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MECHANICAL CIRCULATORY SUPPORT DEVICES FOR PATIENTS WITH SMALL ANTHROPOMETRIC INDICATORS

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Mechanical circulatory support (MCS) devices, designed specifically for patients with small anthropometric parameters, are now emerging. A detailed systematic literature review of existing systems for long-term circulatory support in this patient cohort was conducted. Circulatory support devices and their main technical and biological characteristics were studied in detail. Despite significant scientific and technological progress, there is still no technology for creating an assist pump to support patients with small body surface area (BSA), given the wide range of patient sizes, increased cardiovascular demand due to growth, as well as anatomical and physiological heterogeneity of congenital heart disease.

Keywords: mechanical circulatory support, body surface area, axial pump, centrifugal pump.

Severe cardiovascular disease in adults and children is the leading cause of death worldwide, claiming 17.9 million lives annually [1]. Heart failure (HF) is a consequence of severe heart disease in which the heart muscle is unable to pump blood to provide adequate end-organ perfusion. HF affects the quality of life of people around the world, affecting 64 million adults and children each year [2]. The reported incidence of HF in children worldwide is 0.97% to 7.4% per 100,000 children [3], and most of them require immediate surgical intervention [4]. Infants with complex congenital heart defects may require multiple open-heart surgeries to establish proper cardiovascular anatomy and physiology [5–7]. These complex congenital heart disease (CHD) cases require continuous clinical follow-up throughout the patient's life, as this cohort of patients is at a higher risk of developing premature congestive HF. Heart disease can also manifest with developmental delays, including neurological impairment and growth retardation [8].

Pharmacologic drug therapy slows progression to end-stage HF. Heart transplantation is the gold standard of medical care, but the number of patients requiring transplantation keeps on exceeding the number of available donor organs every year. In pediatric transplantation, a difficult point is the selection of donor-recipient pairs due to anthropometric features of young patients. Statistically, 74% of children receive a donor organ within 90 days of being placed on the waiting list, but the mortality rate among those still waiting ranges from 5% to 39% worldwide [9]. There remains a high clinical need to develop safe and effective mechanical circulatory support (MCS) devices for these HF patients for use as intermediate therapy or long-term chronic disease management.

MCS devices are used as a bridge to transplantation, a bridge to recovery and permanently (or as a definitive treatment option without the possibility of heart transplantation) (bridge to destination). Analysis of the UNOS database shows that this technology has led to a 50% reduction in waiting list mortality [10]. Despite this progress, there remain important aspects in which these devices can be improved. This review presents published data on MCS devices created and under development for patients with small body surface area (BSA) in order to assess progress and provide an informed vision for the development of this industry. Table 1 summarizes the major devices developed and their key technical specifications.

MAIN CRITERIA WHEN DESIGNING MCS DEVICES

According to the characteristics of the devices presented in Table 1, the main design criteria identified were:

1) pulsatile or continuous flow;
2) acute or chronic circulatory support;
3) anatomical location in the patient's abdominal cavity;
4) blood rheology;
5) dynamic pressure and blood flow requirements in patients of different ages.

Pulsatile or continuous flow

Recent clinical evidence in adults show that chronic continuous flow disorders with reduced pulse pressure can lead to harmful side effects and adversely affect outcomes [11–13]. However, it has also been found that

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continuous blood flow conditions are well tolerated for short-term circulatory support and may provide better performance than pulsatile flow devices. Currently, there is still a poor understanding of how small anthropometric patients tolerate long-term implantation of MCS devices whether with pulsatile or continuous flow. Consequently, the development of ventricular support devices that can generate continuous and pulsatile blood flows is an urgent problem in modern medicine [14, 15].

Acute and chronic needs for MCS devices

Of the cases reported in PediMACS, 19% of patients received short-term or emergency support via MCS devices [16]. Treatment outcomes for these patients were better compared to extracorporeal membrane oxygenation (ECMO) techniques, resulting in increased implementation rate, and the mean time to use short-term MCS increased to 19 days [17]. Some MCS devices designed for short-term use (Thoratec Centrimag & Pedimag Blood Pump, Thoratec Corporation, USA) were used as long-acting devices and showed favorable outcomes. The disadvantage of these systems was that they limited patient mobility and prolonged the length of stay in specialized medical centers.

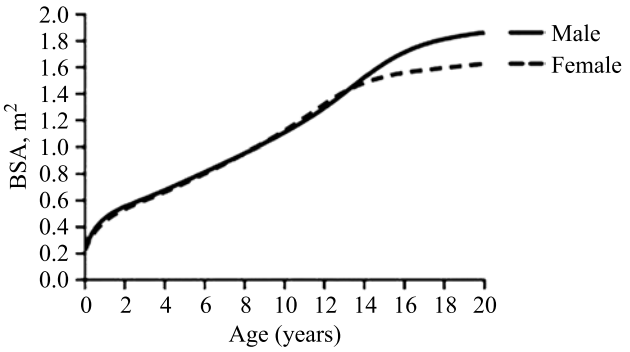

Fig. 1. Change in BSA in healthy individuals aged 0 to 20 years

Anatomical location of MCS devices in the patient's abdominal cavity

In patients with small anthropometrics, there are several requirements for device placement: in terms of anatomical positioning and connection of the inlet and outlet cannula. The BSA for patients can be easily calculated from body weight and height:

$$\text{BSA}\left[\text{m}^2\right] = \sqrt{\frac{\text{Height (cm)} \times \text{Weight (kg)}}{3600}}.$$

The BSA of newborn patients averages 10% of the BSA of a young adult, and it increases dramatically as the infant grows and develops (Fig. 1) [18].

Consequently, anatomical fitting of an MCS device for patients with low BSA is both challenging and ne-

Table 1

Key technical design specifications of the developed MCS devices

Device	Country	Working fluid flow (L/min)	System pressure (mmHg)	Total length (mm)	Body surface area (m^2)	Market position
DON-3 (10 mL)	Russia	1–3	80	60	0.62–1.1	–
Berlin Heart Excor (10 mL)	Germany	0.6–1	225	Paracorporeal system	0.2–0.33	FDA approved for clinical use in pediatric patients
Berlin Heart Excor (25 mL)	Germany	1.3–2.2	175	Paracorporeal system	0.33–0.5	FDA approved for clinical use in pediatric patients
Berlin Heart Excor (30 mL)	Germany	1.3–3	175	Paracorporeal system	0.6–1	FDA approved for clinical use in pediatric patients
Berlin Heart Excor (50 mL)	Germany	3–5.2	175	Paracorporeal system	1–1.7	FDA approved for clinical use in pediatric patients
Berlin Heart Excor (60 mL)	Germany	3.6–6	200	Paracorporeal system	1.2–2	FDA approved for clinical use in pediatric patients
DeltaStream DP3 VAD (240 mL)	Germany	0–8	240		0.18–0.61	–
HeartMate 3 (280 mL)	USA	2.5–10	280	50.3	>1.2	FDA approved for clinical use in pediatric patients
HeartWare HVAD (135 mL)	USA	2–10	–	49	>1.2	FDA approved. But no longer available on the market
Jarvik Infant VAD (60 mL)	USA	0.5–3	–	11	>0.4	
PediaFlow VAD (155 mL)	USA	0.3–2	–	28	0.2–0.8	
Penn State Infant VAD (12–14 mL)	USA	0–1.6	–		>0.5	

cessary. The design of paracorporeal devices also needs to consider the patient's anatomy, which determines which inlet and outlet cannulas would be suitable. For example, the Berlin Heart Excor (Berlin Heart GmbH, Germany) paracorporeal circulatory assist (CA) system has a size range of exit cannulas with diameters of 3, 6, 9, and 12 mm [19–21]. An increase in BSA with age generally suggests that devices designed for younger patients should be suitable for older patients as well, while factoring in the device size for all cohorts.

Blood rheology in patients with low BSA

Patients of different ages differ in blood rheological properties [22, 23]. Hematocrit, which affects blood viscosity, is highest in newborns and rapidly decreases to a steady level as adolescence is reached. Congenital or acquired heart defects in patients with low BSA also affect hematocrit levels, and blood rheological properties affect fluid dynamics, especially in low phase shift CA pumps [24].

Dynamic pressure and blood flow requirements in patients of different ages

Young patients experience increased cardiac volume during growth and development, and hence the dynamic pressure requirements of an MCS assist device change. Cardiac output in children doubles from birth to 1 year of age and doubles again by 10 years of age (Fig. 2).

The size of an MCS device determines the ability to generate a wide range of pressures and flow rates at acceptable shear stress [25]. This poses some challenges related to external design, as device size and hence anatomical positioning is inversely related to pressure and capacity. For long-term mechanical support, patients with small anthropometrics may require replacement of the MCS system with a new one to adapt to the patient's height. The versatility of the design can be utilized to integrate multiple pumps into a single device to increase the operating range of flow and pressure characteristics.

EXTRACORPOREAL CA SYSTEMS AND LVAD SYSTEMS

MCS devices and the challenges faced by physicians and patients using this type of CA systems were reviewed. But two categories of MCS devices are more often used in clinical practice: extracorporeal circulatory support systems and ventricular assist devices.

Extracorporeal circulatory support systems for patients with small anthropometric indicators

One of the earliest technologies and still the most sought after for patients with small BSA is ECMO [26–28]. The ECMO circuit is connected to the patient either by veno-arterial cannulation (via the femoral artery and vein) or by veno-venous cannulation (via the right atrium or jugular vein). The ECMO device circulates and oxygenates the blood, replacing both heart and lung function.

This system is designed for short-term support and requires immobilization and often sedation [29]. Therefore, extracorporeal ventricular assist device (VAD) systems have begun to compete with ECMO.

When the performances of ECMO and VAD were compared for patients with small anthropometric indices, it was found that those who received extracorporeal pump support showed improved outcomes. Waitlist mortality also decreased from 38% (ECMO) to 13% (VAD), while post-transplant survival increased from 80% to 92% in patients receiving VAD support instead of ECMO [30].

Extracorporeal and paracorporeal devices such as Berlin Heart EXCOR (Berlin Heart, Germany), PediMag

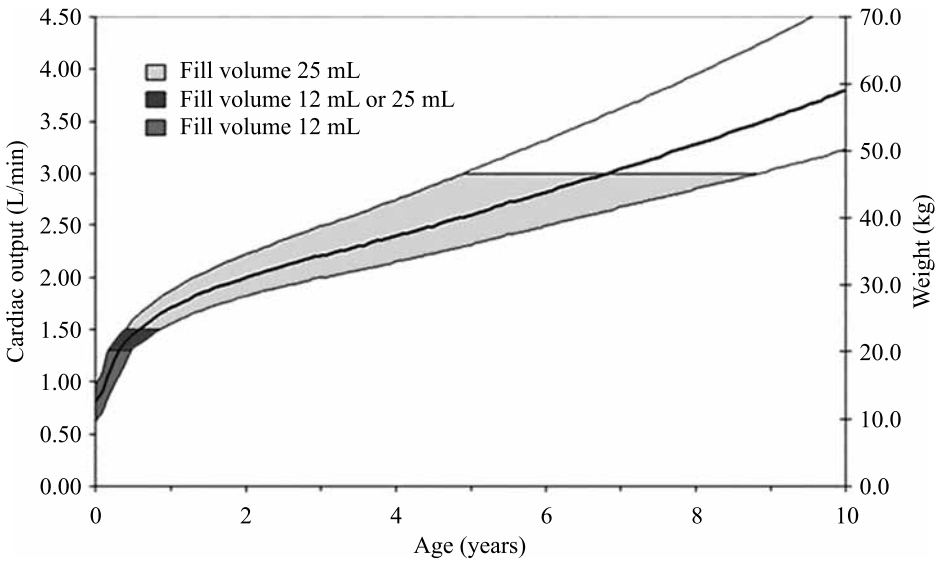

Fig. 2. Cardiac output requirements for children aged 0 to 10 years

(Abbott Laboratories, Illinois, USA), Jostra RotaFlow (Maquet, Germany) and TandemHeart (CardiacAssist, Inc., USA) have been used to support cardiac ventricular function in the short-term without oxygenation. These pumps compare favorably with ECMO for short-term treatment.

Since these devices are placed outside the body, the issue of placing pumps in the patient's abdominal area is no more there. In addition, transferring the patient to another device is less complicated with extracorporeal/paracorporeal devices. However, for long-term support, these MCS devices face several challenges. These designs limit patient mobility, increase thromboembolic complications, increase neurologic risks compared to implantable designs, and limit hospital discharge due to home care challenges [31].

Ventricular assist devices

At their core, VADs increase cardiac output by assisting the left or right ventricle. In 2004, the National Institutes of Health's National Heart, Lung, and Blood Institute (NHLBI) established the Pediatric Ventricular Assist Device Program. These programs have facilitated the development and implementation of implantable devices for patients with small BSA [32–33].

Projects under the program included the development of the following devices:

- An implantable mixed-flow device (PediaFlow VAD) [34];
- An implantable mixed-flow VAD that can be maintained both intravascularly and extravascularly, depending on patient age and size (PediPump) [35];
- Ension's Pediatric Cardiopulmonary Assist System (pCAS) for patients with small anthropometric parameters [36];
- Axial pump (Infant Jarvik) [37];
- Pulsatile flow system (Penn State pediatric VAD) [38].

Other devices have been developed in parallel with this development program, some of which have been approved for clinical use in patients with small BSA.

Clinically approved MCS devices

Berlin Heart EXCOR (Berlin Heart, Germany) is one of the first systems approved by the U.S. Food and Drug Administration (FDA) (Fig. 3) [39–40].

It is a flexible diaphragm pump with chamber fill volumes ranging from 10 to 80 mL and flow rates from 0.4 to 5 L/min. All of them provide sufficient pressure rise to support patients with small BSA [41].

Two other FDA-approved VADs are the implantable HeartMate 3 LVAD (Abbott Laboratories, USA) (Fig. 4), which is designed for patients with a BSA >0.7 m^2 for extracorporeal support and 1.4 m^2 for implantable support [42], and the extracorporeal Abiomed BVS 5000 (Abbott Laboratories, USA).

Fig. 3. Sizes of the Berlin Heart EXCOR extracorporeal pumps (10 to 80 mL fill volume)

Fig. 4. Implantable HeartMate 3 LVAD

The HeartMate 3 adult assist pump (Abbott Laboratories, USA) received FDA regulatory approval for use in patients with small anthropometric indices with progressive right ventricular dysfunction in December 2020 [43]. This fully magnetic suspension pump has demonstrated very good outcomes in adult patients (2-year survival rate is 79%) and has received approval for use in patients with BSA >1.2 m^2.

Implantable heart pump HVAD (Medtronic, USA) was approved by the FDA in 2012 for adult patients with

large BSA. However, after a retrospective analysis of this pump in 14 patients with low BSA, it was rejected for use in this patient cohort. Production of these pumps was suspended in 2021 due to the high incidence of adverse neurologic events [44].

As part of the MCS device development program described earlier, Jarvik Heart has developed a VAD that can be used in patients with low BSA (Fig. 5) [45]. Infant VAD Jarvik can generate flow from 0.27 to 3 L/min, Child VAD Jarvik produces flow from 0.5 to 3 L/min.

The devices received FDA approval for clinical trials in 2012, but were subsequently recalled as of late 2018, and were no longer in clinical use by May 2020 due to connector issues on external cables [46].

The developers of the PediaFlow axial pump (HeartWare International, USA) (Fig. 6) have continued independent development to date, despite no FDA approval. The most recently published fourth-generation version of the device is a compact design (17 mm in diameter and 50 mm in length) that can support patients weighing up to 3 kg and can deliver blood flow rates from 0.5 L/min [47].

Fig. 5. Axial flow pumps: Child VAD Jarvik (left) and Infant VAD Jarvik (right)

Fig. 6. Axial-flow pump PediaFlow (HeartWare International, USA)

MCS devices for patients with small anthropometric parameters are under development

DeltaStream DP3 (Xenios AG., Germany)

The DeltaStream DP3 is a diagonal pump that combines axial and centrifugal pumps to pump blood. This extracorporeal device easily generates the required pressure (240 mmHg increase in systemic pressure) and the required flow rate of up to 8 L/min. In vitro studies have shown that this device works without interruptions in patients with BSA from 0.18 to 0.61 m^2 [48].

DON-3 (Russia)

DON-3 is the first experience in creating a domestic VAD. This MCS device is an axial pump. The development was brought to the stage of experimental studies on animals (sheep). The pump provides operating pressure of up to 135 mmHg with a liquid flow range 1–3 L/min. The design of the development is relatively compact: diameter 25 mm, length 60 mm. Results from animal tests show promising results [49–51].

Drexel Dragon 1S & 1P (Drexel University, USA)

Drexel University is developing hybrid continuous-flow MCS devices in which a magnetically suspended axial pump and a centrifugal pump are combined to increase the active operating time of the device [52]. There are two design concepts: the axial pump is placed in front of the centrifugal pump, and a parallel concept: the axial and centrifugal part of the pump are separated into two separate units. A pump-to-pump switching technology was created to control this unit. The maximum system pressure rise during initial testing on a hydrodynamic bench is 120 mmHg with a flow range of 1 to 5 L/min. Development of this pump is actively continuing.

iCor VAD (Xenios AG., Germany)

The iCor pump (Xenios AG., Germany) is a paracorporeal centrifugal pump. Initial studies of the flow and pressure characteristics of the pump have been performed and have shown overpressurization of more than 100 mmHg at flow rates ranging from 0.2 to 1.8 L/min. The pump continues to be improved and tested.

NIPRO VAD (NIPRO Medical Corporation, USA)

NIPRO VAD (NIPRO Medical Corporation, USA) is another paracorporeal pulsatile VAD. The flow rate is 2–4 L/min at a maximum pressure of 150 mmHg, at which the device can provide pulsatile flow at a rate of 50–130 beats per minute. Bench tests of this pump have been performed and have shown low levels of damage to blood cells [53, 54].

Penn State Infant VAD (Penn State University, USA)

The University of Pennsylvania is developing a pump targeting patients with low BSA. The VAD under development is a pulsatile paracorporeal device with a

valve and pneumatic actuator, a concept derived from the Thoratec pneumatic VAD. It is a small pump with an operating filling volume of 12–14 mL. Animal studies have shown that the pump can deliver a flow rate of 1.6 L/min. This system is suitable for patients with BSA <0.5 m^2, and there is a low level of blood trauma. Developments are ongoing.

CONCLUSION

The results of this review show that there have been significant progress in the development of MCS devices. New engineering and design capabilities are gradually approaching clinical implementation.

Design constraints for CA devices for patients with small anthropometrics, such as target size, are usually determined based on duration of support (acute or chronic) and clinical goals (extracorporeal placement or implantable option). The choice of cannula connection also depends on the patient's anatomy. Table 2 summarizes the main theoretical parameters that MCS devices require for patients with different BSA [57, 58].

Table 2

Expected performance of MCS devices

Theoretical performance indicators	Target range
System pressure	10–150 mmHg
Fluid flow	0.5–7 L/min
Pulmonary pressure	5–30 mmHg
Pump rotor speed	≤8000 rpm
Shear stress	<170 Pa
System power consumption	<10 W

Using this data, it is possible to assess how well the pumps meet the pressure and flow requirements for patients with small BSA. Most devices cope well with increasing pressure, but there are discrepancies in performance when looking at the reported fluid flow ranges.

Factors such as speed and rotational speed can be altered to create higher blood flow, but it is likely that these alterations can drive the device into non-standard operating states, creating physiologic risks (hemolysis and thrombosis).

The above data show that there is no universal pump yet that satisfies certain design limitations and requirements due to the wide range of patient sizes, higher cardiovascular demand as the body grows, and anatomic and physiologic heterogeneity of congenital heart defects.

Although progress has been made in the development of MCS systems, additional research is needed to inform the broader scientific and medical community and stimulate innovation in medical device technologies for patients with small anthropometrics.

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