Introduction

Although cardiac transplant (HTX) is considered the best treatment for terminal heart failure, the scarcity of donors, particularly in pediatrics, limits its use.

The difficulty of identifying heart failure in children causes many to visit our emergency units for the very first time in very advanced stages of the disease. These patients or patients whose status worsened and required vasoactive drugs and ventilator support and had liver and kidney dysfunction (INTERMACS 1 and 2 according to the classification of Interagency Registry for Mechanically Assisted Circulatory Support; Table 1) should be hemodynamically compensated to reverse organ failure before the patients are subjected to HTX. Often, isolated clinical measures are not sufficient, and mortality in these patients awaiting HTX surpasses 90% over 30 days.

Short-term mechanical circulatory supports (MCS) such as extracorporeal membrane oxygenation (ECMO) and centrifugal pumps, CentriMag (Thoratec Corporation, Pleasanton, CA, USA), PediMag (Thoratec Corporation), and Rotaflow (Maquet - Getinge Group, Rastatt, Germany), have been used in an attempt to maintain hemodynamic support in ideal conditions, improving the clinical conditions of patients awaiting HTX. In our clinical setting, due to the financial difficulties faced by the health system, we have used MCS in selected and sporadic cases. ECMO can be used with a certain degree of safety, but it negatively interferes with transplant results when used for periods surpassing 15 days. The use of centrifugal blood pumps has been shown to be an alternative to ECMO, allowing greater ventricular support time, greater mobility for the child, and encouraging results that have been previously published study. Nevertheless, biventricular and/or pulmonary dysfunction limit the use of this method, particularly in cases with advanced circulatory shock.

In late 2011, perceiving the poor progress of these patients, we began to experiment with installing MCS devices in INTERMACS 1 and 2 patients. The availability of the equipment was limited but increased over the course of the study.
The aim of this study was to assess the impact of these devices on the survival of patients while on the waiting list and after HTX.

Methods
This study was approved by the Ethics Committee for the Analysis of Research Projects at the Hospital of Clinics of the Medical Faculty of Medical College at the University of São Paulo (CAPPesq) and registered under the number CAAE: 20282113.2.0000.0068.

During the period of January 2011–December 2013, 40 patients younger than 18 years of age with a diagnosis of cardiomyopathy were admitted to the pediatric intensive care unit (ICU) at our institution. Of these, 20 were at INTERMACS 1 or 2, comprising the population of our study. One of these patients died in 24 h and 19 remained in treatment and on the list awaiting HTX. The other 20 remained stable at INTERMACS 3 or above and were discharged from the ICU (Figure 1).

Demographic and clinical data were collected from each patient’s electronic chart. The patients who had been admitted at any time prior to the study period were assessed from their first hospitalization. Demographic and diagnostic data were analyzed along with transplant wait time (period from the date the patient was listed and date of transplant or death), support time (time between the initiation of circulatory support and transplant or death in those patients who did not undergo transplant), the incidence of complications, and post-transplant hospitalization time (period of time between transplant and discharge or death in hospital).

The patients who were classified as INTERMACS 1 and 2 at any time during their hospitalization were divided into two groups: Group A (without MCS), which comprised patients who were clinically managed for hemodynamic compensation; Group B (with MCS), which comprised those who received some type of short-duration MCS as a bridge to HTX. Clinical characteristics for both the groups at the time they were placed on the transplant list are shown in Table 2.

As observed in Table 2, the groups were very similar; however, there was no randomization. MCS was used when logistical conditions permitted. At the beginning of the study, we depended on the donation of the devices, and later, we depended on the availability of the equipment because this was a public health service.

Devices used
The short-term devices used were isolated ECMO (one case), isolated centrifugal blood pump (eight cases), and one patient initially received ECMO and later was treated with a centrifugal blood pump associated with a paracorporeal ventricular assist device (Berlin Heart Excor, Berlin, Germany). The ECMO circuit utilized was the PLS Maquet (Maquet - Getinge Group, Rastatt, Germany), composed of a hollow polymethylpentene diffusion membrane, centrifugal pump, and tubes treated with platelet anticoagulant material. These were three-eight-inch tubes with no bridge connection in patients > 10 kg and 1/4 inch with a bridge connection in patients < 10 kg. Peripheral cannulation (carotid or jugular vein) or central cannulation (right atrium and aorta) through a median sternotomy, depending on patient’s size and previous cardiac function, was performed.

In the patients who used the centrifugal blood pump, the most common type of cannulation was via the left ventricle (LV) and aorta (seven of eight cases), and via left atrium and aorta (one case). The centrifugal pumps were implanted via a median sternotomy with the help of extracorporeal circulation in those cases where the LV was cannulated. As in the case of ECMO, in patients < 10 kg a one-fourth-inch tube and pre/post pump bridge connections were used, maintaining different flows in the circuit and patient that was controlled by a second independent flow monitor. Two types of pumps were used: Rotaflow (Getting-Maquet Group, Hestat, Germany) and PedMag (Thoratec Corporation, Pleasanton, CA, USA).

Statistical analysis
The data for the continuous variables that showed normal distribution were presented as mean ± standard deviation (SD). The categorical variables were represented as percentages and the continuous variables with their median followed by minimum and maximum values for the
Table 2 – Characteristics of the patients who were managed clinically (Group A) and those who received MCS device implants (Group B)

| Demographic Variables | Group A | Group B | p value |
|-----------------------|---------|---------|---------|
| Age (years) ± SD      | 4.9 ± 4.1 | 4.2 ± 4.5 | 0.59    |
| Weight (kg) ± SD      | 3.0 ± 20.6 | 5.0 ± 19.5 | 0.59    |
| Sex female n (%)      | 3 (30%)  | 4 (44.4%) | 0.51    |

| Clinical Variables    |         |         |         |
|-----------------------|---------|---------|---------|
| Intermacs 1 n (%)     | 3 (30%) | 3 (33.3%) | 0.87    |
| Peritoneal dialysis    | 5 (50%) | 4 (44.4%) | 0.80    |
| Cardiac arrest         | 8 (80%) | 7 (77.8%) | 0.90    |
| Orotracheal intubation | 4 (40%) | 4 (44.4%) | 0.84    |

sample. χ² tests were used to compare the proportions of the categorical data and unpaired t-tests for continuous variables. A p-value < 0.05 was considered to be significant. The data were analyzed using SPSS 20 (SPSS, Inc., Chicago, IL, USA). Each patient who received circulatory support as a bridge to transplant was analyzed as an isolated event, even if they received implants of more than one device, different types of devices, or at different times.

Results

Of the 40 patients admitted to the ICU with dilated cardiomyopathy, six were admitted, for the first time, to INTERMACS 1, 10 patients to INTERMACS 2, 14 to INTERMACS 3, and the remaining 10 to INTERMACS 4–6. This latter group was admitted for reasons other than hemodynamic deterioration, such as respiratory infection, biopsy, or other invasive procedure. Of the 14 patients at INTERMACS 3, four worsened to INTERMACS 2 and 10 remained at INTERMACS 3 or improved. Figure 1 summarizes the evolution of the patients from their first hospital admission by INTERMACS classification according to severity.

In Group A, of the 10 patients who were clinically managed, only two (20%) were able to be hemodynamically compensated with reversal of organ failure and underwent HTX. Among the nine patients in Group B, six were able to receive transplants (66.7%; p = 0.04; Table 3).

None of the patients in Group A were discharged (0%) and three patients in Group B were discharged (33.3%; p = 0.049; Table 3).

The wait time on the transplant list was 32 days in Group A and 62 days in Group B. If we only include those who received transplants, the mean wait time was 47 days (0–149 days).

The mean support time, considering all patients in Group B, was 471 h (6–960 h). Considering only the patients who received transplants, the support time was 349 h (6–984 h). The post-transplant hospitalization time was 49 days (6–115 days).

The two patients in Group A who received transplants died during the post-operative period on day 10 and day 48, respectively. The other eight progressed to multiple organ failure and died, unable to undergo HTX.

In Group B, three (33.3%) died while receiving support via centrifugal pump; two died from complications related to cerebral vascular accident and one died from related multiple organ failure and consumptive coagulopathy. Of the six who underwent HTX, three died after surgery (50%), one died due to neurological complications, and two died due to multiple organ failure on days 21 and 27 after surgery.

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Embolic phenomena and neurological complications affecting motor ability affected six patients in Group B (66.7%), and these complications were directly related to death in three of these cases.

Discussion

Cardiac transplant is the most effective treatment for terminal cardiac failure, although it is limited by the number of donors. Pediatric post-HTX survival in the first year is approximately 90% and 60% over 10 years\textsuperscript{10,11}. These results vary according to age of recipient, diagnosis, period when conducted, and location. The major limitation for the number of transplants is the number of donors. Difficulty in obtaining organs varies according to variables such as blood type, age, the weight of recipient, and geographic distribution\textsuperscript{10,12-15}.

A large number of children, who were diagnosed with cardiomyopathy in advanced stages of heart failure and required vasoactive drugs, visited the emergency departments of specialized hospitals for the first time. This may also be due to the great difficulty in clinically diagnosing heart failure in this age group.

Advanced cardiac failure varies; therefore, the patient may be restricted to the hospital bed or in cardiogenic shock. In addition, there is a requirement to differentiate these two cases because the prognosis is directly related to the patient’s degree of decompensation. The INTERMACS classification proposed by the Interagency Registry for Mechanically Assisted Circulatory Support classifies these patients into levels 1–7, with 1 being the most severe.

The patients who were classified with INTERMACS 1 and 2 had impaired tissue perfusion and required higher doses...
of vasoactive drugs. The clinical response of these patients is poor and once multiple organ failure occurs, the therapeutic window for HTX is lost. The objective of using MCS in these cases is to reverse the low-volume scenario, restoring visceral perfusion, and allowing the patient to wait for a donor in satisfactory clinical condition.

MCS devices can be classified as short- and long term. In the short-term device group, the most commonly used devices in the pediatric population are ECMO and centrifugal pumps; these are generally used on patients at INTERMACS 1 or 2 level for some weeks. Long-term devices allow ventricular support for longer periods of months. They can be used very safely on patients at INTERMACS 3 or 4 level. Their availability in pediatrics is limited, particularly due to the size of these devices and requirement for biventricular support in most of this population. Among these devices, paracorporeal pumps are the most widely used.

Although it provides a limited time of circulatory support, ECMO is still the most utilized device in younger children. In recent years, we have observed a greater number of long-duration device implants such as paracorporeal pneumatic ventricular assist devices in the pediatric population. This is due to the fact that the devices were recently approved in the United States and the experience gathered by Berlin Heart in Europe in small children over the last five years. The use of ECMO is associated with greater mortality after 15 days of assistance due to resulting complications such as alterations in coagulation and renal failure. The development of renal failure in patients using ECMO is an isolated factor in increased mortality during support and post-transplant and can also be related to delayed recommendation to begin support in patients already experiencing systemic dysfunction.

In the United States, despite the high rate of use for offered organs, which surpasses 98%, we observed a recent increase (22% in 2005 and 25% in 2010) in the use of some kind of implanted MCS as a bridge to HTX in the pediatric population. The isolated use of ECMO fell from 9.4% in 2005 to 2.6% in 2010. On the other hand, ventricular assist devices including the complete artificial heart increased from 12.1% to 20.4% in the same period.
The use of MCS as a bridge to transplant in adults is much more common and has significantly increased in the recent years. Furthermore, we observed an inversion in the number of transplants in relation to the number of implanted devices in this population, where the number of devices tend to be greater than the number of transplants conducted.

In our study, ECMO was used in the first two patients, and this device was reserved for patients in serious conditions with established organ failure. The paracorporeal pneumatic device was used in only one patient, who initially received ECMO for hemodynamic compensation (INTERMACS 1). After a period of >20 days of ECMO, a paracorporeal pneumatic device implanted (Berlin Heart Excor), which was donated by the company, as isolated left ventricular support. In addition, with the requirement for simultaneous pulmonary support, we made the transition from VA ECMO to VV, cannulating the right atrium and pulmonary artery, and then to isolated RV support keeping only the centrifugal pump in the circuit with improved pulmonary function, keeping the device on left side during the entire period until the cardiac transplant.

Experience with the isolated centrifugal pump as a bridge to HTX is restricted to few centers and requires further study, particularly because it can be an adequate support for 4–8 weeks, and in general, provides slightly superior results than ECMO. On the other hand, if these devices provide the patient with adequate circulatory support while awaiting transplant, their use may be associated with greater mortality in the post-transplant period due to associated complications. In our study, we used the centrifugal blood pump alone on the left side in seven cases and used it with another device in one patient.

Besides the possibility of reducing mortality in patients awaiting transplant, MCS also offers the opportunity to recover cardiac function in selected cases. Although it is still not completely understood, the recovery of cardiac function was observed with the use of circulatory support in children diagnosed with cardiomyopathy, perhaps as a result of a reverse remodeling obtained by the reduction of ventricular volume obtained using this support. This did not occur in our limited study.

Although few Brazilian centers perform HTX in the pediatric population, we have observed a small increase in their numbers in recent years. Our program began in 1992, and since then, we have performed an average of six HTX per year. Over the past three years, due to improvements in the state funding system and greater availability of air transport for long-distance recovery, we have averaged 17 transplants annually.

Although the number of donations has increased, the current difficulties faced by the public health system lead to low-quality organs, generating a donated organ utilization rate of <10%. In this scenario, mortality while awaiting transplant is still very high. In our personal experience, it reaches around 37% at 30 days for priority patients using vasoactive drugs, who were admitted to the ICU, and using mechanical ventilation or some sort of MCS, according to priorities defined by the National Secretary of Transplants.

Transplantation in children in these clinical conditions, performed on an emergency basis, becomes a challenge. A previous study conducted at our institution showed that transplants performed under these conditions presented higher mortality (25%) than that in patients awaiting transplantation at home or admitted under nonpriority. When we stratify these patients by priority using INTERMACS classification, we observe that when a child has a INTERMACS 1 classification, mortality while awaiting transplant is >98% in 30 days, as shown in the present study.

The use of short-term devices such as ECMO and isolated centrifugal blood pumps increased the wait time by approximately 30 days, considering the average waiting time in both groups; 62 days in Group B and 31.5 days in Group A. Moreover, because such devices present limited use time, their indication is always postponed. In most cases, the implant was performed later, when there was already impaired renal and/or liver function.

The incidence of neurological complications was high in patients receiving MCS. Embolic phenomena related to the devices were probably the main underlying cause and improvements in anticoagulation protocol for these patients are being pursued. However, one cannot discard the fact that almost 80% of these patients were presented with resuscitated cardiac arrests before implanting MCS.

The use of MCS in our study was observed to be extremely effective in providing circulatory support to these patients, allowing the reduction of vasoactive drugs, improvement in hepatic and renal function, and withdrawal of ventilator support in most cases, particularly in cases where the centrifugal pump was used alone (80%). Therefore, an earlier implementation may provide better results.

Limitations

This is a retrospective, nonrandomized study conducted in a single center. The criteria for implementing either treatment were influenced by the logistical availability of the devices and increasing experience in the service.

Conclusion

The use of MCS in pediatric patients at INTERMACS 1 and 2 levels led to higher rates of survival to transplant and hospital discharge.

Author contributions

Conception and design of the research: Canêo LF; Acquisition of data: Canêo LF, Miana LA, Tanamati C, Penha J, Shimoda MS, Azeka E, Miura N, Galas FRBG, Guimarães VA, Jatene MB; Analysis and interpretation of the data and Writing of the manuscript: Canêo LF, Miana LA, Jatene MB; Statistical analysis: Canêo LF, Miana LA; Obtaining financing: Canêo LF, Galas FRBG, Jatene MB; Critical revision of the manuscript for intellectual content: Canêo LF, Miana LA, Miura N, Jatene MB.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.
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Study Association

This study is not associated with any thesis or dissertation work.

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