of patients in each category. Each symbol represents an event and vertical bars 68% confidence limits equivalent to ±1 standard error. Numbers in parentheses represent patients remaining at risk. (B) Instantaneous risk of transition from 'alive on MCS' to each end-state category. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

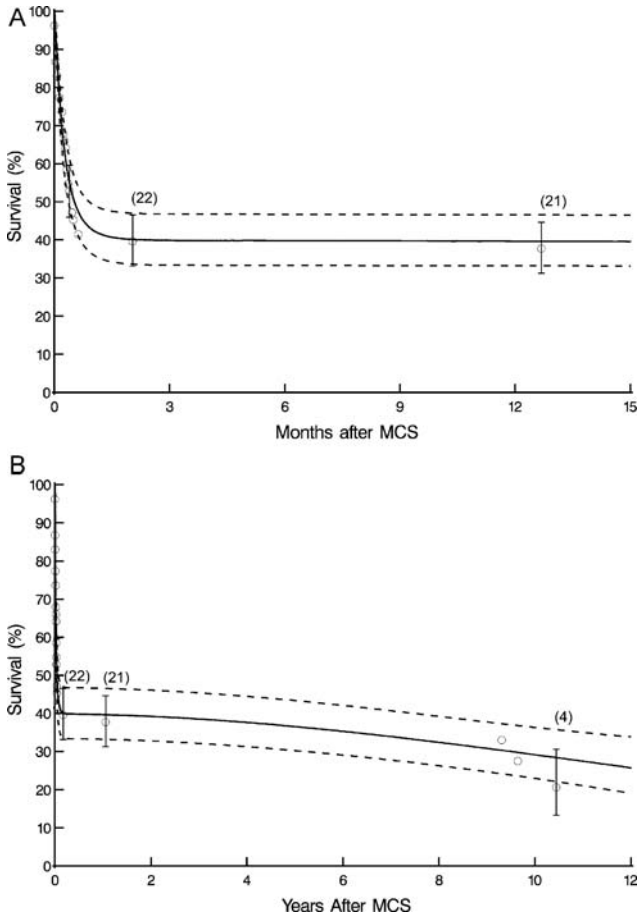

Figure 3: All-cause mortality at any time after instituting mechanical circulatory support. (A) Survival at 0–15 months. Each circle represents a death, vertical bars 68% confidence limits, solid line parametric survival estimate, and dashed line 68% confidence limits around parametric estimate. Numbers in parentheses represent patients remaining at risk. (B) Survival at 0–12 years. Format is as in part (A).

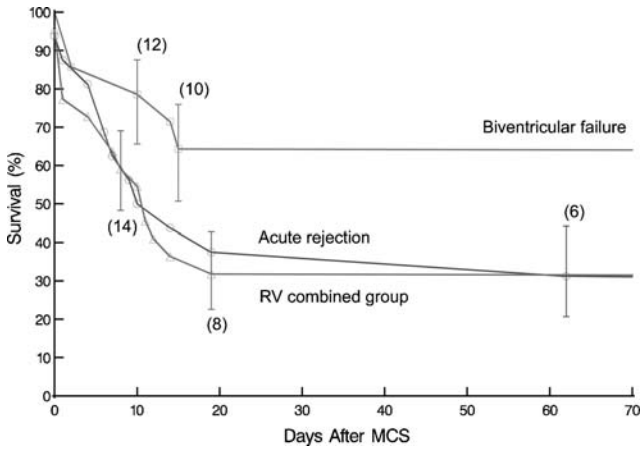

Figure 4: Survival after instituting mechanical circulatory support according to indication. Each symbol represents a death and vertical bars 68% confidence limits. Numbers in parentheses are patients remaining at risk.

DISCUSSION

Primary graft failure after heart transplantation is a rare catastrophic event responsible for one-third of deaths in the early post-transplant period [1, 2]. MCS is the only life-sustaining option for patients in whom primary graft failure is refractory to medical management, and we used it in all patients with primary graft failure during the study period. In this large single-institution study, we determined that MCS represents an effective therapy for salvaging some patients, particularly those with biventricular failure.

Reported prevalence of graft failure varies from 2.4% to 20%, likely reflective of variability in definition of the syndrome [1–3, 9, 14]. Broad definition of primary graft failure includes severe dysfunction of the cardiac allograft with associated hypotension, high filling pressures, and low cardiac output in the absence of secondary causes, including severe pulmonary hypertension and technical surgical problems [2, 3]. In our study, we observed a relatively low prevalence of primary graft dysfunction, which is likely related to the large volume of heart transplants at our institution.

Etiology of primary graft failure is believed to be multifactorial and includes donor–recipient matching, surgical management of the donor heart, ischemic time, and institutional volume [3, 15, 16]. Restrictive cardiomyopathy, pulmonary hypertension, female gender, and renal failure were found to be risk factors for primary graft failure requiring MCS in our study. Although restrictive cardiomyopathy is an uncommon indication for heart transplantation in adults, it is frequently associated with severe

Table 3: All-cause mortality at any time after initiating mechanical circulatory support

Factor	Coefficient ± SE	*P*	Reliability (%)[a]
Early hazard phase			
Indication for MCS other than biventricular failure	−1.12 ± 0.48	0.02	28
BUN	0.16 ± 0.006	0.01	33
Recipient–donor weight ratio	2.07 ± 0.99	0.04	32

Key: BUN, blood urea nitrogen; MCS, mechanical circulatory support; SE, standard error.
[a]Percent of times factor appeared in 500 bootstrap samples.

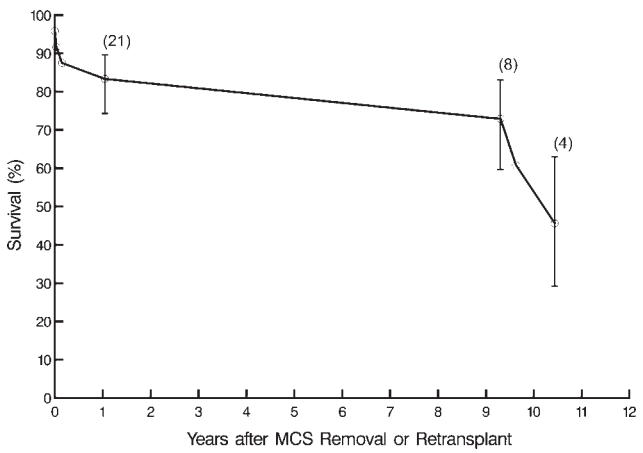

Figure 5: Survival after removal from mechanical circulatory support (MCS). Format is as in Fig. 3.

pulmonary hypertension, leading to potential compromise of right heart function of the transplanted heart [1]. Although outcomes of heart transplantation in women are equivalent to those in men, women tend to have a greater degree of preoperative pulmonary hypertension in our clinical experience and are commonly more sensitized, which may translate to greater risk of primary graft failure. Pulmonary hypertension and renal dysfunction are known factors for adverse outcomes after heart transplantation [1, 3]. Neither donor–recipient matching characteristics nor duration of myocardial ischemia was predictive of development of primary graft dysfunction in our analysis; average ischemic times and donor–recipient characteristics were similar to those in the remainder of the transplant cohort.

ECMO was the most common modality of MCS in our study, similar to other reports from pediatric and adult heart transplant series [6–9]. Ease of insertion and versatility of ECMO, which allows circulatory support and improved gas exchange, make it the optimal first choice for the majority of patients with acute graft failure, in whom hemodynamic compromise is often accompanied by respiratory failure. Our preference is to insert the ECMO using peripheral cannulation (femoral or axillary) and to close the chest to minimize infection risk. Central ECMO cannulation is indicated in rare patients with severe peripheral arterial disease or small and friable peripheral vessels. Ventricular assist devices are used in isolated cases with compromised hemodynamics and preserved left ventricular function. We have also used ventricular assist devices for long-term support in patients who did not have sufficient graft recovery but needed prolonged support. Type of device did not seem to affect the outcome of our patients, which may be explained by the relatively small number of patients and etiological heterogeneity of graft dysfunction. Timing of intervention is primarily dictated by acuity and mode of presentation. Most patients in our study presented with acute primary graft failure and required MCS insertion within the first 3 days after transplantation.

Stroke, infection, and bleeding are known complications of MCS, with cumulative incidence that increases over time [1, 3, 17–19]. Low prevalence of these complications in our study can be explained by relatively short duration of MCS.

Survival after primary graft dysfunction varies from 3.7% to 20%. Such a wide variability in outcomes can be attributed to differences in definition of graft dysfunction and differences in risk profile of patients in different studies. In our study, the definition of primary graft failure was further stratified into acute rejection, right ventricular failure, and biventricular failure. Patients with right and biventricular failure have diminished graft function after transplantation in the absence of rejection. We therefore postulate that this type of dysfunction is related to ischemia–reperfusion injury. Overall survival in our study compares favorably with previous studies, which is a likely reflection of our practice of early ECMO institution in patients in whom we suspect primary graft failure [7]. This is particularly so in patients with right or biventricular failure in the absence of rejection in whom early ECMO institution improves loading conditions and reduces myocardial workload, allowing faster recovery.

Long-term survival of patients who were successfully weaned from MCS is excellent and comparable to overall survival after heart transplantation. Heart retransplantation, in particular early after the primary heart transplantation, is associated with increased operative risk, decreased survival, and additional organ utilization [20–23]. Therefore, it should be carefully considered and performed as early as possible only in suitable patients with severe persistent graft failure despite MCS.

Limitations

This is a single-institution study of the relatively rare need for MCS, which has required us to use data over a 20-year time frame. This limits the number of factors associated with MCS use that we were able to resolve, as well as the number of risk factors for outcomes. Because of the extended time frame of the study, numerous changes in patient selection and management of cardiac transplant patients have undoubtedly occurred, as well as refinement of equipment used for MCS. Nevertheless, strengths of such a study are that indications, complications, and outcomes of this rare event can be examined in detail, which is necessary for adequate analysis of long-term outcomes.

CONCLUSIONS

In summary, primary graft failure after heart transplantation continues to be associated with important morbidity and mortality. In patients who are refractory to medical management, early institution of MCS leads to improved outcomes.

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Conflict of interest: none declared.

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APPENDIX A. CONFERENCE DISCUSSION

Dr E. Flecher (*Rennes, France*): I have two questions. The first one, you said most of your devices were ECMO. What kind of ECMO? I mean, did you implant intrathoracic ECMO or prefer femoral–femoral ECMO?

And my second question is related to the very low rate of bleeding. I'm a little bit surprised. Do you stop the heparin for a while, for example, when you implant the ECMO? When do you start heparin, on day one? I think the rate is very low.

***Dr Mihaljevic*:** Let me answer your questions in order.

When it comes to the types of the ECMOs that we inserted and the way of insertion, it really depends upon the clinical presentation of the patient and particularities of his or her anatomy. We have used predominantly venoarterial ECMOs. They can be implanted centrally for patients who have bad peripheral vascular disease. For patients who, however, have a good vasculature, do not have peripheral vascular disease, typically patients with dilated cardiomyopathy, one can also implant them peripherally. Venous cannulation is typically accomplished through the femoral vein with advancement of the venous cannula into the right atrium. Arterial sites vary. They are either in the femoral artery or axillary artery, either way is fine. What we typically do in the case of axillary artery cannulation is use a graft in an end-to-side anastomosis. Femoral artery cannulation is either accomplished with a graft that allows perfusion of the distal limb and avoids ischemic complication, or with a direct cannulation of the femoral artery, but then we typically also insert the reperfusion cannula that is aimed distally. Because, as you know, for long-term support on ECMO, limb ischemia is a serious potential complication.

When it comes to bleeding after ECMO, and the reasons why we have a relatively low incidence of bleeding, it is because we do not heparinize those patients, not for quite a few days. Most of them are coagulopathic after surgery. We believe that the risk of serious life-threatening bleeding exceeds by far the risk of thromboembolic episodes. So we would typically not heparinize them for quite a while.

Dr D. Nagpal (*London, Ontario, Canada*): Given the extremely high mortality risk in this group of patients, were you able to identify any risk factors in particular for mortality, or specifically a combination of risk factors that would be useful in determining those patients in whom not to proceed with more aggressive therapy?

***Dr Mihaljevic*:** I don't think that we really have an option not to proceed with more aggressive therapy. All these patients are deemed suitable for heart transplantation so a *priori* they should be viable candidates. So if we decide to do a heart transplant and it fails, we are essentially obligated to support them. If standard medical management does not work, they have to get some form of mechanical support.

Risk factors for bad outcomes, as listed, are restrictive cardiomyopathy, female with pulmonary hypertension, and marginal renal function. What is also a bad omen is an acute rejection and, as I said, a right ventricular failure. We believe that these are different processes that affect the final outcome of patients. If they have an acute rejection, it's a serious complication. Right ventricular failure usually indicates either poor patient selection or poor preservation of the donor heart.

Dr H. Gasparovic (*Zagreb, Croatia*): How do you decide whether you want to implant a biventricular assist device or an ECMO? Do you think that the superior unloading that you would get with a BiVAD should play a role in your decision-making process?

***Dr Mihaljevic*:** Well, I think there are several factors when it comes to the choice of devices, which is, ultimately, I believe, the core of your question. Patients who have marginal biventricular function but preserved oxygenation and pulmonary function can obviously be supported with BiVADs or ECMOs.

However, a large number of patients have somewhat compromised pulmonary function as well, for a variety of different reasons: difficult reoperations, bleeding, and so on. Currently we're trying to use ECMOs in most of them for two reasons: it is easier to insert them and most patients require short-term support.

BiVADs have a substantial disadvantage. First, they're more difficult to insert at the primary operation. They do nothing to ameliorate pulmonary dysfunction if it's present. And secondly, in our experience, they are associated with a substantially higher risk of device infection because all of these patients are immunocompromised. Long-term support with a large piece of hardware usually results in an increased risk for infection in immunosup- pressed patients.

Dr J. Wojarski (*Zabrze, Poland*): You mentioned that acute rejection during the support constitutes a high-risk for those patients. But if this is so, would you consider a more aggressive approach? Because we know for sure that we can stop acute rejection. If you give orthoclone, you're pretty safe. So do you do that, or you are more afraid of infections due to this strategy?

***Dr Mihaljevic*:** If they have acute rejection, we will treat an acute rejection as aggressively as we possibly can.

***Dr Wojarski*:** But in that case it seems that it would be better to prevent than to treat. Because you mention it, that if you develop rejection then this is a very bad setup.

***Dr Mihaljevic*:** Well, that is true, we try to prevent it. But when it occurs, it occurs. And when it happens, we have to do something about it. When transplanted hearts fail, we have to use mechanical support.

***Dr Wojarski*:** And the second question, how do you recognize acute rejection in patients on VAD?

***Dr Mihaljevic*:** Patients still can be biopsied when they are on VAD. Diagnosis of acute rejection is possible even when the patients are on mechanical support.