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PEDIATRIC PATIENTS WITH IMPLANTED LEFT VENTRICULAR ASSIST DEVICES END EXPIRIENSE OF PERSONALIZATION OF TREATMENT IN EARLY POSTOPERATIVE PERIOD

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ДОСВІД ПЕРСОНАЛІЗАЦІЇ ЛІКУВАННЯ У ПЕДІАТРИЧНІ ПАЦІЄНТИ З АПАРАТАМИ МЕХАНІЧНОЇ ПІДТРИМКИ ЛІВОГО ШЛУНОЧКА ТА ДОСВІД ПЕРСОНАЛІЗАЦІЇ ЇХ ЛІКУВАННЯ В РАННЬОМУ ПІСЛЯОПЕРАЦІЙНОМУ ПЕРІОДІ

Мазуренко О.П.

У дорослому населенні пристрої безперервного потоку повністю переважають над пульсаційним LVAD, що становить понад 90%. З постійною мініатюризацією приладів серед дитячих кардіологів зростає кількість пропозицій щодо використання ВАД безперервного потоку у дітей. Відповідно до першого звіту PediMACS, приблизно половина (54%; 109 з 200) зареєстрованих пристроїв довгострокового періоду – це пристрої безперервного потоку. Дана стаття описує сучасний стан дитячої підтримки безперервного потоку механічної підтримки кровообігу (МПК) та оцінює перспективи щодо його майбутнього напрямку. Досвід та стратегія Сілезького Центру Хвороб Серця в раннього післяопераційного періоду була дуже схожа на таку, яку застосовували у пацієнтів після операції Фонтана, включаючи спеціальні тактики респіраторної підтримки, додавання оксиду азоту або залишаючи грудину відкритою після початку МПК. Незважаючи на агресивну медичну підтримку у певної частини пацієнтів виникала правошлуночкова недостатність, що потребувало його тимчасової механічної підтримки для відновлення кровотоку до легеневого кровообігу та збільшення попереднього навантаження ЛШ. Рання бівентрикулярна МПК корелює з кращою виживаністю порівняно із затримкою його застосуванні. Таким чином, проведення ретельного передопераційного оцінювання ризику правошлуночкової недостатності обов'зкове для імплантації бівентрикулярної МПК або для трансплантації серця.

Ключові слова: безперервно потоковий апарат механічної підтримки кровообігу лівого шлуночка у дітей, застійна серцева недостатність у дітей.

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Mazurenko O.

For adult patients, devices of a continuous flow of mechanical support of blood circulation completely prevail over pulse ones, which is more than 90%. With the constant miniaturization of devices among pediatric cardiologists, the number of proposals for the use of continuous-flow VAD in children is growing. According to the first PediMACS report, approximately half (54%; 109 out of 200) of registered long-term devices are continuous-flow devices. This article describes the current state of the children's system of a continuous flow of mechanical support for blood circulation and evaluates the prospects for its future direction. The experience and strategy of the Silesian Center for Heart Diseases in the early postoperative period was very similar to that used in patients after Fontaine's operation, including special tactics of respiratory support, adding nitric oxide or leaving the chest open after the start of circulation support. Despite aggressive medical support, a certain part of the patients had right ventricular, which required temporary mechanical support to restore blood flow in the pulmonary circulation and increase LV preload. Early biventricular VAD correlates with better survival compared to a delay in its use. Thus, a thorough preoperative risk assessment of right ventricular failure is required for implantation of a biventricular VAD or for heart transplantation.

Key words: mechanical circulatory support, continuous flow left ventricle assist device, congestive heart failure in children.

Introduction. In the last ten years, the mechanical circulatory support (MCS) has become a valuable therapeutic option in patients with end-stage congestive heart failure (CHF). Several generations of devices have been developed, but they are mainly designed for adult population. The only available solution dedicated particularly to infants and small children are the pulsatile system Berlin Heart. Its superiority in long-term MCS as compared to extracorporeal membrane oxygenation (ECMO) has been established [1], demonstrating at the same time many disadvantages, such as neurological complications, incidences of pump thrombosis, necessity of readmissions and important limitations of quality of life. At present, the intracorporeal continuous flow left ventricle assist device (CF-LVAD) off excellent patient mobility and low complication rates in the adult population. In the adult population, continuous-flow devices completely dominate over than pulsative LVAD, representing more than 90% (12,030 of 13,286 primary implants for left heart support) of the durable VADs implanted between 2006 and 2014 [1]. This phenomenon is driven primarily by improved complication profiles and durability of continuous-flow VADs compared with pulsatile VADs. With ongoing device miniaturization, enthusiasm has been growing among pediatric physicians for the use of continuous-flow VADs in children. According to the first PediMACS report, approximately one-half (54%; 109 of 200) of the long-term devices registered are continuous-flow devices [2]. With the results recorded to date, the use of continuous-flow devices in the pediatric population is rapidly increasing. Continuous-flow VADs compose 62% (179 of 291) of all durable VAD implants in the PediMACS 2016 third quarter report [3]. In this commentary, I describe the current state of pediatric continuous-flow VAD support, and discuss perspectives regarding its future direction.

There is no doubt that continuous-flow VAD technology has had a profoundly positive impact on the outcomes of VAD support in the adult population [4]. It is plausible that nearly adult-sized adolescents would have equally excellent outcomes with continuous-flow VADs that were intended for use in adults [5]; however, it is premature to assume that continuous-flow VADs would have a similar impact across the spectrum of body sizes in the pediatric population. Although anecdotal reports with continuous-flow VADs in children are rather encouraging, careful evaluation of available outcomes data is warranted before definitive conclusions

can be drawn. Nonetheless, whether smaller children will also experience comparable outcomes with adult-sized continuous-flow VADs remains to be seen. A major concern with the use of continuous-flow VADs in smaller children is a patient–device size mismatch [6], particularly because all currently available continuous-flow VADs are designed for adult patients. A recent multi-institutional study evaluating outcomes after implantation of the HVAD system (Medtronic, Minneapolis) in children with a body surface area of <1.0 m2 showed a favorable survival rate, but with a high incidence of complications, including pump thrombosis [7]. Conway et al conducted a worldwide survey evaluating the outcome of the HVAD use in children [8]. This study, involving 250 patients from 35 sites in 12 countries, demonstrated a

tendency toward poorer outcomes in smaller children; the mortality rate at age<12 months was 15.6% (95% confidence interval (CI), 3.96%–28.93%) in children weighing <25 kg and 7.6% (95% CI, 6.2%–28.9%) >25 kg. Although the observed difference in mortality did not reach statistical significance, it warrants close attention from a clinical standpoint. Anecdotally, it is known that both weight and the shape of the chest wall are important factors in successful VAD implantation in children; a smaller child with a broad chest may be a more suitable candidate than a larger child with a narrow chest. Evaluation by "virtual implantation" such as that used for total artificial heart implantation [9], may provide useful guidance in determining compatibility. Nonetheless, the smaller the heart, the more significant the size mismatch between the patient and the device.

Methods. Between 2016 and 2017, three pediatric patients were implanted CF-LVAD in the Department of Pediatric Cardiac Surgery, SCCS, Zabrze, Poland. The indications for initiating MCS were end-stage CHF due to dilated cardiomyopathy in all the patients. Taking into consideration the size of the devices, the HeartWare System (HeartWare Inc., Miami Lakes, FL) was chosen for implantation. The system has been previously described in details. Briefly, it consists of a centrifugal pump, an integrated inflow cannula, an outflow graft, and a percutaneous driveline connected to an electronic controller. The pump has the displacement volume of 50 cc and weighs 140 g. The diameter of the pump is 49 mm, the total height of the pump is 58 mm. The inflow part has a diameter of 20.5 mm and is 25 mm long. The outflow tube has a diameter of 10 mm, and the percutaneous driveline a diameter of 4.2 mm. All the implants were performed with cardiopulmonary bypass. A standard median sternotomy was performed during the surgical procedure. The patient was put on cardiopulmonary bypass after sewing of the ring to the myocardium and coring of the ventricular wall, the inflow cannula was inserted slightly anteriorly to the left ventricular apex. The outflow graft was anastomosed to the ascending aorta, using partial clamping. The driveline was then tunneled under the sternum to the right upper abdominal quadrant and connected to the controller. The position of CF-LVAD with respect to the heart could be observed on postoperative chest X-rays of all the patients. All the patients were supported with

CF-LVAD alone, despite the fact that all had a high degree right heart dysfunction [10]. Postoperative management is characterized in Table II, but in general, the management strategy was similar to that applied in patients with Fontan physiology, including nitric oxide application, a special technique of ventilation and even leaving the chest open in the early post-implantation period. A trans esophageal and subsequently transthoracic echocardiography were used as a primary tool in monitoring ventricular function and optimization of pump speed while weaning the patient from cardiopulmonary bypass following implantation, and for further adjustments.

Results. Patient demographics and preoperative characteristics are listed in Table 1. All the patients met the criteria for INTERMACS score 1 before CF-LVAD implantation. Of the three patients forming the study cohort, all were on intravenous inotropes prior to CF-LVAD initiation, two were on prolonged mechanical ventilation, while one patient was supported with venous-arterial ECMO. Two patients needed resuscitation procedures to be performed several times.

The operative results on the day of implantation of CF-LVAD are summarized in Table 2. All the patients remained on VAD support as the bridge to transplant. Patient 1 and 2 have been over 550 days on VAD support and continue to be supported. The postoperative chest X-ray images of the patients are shown in Fig. 1. None of the patients have developed significant end-organ dysfunction, either in early or long-term follow up. In none of our patients have we observed symptoms of device malfunction. In patient I and III, signs of depression and feeding intolerance were observed.

In all the patients, only the LVAD system was implanted in spite of biventricular dysfunction. The prolonged cardiopulmonary bypass time (Table 2) was related to right ventricular dysfunction and attempts to eliminate the implantation of the right ventricular assist device. Postoperative anticoagulation was started with unfractionated

Table 1. Pre-implantation characteristics of CF-LVAD patients

Characteristics	Patient I	Patient II	Patient I
Age (years)	12	11	12
Gender	M	F	M
Weight (kg)	37	34	34
Diagnosis	Dilated CMP	Dilated CMP	Dilated CMP
BSA [m2]	1.09	1.42	1.20
Drainage of pleural cavity	YES	YES	YES
LVEDD (mm)	60 44 55		
Pre-op inotropes	milrinone, dopamine, levosimendan, amiodarone, adrenaline	milrinone, dopamine, levosimendan, adrenaline	milrinone, dopamine, levosimendan, adrenaline
Mechanical ventilation	YES	YES	YES
ECMO	YES	NO	NO
LVEF [%]	20	23	18

BSA — body surface area, LVED — left ventricular end-diastolic diameter, LVEF — left ventricular ejection fraction, CMP — cardiomyopathy, ECMO — extracorporeal membrane oxygenation.

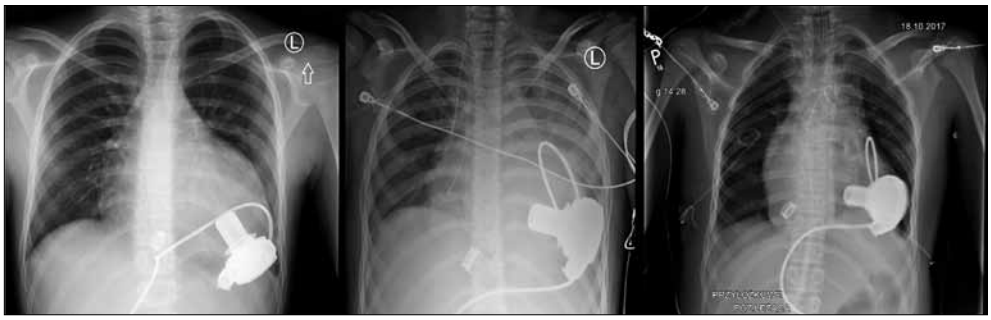
Table 2. Post implantation clinical outcomes in CF-LVAD patients

Characteristics	Patient I	Patient II	Patient I
Operation time (min)	225	195	340
CPB time (min)	96	106	120
Outcome data (days)	570	550	127
Pump speed range (rpm)	2850–2900	2800–3200	2400–2600
Pump flow during first 30 days (L)	2–4	4–5.1	3–4.2
Post-op NO	Yes	Yes	Yes
Delayed chest closure	No	No	Yes

CPB — Cardiopulmonary bypass, NO — nitric oxide.

heparin (the target activated partial thromboplastin time of 50 to 60 s). As the patients tolerated oral nutrition, heparin was switched to warfarin. The targeted INR for this cohort was well within the recommended range of 2–3. The platelet inhibitors used in the patients were acetylsalicylic acid 1 to 2 mg/kg/day. All the patients and their families were trained prior to discharge home. All the patients received treatment after discharge including metildigoxin, aspirin and acenocoumarol with the dose adjusted according to INR. Patient II and III additionally received sildenafil, ACE inhibitors and occasionally furosemide. The patients were advised to check INR, initially every 2 days, then on a weekly basis. Readmission occurred two times in patient 1 and one time in patient 2. The reason for readmissions and adverse events are presented in Table 3. In patient I, drive line infection (defined as appearance of erythema or purulent discharge around the exit site of the drive line) was the reason of several readmissions. CF-LVA-related thrombosis or signs of stroke were not present in any patient. Supra-ventricular arrhythmia was observed only during the post op period in patient II and III, but only in the course of the early post-implantation period. An emergency reference card displaying contact telephone numbers and an algorithm for emergency care was provided to all the patients. Before reintegration to school, school staff members were educated by the family caregiver.

Discussion. In this study, we have demonstrated that children with low weight and BSA <1.5 m2 can be successfully implanted with CF-LVAD and supported for long periods. Moreover, all our pediatric patients have been discharged home and attend their



Picture 1. Position of CF-LVAD after implantation in 3 children on chest X-ray.

schools [6]. There is a growing body of evidence that CF-LVAD is currently the optimal method of long-time MCS, even in pediatric patients. The borderline body weight oscillates about 20 kg, when the patients can be supported, whereas the pulsatile systems, such as the Berlin Heart, remains the option for patients with lower body weight, when the volume of the employed paracorporeal pumps is adjusted to the body mass. One of the major advantages of the CF-LVAD systems is the possibility of discharging patients home; they can even attend schools and be active in everyday life. All the patients in our group are physically very active, what may even pose a risk of damaging the driveline. All our patients demonstrated end-stage CHF, with enhanced pharmacotherapy, being on mechanical ventilation, and in one case on ECMO as the bridge to CF-LVAD. It seems to be one of the reasons that the time from admission to discharge home was about one month. With the center gaining experience, the threshold for starting the MCS may be optimized, so that the patients might be implanted CF-LVAD before reaching the critical status, what may influence the post-implantation course. Some data suggest that ECMO should be generally viewed as increasing the risk of LVAD support in the majority of children. On the other hand, it is possible that ECMO [11], when used strictly for short-term resuscitative support to normalize end-organ function immediately prior to VAD implant, may improve LVAD candidacy in selected patients. Patients with significant problems with left ventricle function have very frequently concomitant right ventricular dysfunction, so the decision must be reached whether the patient needs LVAD only or the biventricular MCS system implantation. The biventricular system is highly demanding and is associated with poorer final results. This is why the majority of centers prefer to start only LVAD and manage patients with RV failure on pharmacological support. Appreciating this strategy, we dedicated much eff ort to preventing biventricular MCS, what was the reason of prolonged time of cardiopulmonary bypass, which was not related to technical issues of CF-LVAD implantation.

In our experience, the management strategy in the post-op period was very similar to that employed in patients after the Fontan operation, including special ventilation settings, nitric oxide administration, or even leaving the chest open shortly after initiation of CMS. Despite aggressive medical support of RV, a certain proportion of patients will still develop RV failure requiring temporary mechanical RV support to restore blood flow to the pulmonary circulation and increase LV preload [7]. Studies suggest that an early planned biventricular assist device (BiVAD) is associated with better survival as compared to delayed implantation [8,9]. Therefore, performing a thorough preoperative risk assessment for RV failure is necessary to implant BiVAD or total artificial heart.

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