Pediatric Mechanical Circulatory Support Challenges and Opportunities

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Cardiomyopathy is rare in the pediatric age group, with an annual incidence of only 6 to 12 cases per million children. In addition to the genetic and acquired cardiomyopathies, heart failure in children also occurs as a complication of congenital cardiac anomalies, ranging from hypoplastic left heart syndrome to tetralogy of Fallot. In the registry of the International Society of Heart and Lung Transplantation (ISHLT), approximately 65% of heart transplantations in infants were performed as the result of congenital cardiac anomalies, whereas in older children that percentage decreases to 24%.4,5

In early stages, heart failure in children is treated pharmacologically, as in adults, although there are comparatively few clinical trial data specific to children.4–8 As the disease severity increases, definitive therapy of heart failure in children consists of heart transplantation. Approximately 350 pediatric heart transplantations are performed in the United States annually, and, because of a robust national database, outcomes after transplantation are well characterized.4 Less is known about outcomes in pediatric patients awaiting heart transplantation. For children, mortality rates of 7% at 30 days have been reported, whereas mortality rate for infants—a uniquely challenging group in terms of donor availability—ranges from 25% to 31% at 6 months in multi-institutional studies.9–11 Some centers report improved pretransplantation survival in more recent eras as the result of improved medical therapy, innovative strategies to improve the efficiency of donor allocation (eg, ABO incompatible transplantation in infants), and increased use of mechanical support devices in children.12–15 Because sudden death in children awaiting heart transplantation is rare, the majority of deaths in this population are due to progressive heart and multi-organ failure and are therefore, at least in theory, amenable to salvage therapy with mechanical circulatory support (MCS).10

The experience with adults supported long-term by MCS is sobering, with a 66% mortality rate at 1 year.16 Shorter courses of support are more promising, with a survival rate of 83% at 1 month.16 In adults, risk factors for death are reasonably well understood and include older age as well as the need for biventricular support. An important difference between the use of MCS in adults and children is the suitability of the devices. For adults, there are many choices of devices designed specifically for these patients, whereas for children, the choices have included only extracorporeal membrane oxygenation (ECMO; a technique best reserved for short-term support), the Thoratec (Pleasanton, Calif) ventricular assist device (VAD; a device designed for adults, but which can be placed in larger children and adolescents), the EXCOR Berlin Heart (Berlin Heart AG; Berlin, Germany), and the MEDOS VAD (MEDOS Medizintechnik AG; Stolberg, Germany). The latter 2 devices are the only devices designed specifically for children and have until recently been available in Europe and Canada but not the United States.

In comparison to adults, experience with MCS in children is quite limited. The current indications for MCS use in children are bridge to transplantation, and, occasionally, bridge to recovery. There are several single-center reports of MCS use in children, and 1 larger series of Thoratec use in older children.17–21 Reports from Hetzer, Stiller, et al22–24 at the Berlin Heart Institute describe results in 45 pediatric patients, using one of the few available devices designed specifically for children, with excellent results.

In this context, the report by Blume et al25 in this issue of Circulation provides important insight into the field of pediatric MCS in North America. This study used the Pediatric Heart Transplant Study (PHTS) database to trigger secondary data collection, and thus represents a comprehensive overview of MCS use in children. Within this database of more than 2000 pediatric patients listed for heart transplantation between 1993 and 2003, there were 99 patients with pediatric MCS that were identified and for whom data were collected. The overall survival to transplantation rate was 86%, which is similar to that in adults on MCS and significantly better than earlier reports in children.16,19 Once transplanted, survival of patients with MCS was identical at 1 and 5 years after transplantation to those without MCS, indicating that these patients do not represent a higher risk group for posttransplantation death. However, the incidence of complications during pediatric MCS is greater than that in adults. The incidence of stroke was 19%, and this was often a fatal event (11 of 19 cases). This is higher than in adults but similar to other small pediatric series.16,21 The incidence of reoperation for bleeding was very high, at 35%, which may reflect the technical challenges of device placement in patients with congenital heart disease or in small patients, particularly as the only true pediatric chronic devices (EXCOR and Medos) were scarcely represented in this series. Only the incidence of infection (35%) was similar to that in adults. Median waiting

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time until transplantation was 25 days. However, there was enormous variability in waiting times, with a range of 1 to 465 days. Risk factors for poorer outcome include a diagnosis of congenital heart disease and earlier era of implantation, whereas the use of biventricular support did not confer additional risk, which differs from the findings in adults. However, the small number of patients on bilateral ventricular assist device support limits the ability to make these comparisons. Whether pediatric patients on bilateral ventricular assist device support are more likely than adults to remodel their pulmonary vascular beds after left ventricular unloading remains to be determined.

One of the most striking aspects of the report by Blume et al\textsuperscript{25} is the fact that there were only 99 cases over 10 years in 23 major pediatric transplant centers. This contrasts with the 655 adults enrolled in the Mechanical Circulatory Support Database over a 3-year period.\textsuperscript{16} Nearly half of the centers in the pediatric report implanted only 1 or 2 VADs during the 10-year study period, and only 2 centers had as many as 10 implantations. This is clearly a challenging environment in which to provide MCS, and it is remarkable in this context that the results in this series were as good as they were. The data in the report by Blume et al\textsuperscript{25} also suggest a rather low utilization rate of MCS in the pediatric population, with MCS used in only 4% of the transplanted patients (99 of 2375 patients). This is much lower than the rate of 27% of MCS use in adult transplantation candidates.\textsuperscript{26} The barriers to MCS use in children include lack of appropriate equipment and limited expertise, factors that certainly contribute to the low MCS use rates. Whether patient-specific differences, such as the presence of complex congenital heart disease, also contribute to the differential utilization of MCS in children versus adults remains unknown.

Subsequent to the close of data collection in the report by Blume et al,\textsuperscript{25} use of the Berlin Heart EXCOR dramatically increased in the United States. Although this device is not approved by the Food and Drug Administration (FDA) for routine use in children, it has been possible to have the EXCOR approved on the basis of compassionate use on a case-by-case basis. Despite the necessity to petition the FDA for approval in each case, the EXCOR has been implanted in approximately 40 young children over the past 18 months (Berlin Heart AG, written communication, 2006). This confirms the notion that there is a significant unmet need for pediatric MCS, particularly in younger children, who are not well served by the Thoratec VAD and who are notably absent from the series presented by Blume et al, which ended data collection in 2003. With the availability of the EXCOR, the volume of pediatric cases can be expected to continue to grow, although it will not likely exceed 100 cases per year, based on the number of pediatric heart transplantations performed annually and extrapolating from current utilization rates in adult patients.\textsuperscript{26}

Thus, MCS in children will remain uncommon. It will be difficult for centers to acquire significant expertise in the field. Similarly, it will be unprofitable for companies who might wish to bring a pediatric device to market. Development costs are no less for pediatric devices than for those suited for adults, but the potential market is much more limited. In recognition of this problem, the National Institutes of Health (NIH) recently initiated a development program in pediatric MCS, funding a number of sites in the United States to perform device development work.\textsuperscript{27} It is hoped that this effort will result in one or more devices being available for clinical trials by 2009. This is a welcome and critical first step toward improving the quality and availability of MCS devices for children. However, device development is only the first obstacle to be overcome. Conducting a suitable clinical trial to obtain regulatory approval for a pediatric MCS device will be daunting and expensive under current regulatory standards. Such a trial would require participation from the vast majority of sites performing pediatric heart transplantation in the United States and would necessarily extend over several years to accrue sufficient patients. These are considerable practical problems. Given the limited size of the market for these devices, it is unclear whether market forces would be sufficient to generate funding for such trials or whether the NIH might again find it necessary to step forward to provide funding, so that this field might continue to advance.

Under existing guidelines, MCS devices must be approved either through the PMA (pre-marketing approval) pathway, or through the HDE (Humanitarian Device Exemption) pathway. The first of these is the more rigorous and is the pathway by which current adult devices such as the Novacor and Thoratec have been approved for use in the United States. The HDE pathway is available only for conditions that occur in less than 4000 patients per year and does not require demonstration of “effectiveness,” which is a key component of the PMA. Thus, the HDE approval is in some aspects more accessible than the PMA, and it certainly appears consistent with the epidemiology of pediatric heart failure. However, it is still necessary to show that the device does not pose a significant or unreasonable risk of injury, and that the probable benefit outweighs the risks of its use.\textsuperscript{28} Importantly, although manufacturers can recover direct costs associated with a device approved by the HDE pathway, there is no opportunity to generate profit from such devices. This provision may well prove fatal to the HDE pathway for pediatric MCS devices. A careful examination of the HDE regulation and its applicability to pediatric MCS devices is warranted.

What should be the agenda for the next decade in the field of pediatric MCS? First, we need improved, pediatric-specific devices to emerge from the current development pathways. Second, we need to develop better treatment protocols for anticoagulation management, given the higher risks of both bleeding and stroke in the pediatric age group. Third, investigators across the United States will need to work cooperatively on a very limited number of devices and protocols. Fragmentation of effort will render the conduct of any meaningful trial impossible. Cooperation is also a necessity if investigators are to develop sufficient expertise to use existing and future devices effectively. Fourth, Congress and the FDA will need to reevaluate the regulatory environment to be certain that it provides a proper balance of safety and opportunity. Without this scrutiny, the chances of bringing a device to market appear slim. The NIH will likely find it necessary to provide funding for clinical trials in areas traditionally funded by industry. Finally, we will need to
continue to evolve the criteria for making the switch from pharmacological support to MCS, especially as pediatric-specific devices become more readily available. The trend in the study by Blume et al toward higher mortality rates for patients on mechanical ventilatory support at the time of initiation of MCS suggests that earlier switch to MCS is beneficial, but when is it too early?

The payoff for this effort will be, in the short term, the ability to save the lives of those children with advanced heart failure who now die waiting for a suitable donor. In the long term, the possibilities are even more exciting, as improved technology offers the hope of long-term cardiac support for children with more indolent forms of heart failure such as the palliated univentricular heart.

Disclosures

None.

References

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