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REVIEW

Current status and future directions in pediatric ventricular assist device

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Abstract
A ventricular assist device (VAD) is a form of mechanical circulatory support that uses a mechanical pump to partially or fully take over the function of a failed heart. In recent decades, the VAD has become a crucial option in the treatment of end-stage heart failure in adult patients. However, due to the lack of suitable devices and more complicated patient profiles, this therapeutic approach is still not widely used for pediatric populations. This article reviews the clinically available devices, adverse events, and future directions of design and implementation in pediatric VADs.

Keywords Pediatrics · Ventricular assist device · Mechanical circulatory support · Heart failure

Introduction

Pediatric heart failure (HF) is an important cause of mortality in childhood. The incidence of HF in children and adolescents has been reported to range from 0.87/100,000 to 7.4/100,000 [1], with a 5-year mortality or heart transplant (HT) rate of 40% [2]. The approaches to HF treatment are similar in both adult and pediatric patients and include medication, device therapy, surgical treatment, mechanical circulatory support (MCS) and HT. For those patients who retain severe and persistent symptoms of HF despite optimal guideline-directed medical treatment, due to the inefficiency of other approaches, HT was viewed as the last resort and the only long-term solution. However, the overall shortage of suitable donors is an important obstacle to their treatment.

Therefore, as one of the alternative treatments for patients suffering from HF, ventricular assist devices (VADs) have drawn increasing attention and have revolutionized this field. The concept of using a mechanical pump to assist or take over heart function was initially put into practice in the early 1960s. After the first successful clinical use of a VAD as postsurgical support in a 37-year-old female [3], the first use of VADs in pediatric patients was performed by Dr. Debakey in 1967. A 16-year-old girl received mitral valve replacement and was supported by a paracorporeal VAD postoperatively until medically stable. The technique and products have improved after decades of development since that time. However, it was not until the 2000s that pediatric VAD applications underwent a burst of continual growth. Accordingly, a significant increase in waiting-list survival was observed in the era where pediatric VADs initially started to be employed [4]. Indeed, the VAD has changed the management strategy of pediatric HF. However, we are still facing difficulties such as a lack of suitable devices, more severe and complicated patient profiles, less practice experience and higher complication rates, which all limit the application of pediatric VADs.

This article reviews the clinically available devices, adverse events, and future directions of design and implementation in pediatric VADs. Additionally, in this article, by introducing differences in the current status of VAD

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application in pediatric and adult patients, we try to clarify the large "gap" in devices and patient management and to provide our analysis and advice.

Classification and properties of clinically available pediatric VADs

Pediatric VADs are classified in a number of ways for better description. They can be separated by the anticipated duration of therapy: short term (temporary) and long term (durable). Short-term pediatric VADs are designed for a limited duration of support, usually ranging from several hours to up to 30 days. Temporary VADs are usually applied in acute processes for bridge to transplant (BTT), bridge to recovery (BTR) or bridge to durable VAD support; or applied for prolonged support in cases of small children and patients with complicated circulation. Long-term VADs are mostly applied for BTT and destination therapy (DT). It should be noted that in clinical practice, limitations regarding the duration of support are unclear [5].

The mode of blood flow created by the device could better reflect the mechanism of VADs, as it is strongly related to the outcome of patients, and is briefly introduced in this section. Generally, there is pulsatile flow (PF, by first generation devices) and continuous flow (CF, by second- and third-generation devices). In addition, VADs are also classified based on the location of the pump relative to the patient: percutaneous (intravascular), implantable and paracorporeal.

Based on the major registries and studies, we enrolled the devices frequently used in pediatric patients or in studies focusing on pediatric populations, regardless of whether they were specifically designed for children. Sorted by the recommended duration of support, clinically available devices are shown in (Table 1) along with their key information.

First-generation VADs

The first-generation VADs consist of a volume displacement pump that is actuated pneumatically or electrically to generate PF. Berlin Heart EXCOR VAD (Fig. 1a) is currently the most widely used pediatric PF device. First-generation VADs have shown clinical advantages over optimal medical therapy since their application [6]. Meanwhile, first-generation VADs have also shown flaws. Other than limited patient mobility due to large driving consoles and noise generated by mechanical heart valves [7], most importantly, PF devices consist of multiple moving mechanical parts and prosthetic valves, which leads to limited reliability and durability and a higher risk of thrombus formation. A study revealed that the probability of PF device failure was as high as 35% at 24 months [8], making it one of the major concerns. Moreover, another study reported that patients with PF devices had a far worse survival rate at 2 years with more frequent

Table 1 VADs most implanted in pediatric patients, sorted by recommended duration of support

Device	Location	Generation	Output (L/min)	Body surface area (BSA, m^2) or body weight (kg) recommended
Short-term VADs				
CardiacAssist TandemHeart [87]	Percutaneous	2	0–5	/
Maquet RotaFlow [88]	Paracorporeal	2	0–10	/
Abbott PediMag [89]	Paracorporeal	3	0–1.5	/
Abbott Centrimag [90]	Paracorporeal	3	0–10	/
Abiomed Impella 2.5/CP/5.0 [91]	Percutaneous	2	up to 2.5/3.7/5	/
Long-term VADs				
Berlin Heart INCOR [92]	Intracorporeal	3	/	/
Berlin Heart EXCOR (10 ml) [93]	Paracorporeal	1	0.5–1.1	2–8.5 kg
Berlin Heart EXCOR (15 ml)[93]	Paracorporeal	1	0.9–1.7	6.5–15 kg
Berlin Heart EXCOR (25 ml) [93]	Paracorporeal	1	1.5–2.6	13.5–25 kg
Berlin Heart EXCOR (30 ml) [93]	Paracorporeal	1	1.8–3.2	16–30 kg
Berlin Heart EXCOR (50 ml) [93]	Paracorporeal	1	3–5.5	30–55 kg
Berlin Heart EXCOR (60 ml) [93]	Paracorporeal	1	3.6–6	35–60 kg
Abbott HeartMate II [94]	Intracorporeal	2	2.5–10	>1.2 m^2
Abbott HeartMate III [95]	Intracorporeal	3	2.5–10	>1.2 m^2
Medtronic HeartWare HVAD*[96]	Intracorporeal	3	2–10	>1.2 m^2

The key metrics extracted from the latest manuals or product catalog provided by suppliers. Information not provided in official manuals is presented as "/"; "*" indicates that the VAD is no longer available in the market

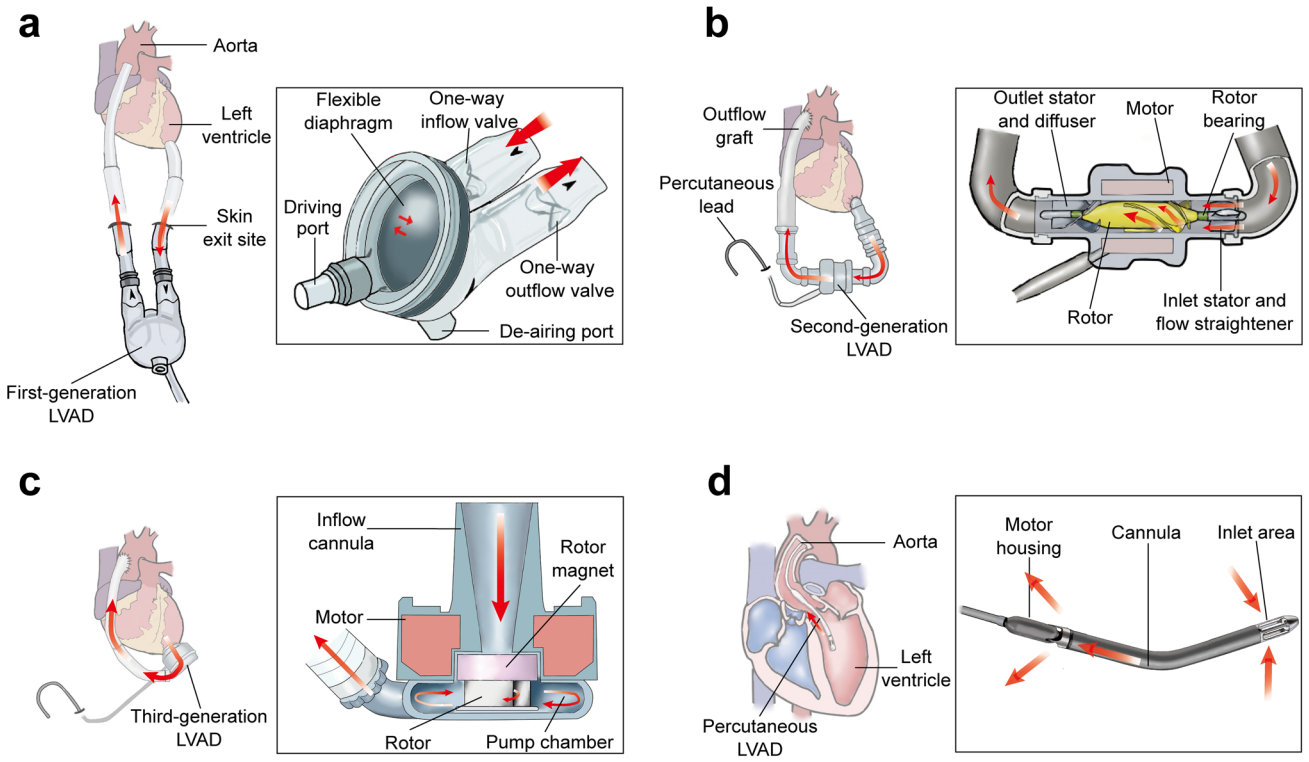

Fig. 1 Diagrams of representative VADs applied in children. Red arrows represent the direction of blood flow. **a** First-generation pediatric LVAD (Berlin Heart EXCOR). **b** Second-generation axial CF LVAD (HeartMate XVE LVAD). **c** Third-generation centrifugal CF LVAD (HeartMate III). **d** Percutaneous LVAD (Abiomed Impella)

adverse events and device replacements than patients with CF devices [9]. This study is seen as a milestone and has revolutionized the choice of device.

Second- and third-generation VADs

Second- and third-generation VADs both pertain to CF pumps. All rotary blood pumps, except if full levitation of the impeller within the pump housing is achieved under normal operating conditions (referring to third-generation VADs), are defined as second-generation devices [7]. The CF pumps are widely used, and they could serve as short-term paracorporeal VADs (Maquet RotaFlow, Abbott Centrimag, etc.), percutaneous VADs (CardiacAssist TandemHeart, Abiomed Impella, etc.) (Fig. 1d) or durable intracorporeal VADs (Medtronic HeartWare HVAD, Abbott HeartMate III, etc.) (Fig. 1b, c). Theoretically, the durability and hemocompatibility could be further improved with a wear-free operation mode, which is the primary motivation for the development of third-generation VADs. The MOMENTUM 3 trial reported that, at 2 years, the composite endpoint of survival free of disabling stroke and reoperation to remove or replace a malfunctioning device was significantly better with HeartMate III (third-generation VADs) than with HeartMate II (second-generation VADs) in both the BTT and DT groups [10]. However, other third-generation devices, such as Berlin Heart INCOR and Abbott PediMag, still need constant observation to clarify their superiority in patient outcomes.

Adverse events of pediatric VADs

Pedimacs (the Pediatric Interagency Registry for Mechanical Circulatory Support), Paedi-EUROMACS (The European Registry for Patients with Mechanical Circulatory Support) and ACTION (Advanced Cardiac Therapies Improving Outcomes Network) are the three major pediatric VAD registries [11–13] reflecting the current situation of this field. However, their reports of adverse events are not quite comparable, as there are differences in the type of adverse events concluded between the studies, and the categorization of "early" or "late" adverse events varies. To avoid confusion, the data referred to in this section are mainly based on the Pedimacs registry, who might be more representative as it so far has included more cases than other registries along with more dispersed distribution of patients' ages. We also reviewed studies including ≥ 25 patients published in the last 5 years

Table 2 Reported adverse events of pediatric VADs

First author	Source of data	Cohort period	Patient number	Age/weight	Notes	Bleeding		Infection	Device malfunction/ exchange	Neurological dysfunction		Renal dysfunction	Right heart failure	Respiratory failure	Hepatic dysfunction	Arrhythmia
						GI bleeding	Non-GI bleeding			Cerebrovascular accidents	Others					
Bleiweis et al. [97]	University of Florida, USA	2009–2021	36	<10 kg	Berlin Heart EXCOR only	25%		/	/	42%	/	/	/	/	/	/
Adachi et al. [12]	Pedimacs registry	2012–2021	1047	7.6 ± 6.4 years[a]	/	2% (within 2 weeks); 5% (beyond 2 weeks)	14% (within 2 weeks); 9% (beyond 2 weeks)	12% (within 2 weeks); 21% (beyond 2 weeks)	/	4% (within 2 weeks); 7% (beyond 2 weeks)	7% (within 2 weeks); 7% (beyond 2 weeks)	/	/	/	/	/
de By et al. [11]	Paedi-EUROMACS	2000-2020	480	8.13 ± 6.53 years[a]	/	0.7 events per patient-year (within 3 months); 0.05 events per patient-year (beyond 3 months)		0.78 events per patient-year (within 3 months); 0.42 events per patient-year (beyond 3 months)	1.59 events per patient-year (within 3 months); 0.67 events per patient-year (beyond 3 months)	0.71 events per patient-year (within 3 months); 0.11 events per patient-year (beyond 3 months)		/	/	/	/	/
Rohde et al. [98]	Erasmus University Medical Center, Netherlands	1998–2018	28	10.7 (2.9–13.0) years[b]	Berlin Heart EXCOR only	/	50%	4%	54%	50%	/	11%	7%	/	/	/
Mantell et al. [99]	Morgan Stanley Children's Hospital, USA	1993–2017	88	13.1 (6.7–16.2) years[b]	/	/		/	/	28%	/	50%	/	/	/	/
Menéndez et al. [100]	Spain (6 centers)	2006–2020	118	2.3 (0.7–7.7) years[c]	/	39%		/	33.9%	38.1%	/	/	/	/	/	/
Joong et al. [101]	Action registry	2018–2020	30	0.9 (0.1–25) months[c]	Stage 1 single ventricle palliation patients	7%	10%	43%	3%	20%	10%	13%	/	30%	7%	/
Fu et al. [102]	National Taiwan University Hospital, Taiwan	2008–2021	33	9.6 (0.6–16.1) years[c]	/	/		18.8%	/	30.3%	/	27.3%	/	/	/	/
Rohde et al. [103]	Paedi-EUROMACS	2011–2021	230	2.0 (0.6–8.0) years[b]	Berlin Heart Excor only	11.3% (within 30 days)		9.6% (within 30 days)	13.5% (within 30 days)	20.0%	/	/	/	/	/	/

Table 2 (continued)

First author	Source of data	Cohort period	Patient number	Age/weight	Notes	Bleeding		Infection	Device malfunction/ exchange	Neurological dysfunction		Renal dysfunction	Right heart failure	Respiratory failure	Hepatic dysfunction	Arrhythmia
						GI bleeding	Non-GI bleeding			Cerebrovascular accidents	Others					
Adachi et al. [65]	Texas Children's Hospital, USA	2011–2018	39	11 (4–18) years[c]	HeartWare VAD only	41%		49%	10%	28%	/	10%	/	/	/	/
Bansal et al. [19]	Action registry	2018–2021	506	not mentioned	/	/		27.5%	/	/		/	/	/	/	/
Vander-Pluym et al. [31]	Pedimacs registry	2012–2017	12	5.6 ± 2.5 years[a]	HeartWare HVAD only	/		17% (within 3 months)	8% (within 3 months)	25% (within 3 months);8% (beyond 3 months)		17% (within 3 months)	/	8% (within 3 months)	/	17% (within 3 months)
			192	14.4 (2.7-19.0) years[c]		21% (within 3 months);4% (beyond 3 months)		21% (within 3 months);8% (beyond 3 months)	7% (within 3 months);5% (beyond 3 months)	7% (within 3 months);4% (beyond 3 months)	16% (within 3 months);4% (beyond 3 months)	8% (within 3 months);1% (beyond 3 months)	/	9% (within 3 months);1% (beyond 3 months)	3% (within 3 months);1% (beyond 3 months)	9% (within 3 months)
Auerbach and Simpson [32]	Action registry	2018–2020	50	12.9 (3.4–19.1) years[c]	HeartWare HVAD only	17%		17%	7%	7%		5%	7%	7%	0	5%
Yu et al. [104]	Lucile Packard Children's Hospital at Stanford University, USA	2014–2020	78	not mentioned	/	/		/	/	19%	12%	/	/	/	/	/

Studies referring to adverse events of pediatric VADs published in the last five years. Cohorts including fewer than 25 patients are not listed. In different studies, the age of patients is presented as the mean ± standard deviation ("a"), median (interquartile range) ("b"), or median (range) ("c"). Unless otherwise specified, the incidences of adverse events are presented as the percentage of patients (%). Adverse events not provided in these studies are presented as "/"

(2019–2023) referring to adverse events of pediatric VADs in (Table 2), including Paedi-EUROMACS and ACTION. Numerous variables could have an impact on the VAD risk profile, including patient age, body size, anatomy, developmental hemostasis, device type, illness severity and comorbidities prior to implantation [14], and these interdependent factors greatly amplify the complexity of patient outcome.

Bleeding

Bleeding, especially gastrointestinal (GI) bleeding, is a significantly common complication that leads to recurrent hospitalizations, along with increased lengths of stay, costs, blood transfusions, and time off anticoagulation or antiplatelet therapy [15]. The risk of bleeding in the setting of VAD support is multifactorial and is related to anticoagulation/antiplatelet therapy, dysregulated angiogenesis, arteriovenous malformations, VAD-associated von Willebrand syndrome, mucosal hypoxia induced by lack of pulsatility in CF VADs, etc. [16]. Adding up both GI and non-GI bleeding, the rate of bleeding events in the Pedimacs registry is up to 5.1 per patient-year within the first 2 weeks and 0.6 per patient-year afterward [12]. Since pediatric patients have distinct differences in blood rheology and behavior [17], the patient management should be actively and repeatedly evaluated.

Infection

Infection is another common adverse event occurring in VAD-supported children. The Pedimacs registry found that infections occurred in 12% of pediatric patients within 2 weeks of implantation and 21% after 2 weeks or more [12]. Among adult patients, the most common VAD-specific infections are driveline infections, with an overall event rate of 14 to 48% between various studies [18]. The ACTION registry further reveals that, in children, the three most common types of infection are sepsis, localized non-device infection, and percutaneous site and/or pocket infection [19]. Paracorporeal devices are strongly related to a higher risk of infection than intracorporeal devices [19].

Device malfunction/pump thrombus formation

Device malfunction/pump thrombus formation is the most frequently reported major adverse event in pediatric population [5, 11]. Pump thrombus is the most common reason for device exchange and could be a risk factor for stroke leading to morbidity [20]. Although pump thrombus is a significant adverse event, a study noted that only 13% to 15% of device malfunctions are attributable to pump failure [21]. The true incidence of malfunction of the broader system components might have been neglected. CF-VADs greatly ameliorated the outcome, with 90.4% of adult patients at 1 year and 82.6% at 2 years free from device malfunction/pump thrombi [22]. Similarly, in a recent study of pediatric patients implanted with the HeartMate 3 device, there were no episodes of pump thrombosis or pump dysfunction requiring operative exchange with a median 78 days of follow-up [23]. However, due to the difference in device type and the lack of experience, it seems much less optimistic for the overall pediatric patients, especially those supported by paracorporeal devices [24].

Neurological dysfunction

Neurological adverse events are defined and recorded differently among studies, most of which mainly focus on cerebrovascular accidents (CVAs). Ischemic strokes usually result from embolic sources on the aortic valve, the inflow cannula, or intracardiac chamber, and hemorrhagic strokes may occur mainly secondarily to hypertension or coagulopathy [25]. The Pedimacs report reveals that stroke occurs in 11% of all pediatric patients [12]. CVAs are one of the leading causes of death in Paedi-EUROMACS (24.17% of deaths), as in the Pedimacs cohort [11, 12]. It is important to recognize that adverse neurological events comprise a broad category of complications. Other than CVAs, there are seizures, encephalopathy, asymptomatic neuroradiological findings, confusion, extra-axial bleeding, etc. [26].

Beyond these complications, right ventricular failure [27], aortic regurgitation [28, 29], peripheral infarction [30], arrhythmia [31, 32], renal dysfunction, respiratory failure, wound dehiscence, allosensitization, psychiatric episodes, and hemolysis are also observed adverse events post-VAD implantation [22, 33] and yet are less discussed in pediatric cohorts. Despite improvements in VAD technology and increasing familiarity with pediatric VAD patients, the outcome and survival of pediatric patients are still not optimal and not comparable with those of adults. For better determination of the incidence of adverse events and for improved reporting of how to effectively manage them, sharing experiences across centers is of great value.

Future directions of pediatric VADs design

Ideally, VADs should be able to provide suitable cardiac output both at rest and during exertion, high durability, a less invasive implantation approach, a nonblood contact design, and a fully implantable system to avoid skin barrier penetration [34]. Whereas each of these ideals may have been achieved and implemented in different designs, we are far from fulfilling all of these criteria. Here, we put forward a few possible trends of pediatric VADs design and research.

Suitable devices for different age groups

Lack of suitable devices designed to address the unique anatomic and physiologic needs of children in different age groups remains the biggest obstacle. The development of pediatric VADs lags behind that of adults due to both technological limitations and economic unsustainability. As a result, many larger children are implanted with adult devices. Using adult-sized devices in children ("off-label" or "off-design" application) results in patient-device size mismatches, creative implantation strategies, and blood flow beyond the range recommended [35]. Adapting adult VADs for children has the risk of unexpected complications. Indeed, worse patient outcomes compared to adult patients have been observed. A multicenter registry analysis showed promising outcomes in a cohort of pediatric and younger adult patients undergoing implantation of HeartMate III [23], but only 57% of these patients were discharged. While in adult patients supported by HeartMate III, the discharge rate could reach 94.2% [36], showing an obvious gap between the two populations. Similarly, in another study, the rate of discharge for HVAD was 80% in young adults and only 48% in children [31]. Numeric simulations and in vitro measurements indicate that in the pediatric condition, HVAD washout of old blood is 2 times slower and the residence time of blood within the pump is twofold prolonged compared with a typical adult case [37], which are potentially unfavorable mechanisms in terms of blood trauma and thrombogenicity. Thus, adapting adult VADs for larger children could be a temporal solution in this era, but devices specially designed for them are expected.

As to smaller children supported by VADs, the outcome is even worse and with more limited options. When we look at survival by age group, the youngest patients have the lowest overall survival [5]. Factors associated with the lowest survival are frequently observed together (infants, Pedimacs patient profile level 1, paracorporeal continuous VADs, and congenital heart disease) [12]. In these cases, implantable devices are barely possible to be applied due to the body size. Challenges such as a complex anatomy, a more invasive procedure for implantation and risks related to mechanical valves make the durable PF VAD support less ideal. On the one hand, innovations of PF VADs, such as a valveless design (Fig. 2), could be beneficial to them in the future; on the other hand, short term paracorporeal CF VADs has currently become a very important option. Although the devices were designed for short-term support, a prolonged duration is proven to be feasible. The median duration varies between 6 to 20 days [38–42] with a longest duration of 227 days [41] reported in different studies. A study shows that 71% of patients had positive primary end point [41], which is acceptable considering the patient profile, but still far from optimal. The safety duration of temporary devices should be reevaluated with more clinical evidence collected, and the development of extracorporeal PF and CF devices with suitable range of output is also crucial for small children.

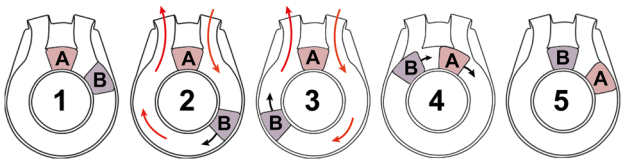

Fig. 2 Mechanism of TORVAD pulsatile pump. "A" and "B" are two pistons that cyclically move around a toroidal pumping chamber via magnetic coupling to a motor. Black arrows indicate the movement of pistons, and red arrows represent blood flow generated. By cyclically actuating one piston around a toroidal pumping chamber via magnetic coupling to a motor, TORVAD could generate a pulsatile blood flow without an area of stasis

In conclusion, there are challenges and an urgent need for suitable devices for each age groups. Devices specifically designed for children should be further developed, and the full potential of VAD therapy for children has yet to be realized.

Non-blood-contacting devices

The development of non-blood-contacting devices is a very attractive research direction. Reduction or even elimination of direct contact between the blood flow and the device could theoretically avoid the use of anticoagulation agents and could reduce complications such as gastrointestinal bleeding, neurologic injury and device-related thrombosis. Non-blood-contacting devices directly compress the heart using artificial muscle or pressurized cups that either cover the entire epicardial surface or target just one of the diseased ventricles. Several non-blood-contacting devices have been tested in animals [43]. For example, a "soft robotic sleeve" could use compressed air to power artificial silicone muscles [44]. By being selectively activated to compress and twist, the silicon muscles mimic the movements of the normal human heart (Fig. 3). However, complications related to local mechanical lesions, such as bleeding, ecchymosis and adhesions, should not be ignored, and the outcome and stability require further research.

Wireless power system for implantable VAD

A wireless power system could greatly reduce percutaneous site infections (PSIs), especially in pediatric patients supported by implantable devices. All current VADs are either paracorporeal/intravenous devices that have catheters inserted across the skin barrier to transfuse blood or implantable devices with a percutaneous drive line to power the VAD, which are associated with PSIs. It has

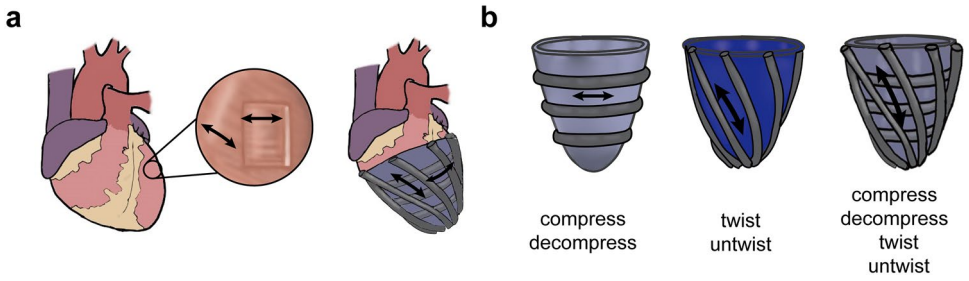

Fig. 3 The structure of a bioinspired nonblood-contacting VAD with "soft robotic sleeves". **a** The design is inspired by the muscle fiber orientations of the outer two layers of the myocardium. **b** Individual active layers composed of fluidic actuator contractile elements could perform compression and decompression or twisting and untwisting, or could simultaneously perform both actions to provide proper support

been reported that at 1 year after implantation, nearly 19% of adult CF left ventricular assist device (LVAD) recipients develop a PSI [45]. Younger age may be a predictor of a higher incidence of PSIs, and being more physically active is suspected to be an important reason [45]. With less control of their actions, pediatric patients could more likely disrupt the integrity of the driveline–integument barrier, and the self-nursing of percutaneous sites may not be well performed unless there is intense assistance and supervision from adults. As a result, the elimination of the driveline of implantable devices is feasible and very advantageous for pediatric patients.

Previous transcutaneous energy transfer systems have been limited by restrictions on the separation distance and alignment between the transmit and receive coils [46], and there are some breakthroughs. For example, a coplanar energy transfer system characterized by coil-within-the-coil topology could ensure high and robust resonance energy powering. It has been tested in animal trials for up to 6 months, and the first two applications in human use were reported in 2019 (both supported for more than 30 days) [47]. The free-range resonant electrical energy delivery (FREE-D) system allows power delivery at larger distances without compromising safety and efficiency [48]. The wireless powering system may offer a new perspective on quality of life (QoL), a decrease in the caregiver burden, and the elimination of driveline infection for patients supported by implanted devices [49].

In addition, better anticoagulation surface materials, better anticoagulation management protocols [50] (to consist with developmental hemostasis [14]), a larger range of support, miniaturization and better mobility are all directions worth working on. Here we reviewed published materials on pediatric VADs under development (Table 3) mostly focusing on blood pump innovation. Other than basic information, their unique innovations of design are also provided. We look forward to encouraging outcomes in future investigations to provide better choices for children.

Future directions of pediatric VADs implementation exploration

Exploration of PF generated by CF pumps for children

PF devices are currently less preferred when CF pumps are optional, but the pulsatility of blood flow does have positive effects on patients. It has been proved in both pediatric and adult population that patients with PF devices had a far worse outcome compared to CF devices [9, 12], there has been a clear trend of transition in device type in the adult population over time, and PF devices are almost abandoned for long-term support. Of all durable VADs implanted in adult patients in the last decade, only 0.4% have been driven by PF pumps [51]. While as to pediatric patients, PF VADs are implanted in more cases, accounting for approximately 27.6% of all pediatric VADs implanted in North America and for 52.9% in Europe [11, 12], and this could be explained by the difficulty of device implantation into children, different preferences for treatment strategies and the lack of suitable CF devices for smaller and younger children. PF pumps seem to be applied only in unavoidable circumstances. However, it is mainly because of how the pumps work, instead of the pulsatility of blood flow. It is undeniable that PF has many advantages over CF, including reduced incidence of aortic valve complications [52], gastrointestinal bleeding [53, 54], ventricular suction and pulmonary congestion [6]; and improved volume unloading [55] and bridge to recovery outcomes [56].

Thus, combining the safety of the CF pump and the hemocompatibility of PF could be beneficial, but it should be prudently applied. Other than the pulsatility generated by the intrinsic cardiac cycle, a PF can also be actively generated with CF pumps by periodically adjusting the pump speed. A few attempts have been made in adult population. The Lavare cycle [57] is a periodic speed modulation designed for better washout of the pump. It significantly reduced the

Table 3 Pediatric VADs under development

	Blood flow (L/min)	Body surface area (BSA, m^2) or body weight (kg)	Duration of support	Device type	Technological innovations
Infant Jarvik 2015 [105]	0.5–3	0.4–1.0 m^2	<180 days	Implantable CF VAD	/
PediaFlow VAD [106]	0.5–1.5	3–15 kg	<60 days	Implantable CF VAD	Small in size (as large as an AA battery), minimal hemolysis in both in vitro and in vivo assessment
Penn State Infant VAD [107–111]	0–1.6	<0.5 m^2	Not mentioned	Paracorporeal PF VAD	Automatically controlled beat rate in response to preload pressure; high inflow velocity for effective washing, with low blood trauma levels and minimal device thrombi
TORVAD pump [112–115]	0–4	0.6–1.5 m^2	Not mentioned	Paracorporeal PF VAD	Valveless, dual-piston pulsatile pump with less shear stress and blood trauma, and without area of stasis; synchronous pulse or synchronous counterpulse; longer wear life
Drexel Dragon VAD [116]	1–5	>0.7 m^2	Not mentioned	Paracorporeal/intracorporeal CF VAD	Integration of an axial and a centrifugal blood pump in series, optional mode of working (one pump or two pumps) for wider range of output
Deltastream DP3 [117–121]	0–8	Neonates to adults (no specific range given)	<7 days	Paracorporeal CF (diagonal) VAD	Optional pulsatile flow mode (CF or PF); zero-flow mode to prevent backflow
i-Cor VAD[122, 123]	0.2–1.8	Neonates to pediatric patients (no specific range given)	Short-term (no specific range given)	Paracorporeal CF (diagonal) VAD	Optional pulsatile flow mode (CF or PF)
Sputnik Pediatric Rotary Blood Pump (PRBP) [124, 125]	1–5 (optimal 3–5)	12–40 kg	Not mentioned	Implantable CF VAD	/
NIPRO VAD (M size) [126, 127]	2–4	0.6–0.8 m^2	Short- or mid-term (no specific range given)	Paracorporeal PF VAD	/
Inspired Therapeutics NeoMate (V3) [128–130]	0.5–3.5	<40 kg	<30 days	Paracorporeal CF VAD	A family of interchangeable, single-use pumps for wider range of output
NeoVAD [131]	0.5–2	5–20 kg	Long-term (no specific range given)	Implantable CF VAD	/

The key metrics extracted from published materials. Technological innovations emphasize breakthroughs in mechanical design or control systems compared to widely applied devices

rates of stroke, sepsis and right heart failure, with no difference in the transplant or recovery rates [57]. Similarly, by periodically changing the pump speed, the HeartMate III system could generate an artificial pulse every 2 s [58]. By evaluating middle cerebral artery flow dynamics, it was found that the pulsatility and improved hemocompatibility of HeartMate III may improve cerebrovascular metabolic reactivity compared with HeartMate II, which matches the decreased rate of stroke and better clinical outcomes [59]. A computational fluid dynamic simulation showed that the artificial pulse contributes to the removal of blood components from pump surfaces [58]. These evidences show potential in pediatric patients' outcomes, especially for those supported by CF pumps. Despite all the advantages, similar "artificial pulse" applications in pediatric patients should be highly cautiously reviewed. It is currently not well understood how pediatric patients tolerate mechanical support in either pulsatile or continuous-flow scenarios [60]. It has been observed that artificial pulses increase turbulence and total stresses, whose biological effects are not known in detail but might contribute to clinically observed issues related to hemocompatibility [58]. In addition, if introduced into pediatric application, the range of pump speed change for generating PF should be carefully titrated and dynamically adjusted for each patient, as a very high speed may lead to suction events and arrhythmias [25]. In conclusion, attempts to adjust the currently available CF devices to mimic PF could be beneficial and are worth exploring for children; and to avoid collateral harm, both the biological and clinical implications of the technique remain to be resolved.

From salvage therapy to standard routine

Due to lack of experience and fear of device-related complications, pediatric VADs were mainly used as an approach to rescue patients with critical conditions. In the Pedimacs cohort, 87.1% of patients had INTERMACS profile 1 (critical cardiogenic shock) or 2 (progressive decline) at VAD implantation, which is more advanced than the 50.9% in the adult population [12, 51]. As improvements in technology and medical care continue to reduce the risk of morbidity associated with VAD support, strategies regarding candidacy and timing for device implantation should also evolve. Outcomes are worse when patients have developed cardiogenic shock with significant end-organ dysfunction prior to implantation [5, 61]. A more proactive device placement strategy could stop and even reverse the worsening general condition, and mechanical unloading has many positive effects on preservation and recovery of cardiac function [62]. Thus, VAD should gradually shift to a component of standard pediatric HF therapy, rather than primarily as a means of hemodynamic support [63], and proactive implantation may promote the process of recovery.

Better choice of duration VAD "bridge"

A recent analysis showed that more than 1200 children have been bridged to heart transplant in the last 15 years with MCS, including VADs and total artificial hearts [64]. For pediatric patients, there is yet no consensus reached regarding the duration of "bridge", and how to make full use of both VAD support and heart transplantation to optimize patient survival is worth discussing.

Heart transplantation seems to be carried out more radically in pediatric patients. At 6 months after VAD implantation, more than half of pediatric patients in North America were reported to receive a heart transplant [65], as did 33% of patients in Europe [66]. Meanwhile, for adult patients, only 7.3% of them received a heart transplant, and 76.6% survived on support at 1 year post-implantation [51]. Possible reasons are that the proportion of qualified receivers in children is higher, and the mindset of pediatric physicians overemphasizes the benefit of minimizing the support duration [67], which results in anticipative transplantation. Once such support commences, medical teams seem to be in a race against the "complication clock," and they try to shorten the bridge to transplantation.

However, some experts propose that being in a rush to eliminate VAD support may not be beneficial. This "bridge" of the VAD here plays an important role, more than just helping the patients to live long enough for a suitable donor graft. Prolonged BTT support duration leads to stabilization and rehabilitation of the patient prior to transplantation, with improved end-organ function, decreased inotrope and ventilator dependence, and improved nutritional and functional status [4], which can all improve patients' pretransplant conditions and candidacy for heart transplantation. Moreover, this can also provide an opportunity for myocardial recovery [65] and, in certain cases, free them from having a heart transplant [68, 69]. Additionally, transplantation that is performed too soon has potential risks, such as graft failure and a missed opportunity for recovery [70]. Keeping both VAD-related complications and risks of early heart transplantation in mind, the optimal balance between these two competing risks determines the optimal timing of explantation. A study concerning 1064 children who underwent VAD implantation prior to a heart transplant indicated that a longer duration (within 30 days versus $\geq$ 30 days) of VAD support prior to heart transplantation is associated with a one-year survival benefit in children [71]. A multicenter review of pediatric VAD support analyzing the association between the duration of support and posttransplant survival identified a potentially optimal duration of VAD support: 2–4 months in patients supported with a paracorporeal pulsatile VAD and any time after 3 weeks in patients supported with an intracorporeal continuous VAD [72]. Texas Children's Hospital has adopted a 3-month waiting period after CF VAD implantation [65]. These patients are inactivated on

the transplant waitlist after implantation to allow sufficient time for systemic recovery, which has shown promising survival, cardiac recovery and QoL improvements. In conclusion, a prolonged "bridging period" is likely to be beneficial, but the optimal timing is yet to be determined.

Further improvement in physical activity performance after VAD implantation

Patients on LVAD support demonstrate improved physical activity and QoL, but well below that of healthy people [73]. Low physical activity levels are associated with increased risk factors for cardiometabolic diseases, impairments in cognitive function and lower academic achievement for children [74], and such activity deficits also affect muscular strength, patient-reported health outcomes [75], functional capacity, social interactions and mental health [76]. Thus, generalized treatment, rehabilitation and exercise prescriptions should timely step in. To coordinate this process, finely adjusted VAD output is needed for proper support.

Upmodulation of pump speed within a limited range during exercise is worth exploring but yet debatable. In the healthy population, cardiac output increases threefold to fivefold to meet the demands of exercising [77]. Under VAD support, the pump speed, delta P (pressure difference between systemic arterial blood pressure and left ventricular end diastolic pressure) and native heart contractility determine the actual total cardiac output (CO) [78]. Since mechanical pumps have approximately half the sensitivity of the natural heart to preload and three times greater sensitivity to afterload [78], when exercise is completed at the baseline pump speed of CF LVAD, an increase in total output can be observed but is not sufficient to maintain low filling pressures. Thus, increasing total CO during body exercise by increasing the pump speed within a limited range may provide better support. Several studies have shown positive effects of upmodulation of pump speed on CO and on tolerance of body exercise [77, 79, 80], including both adult and pediatric cohorts. In contrast, some studies indicate that the high-speed setting does not improve exercise tolerance [81, 82]. Given the limited patient volume, the variety of patients and pumps involved, and the heterogeneity of modulation and exercise protocols of these studies, the conclusion is still controversial and needs to be discussed separately. Additionally, the exercise physiology needs to be further elucidated in VAD patients, and smarter and automatically adjusting device algorithms are expected.

Balancing interagency and international development

The accessibility of proper medical care, convenience and cost of follow-up largely depend on the distribution of qualified centers. It is clearly seen that pediatric VADs are not yet widely applied even in developed countries and regions, and there is an obvious interagency imbalance. For example, only 13 large-volume hospitals (defined by > 30 patients reported) out of 47 hospitals carry out 63% of pediatric VAD implantations in North America [12], and the situation is quite similar in Europe [11]. From an international perspective, fewer centers and cases are reported in other countries and regions, and the gap is much wider. Taking China as an example, a nation-wide survey indicates that by June 2017, the total case number of pediatric VAD implantation in mainland China was 39 [83]. The first application of implantable LVADs in pediatric patients was carried out in 2022 at Fuwai Hospital using Corheart 6 (full magnetic levitated LVAD designed and fabricated by a local company) [84]. Thus, pediatric VAD support is far from widely applied. Although the superiority of VAD support over extracorporeal membrane oxygenation (ECMO) is widely observed [85, 86], ECMO is still the most attainable option of MCS in most cases. The imbalanced interagency and international development of pediatric VAD largely restricts the accessibility of medical care and overall survival of patients, and the road ahead will be long.

Conclusion

VAD support plays an important role in the management of end-stage HF. Great accomplishments have been made in recent decades, but VAD application to pediatric patients very much lags behind that in adult patients in many aspects, and there are still many unsettled questions to be answered. To overcome these challenges, more registries enrolling a larger number of pediatric patients should be established to provide comparative data and to guide clinical decisions. Regarding the technological development of pediatric VADs, forward-thinking design solutions are needed. We believe that VAD will better serve pediatric HF patients in the future.

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Declarations

Competing interests The authors declare no competing interests.

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