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Original Research

Feasibility, Safety, and Efficacy of the Atrial Flow Regulator in Pediatric Patients: A Single-Center Experience

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ABSTRACT

Background: The Atrial Flow Regulator (AFR; Occlutech) can be used to create interatrial communication with a predetermined diameter in various pathophysiological settings. In the pediatric population, the experience is limited to a few case reports. We aim to report the initial single-center experience of AFR implantation in children with congenital and acquired heart disease.

Methods: From December 2021 to June 2023, we enrolled 10 patients (aged 6 months-16 years). Indications to treatment were: left ventricular systolic dysfunction (n = 6), restrictive cardiomyopathy with pulmonary hypertension (n = 2), postoperative right ventricle dysfunction after surgical repair of a native Tetralogy of Fallot in a 12-year-old child (n = 1), and failure Fontan (n = 1). AFR implantation was successfully performed in all patients. Transseptal puncture was needed in 8 cases; in the other 2 cases, preexisting patent foramen ovale and fenestrated atrial septal defect were used. Balloon predilation was performed in 9 cases. An 8 mm device was implanted in all cases. The mean time of the procedure was 50 minutes, the median fluoroscopy time was 17 minutes, and median radiation exposure dose was 2.3 Gy × cm^2.

Results: No complications were reported during the procedure. Three patients died during the follow-up: 1 due to sepsis (16 days after the procedure), 1 due to disease progression (8 months after), and 1 due to failure of ECMO decannulation 7 days after the atrial venting. In the remaining patients, a reduction of LA dilation, postcapillary pulmonary hypertension, and heart failure symptoms were observed.

Conclusions: AFR is safe and feasible in children and critical settings, allowing right/left cavities unloading and improvement of hemodynamics and symptoms.

Introduction

The Atrial Flow Regulator (AFR, Occlutech) is a small, self-expanding, nitinol, implantable device (Central Illustration). It is similar to a self-centering interatrial defect occluder device, consisting of two 21- or 23-mm discs connected with an 8- to 10-mm hole at the center of the prosthesis. The device can be implanted through a transvenous approach into an existing atrial septal defect (ASD) or a patent foramen ovale (PFO), or after transseptal puncture and predilatation with a 6- to 10-mm balloon catheter. The goal of this therapy is to maintain stable and predetermined interatrial communication to reduce the left atrial pressure (in left heart diseases) or to unload the pulmonary blood flow to increase the cardiac output (in pulmonary hypertension and right heart diseases).

The effectiveness of AFR in adult patients with heart failure (HF) has been evaluated in 2 large, ongoing clinical studies (PRELIEVE and PROLONGER),[1,2] a prospective registry (AFteR Follow-up Study to Monitor the Efficacy and Safety of Occlutech AFR in HF Patients),[3] and a clinical trial in patients with pulmonary arterial hypertension (PROPHET Pilot Study to Assess Safety and Efficacy of a Novel Atrial Flow Regulator in Patients With Pulmonary Hypertension).[4] The prospective, nonrandomized, multicenter, phase 2 study PRELIEVE reported the first human use of AFR in adult patients with HF and preserved ejection fraction (EF) (HFpEF) (EF > 40%; n = 24) or reduced ejection fraction (HFrEF) (EF 15%-39%; n = 29). The resting pulmonary capillary wedge pressure decreased by 5 mm Hg at 3 months after AFR implantation. No complications occurred, particularly no shunt occlusion, stroke, or right HF during the 1-year follow-up period, with clinical improvements in some patients.[5]

Abbreviations: ASD, atrial septal defect; ECMO, extracorporeal membrane oxygenation; EF, ejection fraction; ICU, intensive care unit; LA, left atrium; PFO, patent foramen ovale; RV, right ventricle; TEE, transesophageal echocardiogram.

Keywords: atrial flow regulator; cardiomyopathy; device; end-stage treatment of heart failure; heart failure.

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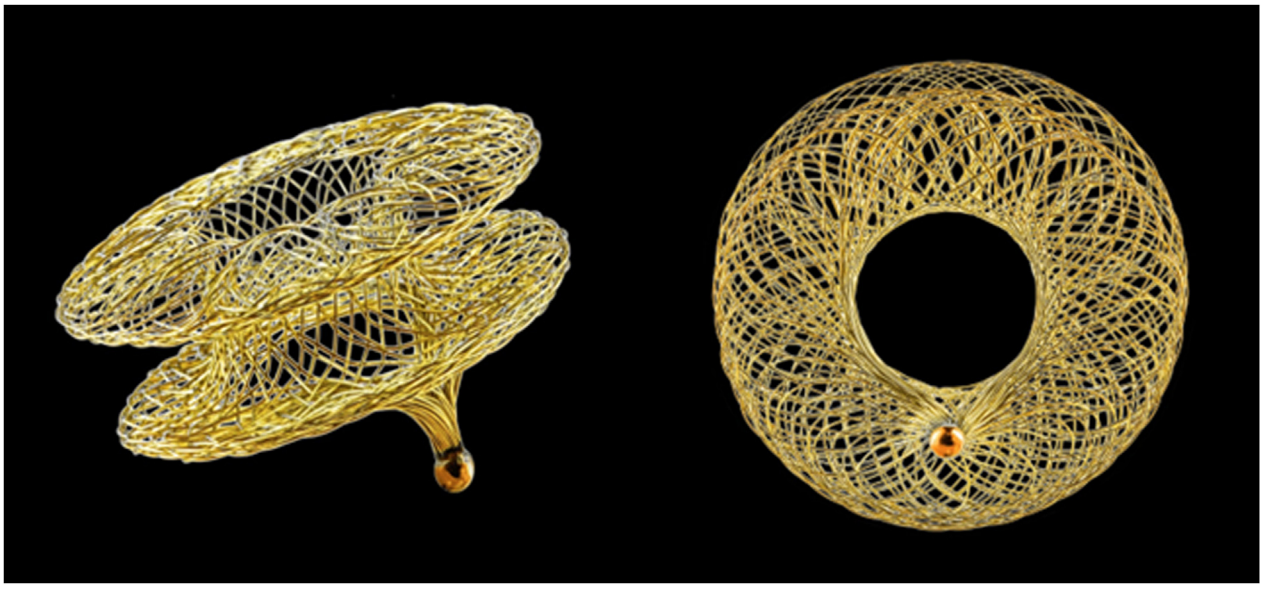

Central Illustration.
Atrial Flow Regulator device.

In the pediatric population, several case reports have described the safety and feasibility of the procedure in patients with pulmonary hypertension,[6] failing Fontan circulation,[7] and infants.[8] In a recent multicenter experience in the United States, the AFR device was implanted in 6 pediatric patients, 5 of whom had Fontan circulation HF and 1 with left ventricular dysfunction. All patients survived without complications. Oxygen saturation increased in all Fontan patients and was maintained up to the 8-week follow-up, and the NYHA (New York Heart Association) class improved as well.[9] Currently, AFR in the pediatric population has been more frequently used in patients with pulmonary hypertension or Fontan circulation with high pressures in the pulmonary circuit, and less commonly for HF, compared with adults. However, a recent case series of 3 patients (aged 6-13 years) with restrictive cardiomyopathy underwent AFR implantation with the goal of reducing left atrial volume overload and postcapillary pulmonary hypertension. The procedure reduced left atrial dilation, postcapillary pulmonary hypertension, and HF symptoms in all 3 patients.[10]

The aim of the study is to monitor the safety profile and effectiveness of AFR device implantation in the pediatric population with HF secondary to cardiomyopathies or congenital heart diseases.

Methods

This study is a retrospective study conducted at the pediatric cardiology department of the Padua University Hospital.

Safety was monitored by tracking the number of adverse events and complications, while efficacy was assessed through survival rates, hospitalizations, and echocardiographic parameters. AFR implantation was offered to pediatric patients suffering from HF secondary to cardiomyopathy or other congenital or acquired heart diseases. These patients remained symptomatic despite optimal medical therapy and required frequent hospitalizations or were unable to transfer out of intensive care.

The decision to implant AFR was made collectively by a multidisciplinary team consisting of pediatric cardiologists, interventional cardiologists, and cardiothoracic surgeons from our institution. Before each implantation, the supplying company required the submission of a patient form, through which they conducted an internal assessment of procedure appropriateness. All the implants were performed by a skilled interventional cardiology team after written consent from the parents. The study protocol was submitted to the local ethics committee.

Clinical, echocardiographic, and procedural data

Upon admission to the hospital, patients underwent a cardiac evaluation, including electrocardiogram, transthoracic echocardiogram, and comprehensive blood tests (blood cell count, renal and hepatic function, electrolytes, and cardiac enzymes). Follow-up transthoracic echocardiogram was performed in all the patients 24 to 48 hours after AFR implantation and subsequently as per clinical needs. From discharge, patients were followed by their regular cardiologist according to their institutional protocols. The NYHA classification or Ross classification was used to assess the functional status of the patients before and after the procedure, depending on the patient's age. Furthermore, clinical, echocardiographic, and procedural data were collected, including technical details, intervention duration, type of device, complications, pharmacologic therapies, and duration of stay in the intensive care unit (ICU) and blood sample tests. For the patients under inotropic therapy before AFR implantation, we calculated the inotropic score, proposed by Gaies et al[11] at baseline, 24 hours, and 7 days after the procedure.

Description of the procedure

All transcatheter interventions were performed in the cardiac catheterization laboratory under general anesthesia, with the assistance of transesophageal echocardiography (TEE). After obtaining femoral venous access, 100 IU/kg of heparin was administered. In all the cases, prophylactic intravenous antibiotics were given. In the absence of preexisting atrial communication, access to the left atrium was obtained through a transseptal puncture.

Prior to AFR implantation, each patient underwent a comprehensive hemodynamic study to obtain all necessary measurements for calculating cardiac output, pulmonary vascular resistance, and assessing cardiac function.

Table 1. Summary of clinical features of the patients enrolled.

	Cardiac anatomy	Indication for AFR implantation	NYHA class	Comorbidities	Type of procedure	Outcome
Patient 1	CHD, TOF	Diastolic dysfunction, high filling pressure	IV	Pleural effusion, active TB	Rescue	Follow-up, 22 mo
Patient 2	DCM	Left heart failure, weaning ECMO	IV	ECMO support	Rescue	Death after 16 d due to sepsis
Patient 3	DCM	Left heart failure	IV	None	Rescue	Follow-up, 15 mo
Patient 4	RCM	Diastolic dysfunction, high filling pressure, high PVR	III	None	Elective	Death after 8 mo due to refractory heart failure
Patient 5	DCM	Left heart failure	IV	None	Rescue	VAD implantation after 7 d, transplant after 9 mo
Patient 6	DCM	Left heart failure	III	None	Elective	Follow-up, 9 mo
Patient 7	DCM in muscular dystrophy (Emery-Dreifuss)	Left heart failure	IV	ECMO support	Rescue	Death after 7 d due to multiorgan failure
Patient 8	DCM	Left heart failure	III	None	Elective	Follow-up, 4 mo
Patient 9	RCM	Diastolic dysfunction, high filling pressure	III	Metabolic disease	Elective	Follow-up, 3 mo
Patient 10	TGA with hypoplastic right ventricle, s/p Fontan	High pressure in Fontan circuit	II	Fontan failure, Budd–Chiary like syndrome	Elective	Follow-up, 2 mo

AFR, Atrial Flow Regulator; CHD, congenital heart disease; DCM, dilated cardiomyopathy; ECMO, extracorporeal membrane oxygenation; RCM, restrictive cardiomyopathy; TB, tuberculosis; TGA, transposition of great arteries; TOF, tetralogy of Fallot; VAD, ventricular assist device.

In all cases, predilation of the interatrial septum was performed by using a compliant balloon catheter with a diameter between 6 and 10 mm. A single balloon was used in all the procedures. The balloon size was chosen 2 mm larger than the final desired defect size. In all the cases, an 8 mm device was implanted because smaller sizes were not available in Europe (the CE mark was obtained for 8-mm and 10-mm devices only). After creating an atrial defect, a long 12F delivery sheath was introduced over a stiff guide wire positioned in the left superior pulmonary vein. Once the sheath was advanced into the left atrium, the left atrial disc was pushed out of the sheath, shaped, and then retracted to adhere to the left side of the septum. With slight tension, the right disc was opened. After confirming the proper positioning and efficacy of the prosthesis using TEE, the device was released by removing the delivery cable. The size of the fenestration device was chosen based on the patient's weight, left atrial pressure, interatrial pressure gradient, and underlying pathophysiology. Following device implantation, the patency and presence of the shunt were confirmed by TEE and hemodynamic measurements. Antiplatelet therapy (aspirin 5 mg/kg or 100 mg) was administered to all the patients for at least 6 months after the procedure; unfractionated heparin infusion (10-20 IU/kg/h) was administrated for the first 24 to 48 hours after the procedure.

Statistical analysis

Statistical analysis was performed using SPSS version 27.0 (IBM). Categorical variables are presented as absolute numbers and percentages. Continuous data are reported as median (interquartile range). The normal distribution of the variables was verified by the Kolmogorov-Smirnov test. Comparison between groups was made by the *t* test for unpaired data. Comparison between different follow-up phases was performed by using the Wilcoxon test. Correlation between continuous data was performed with the Spearman test. The comparison between 3 or more groups of variables was performed by ANOVA analysis and post hoc Bonferroni Test or by Kruskall-Wallis test, when appropriate. A null hypothesis was rejected for $P < .05$.

Table 2. Procedural data.

Age at procedure, y	10.9 (0.5-16)
Weight at procedure, kg	27.5 (20-56)
Right atrial pressure, mm Hg	8 (7-10)
Left atrial pressure, mm Hg	20 (15-23)
Pulmonary artery pressure, mm Hg	39 (20-41)
Gradient across Atrial Flow Regulator at the end of the procedure, mm Hg	5.5 (4.5-7)

The values are median (IQR).

Results

Demographic characteristics

From December 2021 to July 2023, a total of 10 patients were enrolled. The demographic and clinical characteristics are listed in Tables 1 and 2. Median age was 10.9 years (IQR, 0.5-16; range, 6 months-18 years), median weight was 27.5 kg (IQR, 20-56; range, 6.3-67 kg). In terms of anatomy, 2 patients had congenital heart disease (patient 1, surgically corrected Tetralogy of Fallot; and patient 10, Fontan palliation in univentricular heart) and 8 patients had primary cardiomyopathy (6 with dilated cardiomyopathy and 2 with restrictive cardiomyopathy). The indications for AFR implantation were: severe left HF in 6 patients, pulmonary hypertension secondary to restrictive cardiomyopathy in 2 patients, postoperative right ventricular dysfunction in late correction of Tetralogy of Fallot in 1, Fontan failure associated with liver disease (Budd–Chiari-like syndrome) in 1.

Procedural data

The median procedure duration was 50 minutes (IQR, 34-65), and the median radiation exposure was 2.3 Gy $\times$ cm^2 (IQR, 1.8-4.3; range, 0-7.1 Gy $\times$ cm^2). All the procedures were performed under general anesthesia and transesophageal monitoring. Femoral venous access was used in 9 patients (90%), while 1 patient (#3) underwent a hybrid peratrial approach in the operating room during a hybrid procedure that also included pulmonary artery banding.[12] Heparin was administered at the beginning of the procedure to all patients, with a dose between 50 to 100 IU/kg. The largest introducer sheath used was 12F. Access to the left atrium was obtained through transseptal puncture in 8 patients (80%), and in 2 patients the device was placed through a preexisting communication (PFO and postsurgical ASD). The preexisting or new interatrial communication was dilated with a balloon catheter before AFR implantation in 9 patients. An 8-mm AFR device was used in all the patients. No periprocedural complications were reported, and there were no acute or subacute shunt occlusions.

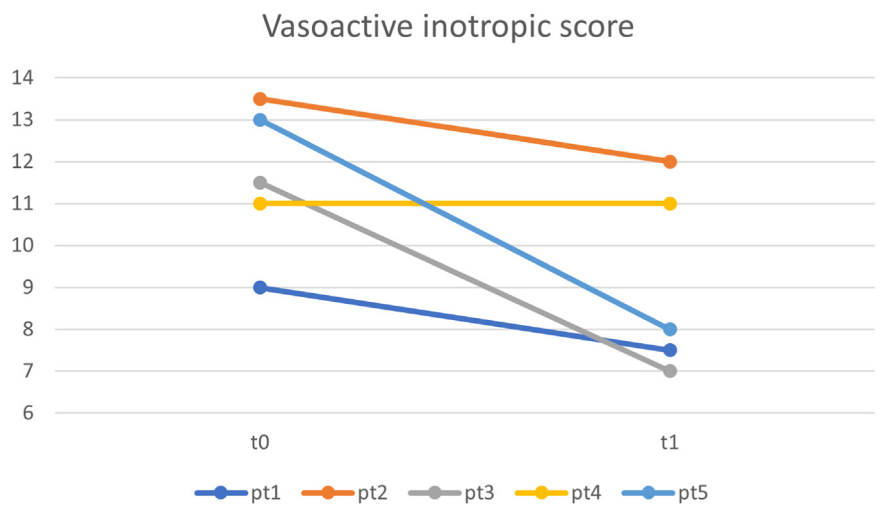

Figure 1.
Vasoactive-inotropic score before and 24 hours post Atrial Flow Regulator implantation ($P = .046$).

Postprocedure data

AFR implantation in acute/ICU settings. Five patients underwent AFR implantation as a rescue procedure due to critical conditions. The patients were in the ICU and were unable to wean from inotropes. In all these patients, the procedure was successfully completed without complications. The median length of hospital stay was 7 days (IQR 3-22). Two in-hospital deaths occurred: 1 patient died due to sepsis 16 days after the procedure (#2), and 1 patient was unable to wean off ECMO (#7). One subject with Emery-Dreifuss muscular dystrophy was not a candidate for heart transplantation or a left ventricular assist device. One patient with acute severe dilated cardiomyopathy, high ventricular filling pressures, and secondary pulmonary hypertension achieved a reduction in end-diastolic pressures and normalization of pulmonary pressures after AFR implantation (#5). This patient was then able to continue the therapeutic process with the implantation of a ventricular assist device and subsequent heart transplantation during the same hospitalization. Two patients were weaned from inotropes and discharged home (#1 and #3). Currently, both are in good condition 22 months and 15 months after the procedure.

A subgroup analysis of patients admitted to the ICU who required inotropic therapy was performed, demonstrating that the vasoactive-inotropic score[11] at 24 hours and 7 days after AFR implantation significantly decreased ($P = .046$) (Figure 1).

AFR implantation in chronic HF in cardiomyopathies

Four patients underwent AFR implantation as an elective procedure for left or biventricular failure in cardiomyopathy. In all these patients, the procedure was successfully completed. The hospitalization length was 3 days for all patients. In the follow-up, 1 patient died 8 months after the procedure due to disease progression in restrictive cardiomyopathy with worsening biventricular dysfunction and severe pulmonary hypertension (#4). Echocardiographic data in this subgroup of patients showed that there was a statistically significant improvement in EF at 7 days ($P = .04$) and 30 days ($P = .02$) following AFR implantation (Figure 2). The size of the left atrium significantly decreased after AFR device implantation ($P = .04$). Right ventricular pressures decreased in the 2 patients with biventricular and primarily right ventricular dysfunction. All the devices were found to be patent on subsequent echocardiographic follow-ups, with a mean gradient of 6 mm Hg.

In 1 patient, the indication for AFR implantation was a failing Fontan circulation with high pressure in the conduit and signs of severe hepatic cirrhosis (#10). In this patient, a Cheatham-Platinium stent was previously implanted into the extracardiac conduit in another hospital. We found the

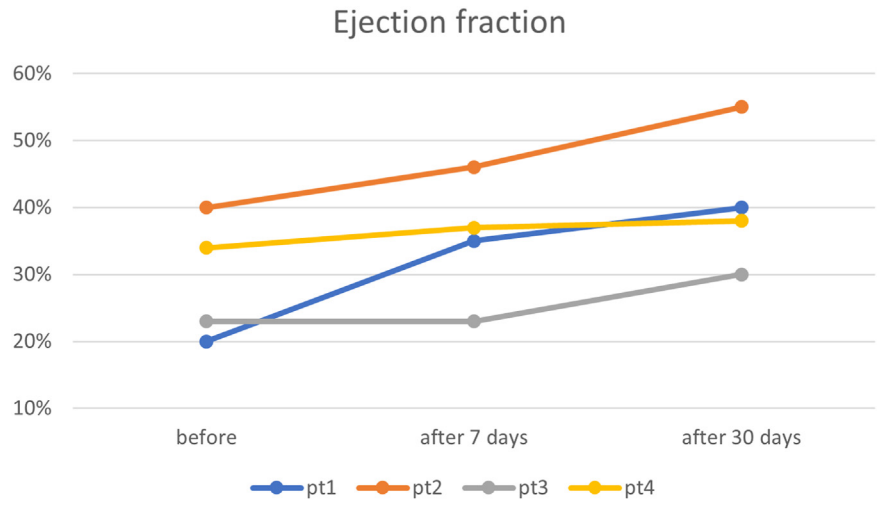

Figure 2.
Ejection fraction before, at 7 days, and 30 days after Atrial Flow Regulator implantation.

Table 3. Major indications for Atrial Flow Regulator implantation.

	Diameter	Durability	Size control	Need to cross	Protrusion matters	Reclosure probability	Thick/Stiff septum
Complex CHD	>12 mm	Long	Low	Yes	Low	No	+/–
PAH	5-8 mm	Long	High	Yes	Mid	Low	+
Acute HF	6-10 mm	Short	Low	No	Mid	Mid	–
Venting ECMO	10-12 mm	Very short	Low	No	High	High	++/–
Chronic HF	5-8 mm	Long	High	Yes	Mid	Low	++
Fontan fen	4-5 mm	Very long	Very high	No	Very high	Very low	+++

CHD, congenital heart disease; ECMO, extracorporeal membrane oxygenation; HF, heart failure; PAH, pulmonary artery hypertension.

stent underexpanded compared to the conduit size and was further dilated with a 22-mm Atlas Gold balloon (Bard). Despite the larger conduit caliber, the pressure in the Fontan track remained high. Thus, the AFR device was used to create a fenestration between the extracardiac conduit and the right atrium. We used the transseptal needle to create a communication between the conduit and functionally left atrium just below the caudal strut of the stent. The procedure was easier than expected because the further expanded stent resulted in foreshortening and exposed softer tissue for the transseptal procedure. Once the left atrium was entered, the fenestration was dilated with a 6 mm Sterling balloon. Finally, an 8-mm AFR device was implanted. The patient was discharged 2 days after the procedure without complications. He continued oral anticoagulant therapy with warfarin.

Discussion

The AFR is a new device designed to create stable interatrial communication with a predetermined diameter. The goal is to reduce left ventricular filling pressures and improve the quality of life by alleviating symptoms. Several studies in adult patients have demonstrated the safety of AFR device implantation in the advanced HF[1–3,5]; however, the criteria to better identify the clinical "super-responders" to this therapy are still unclear.[13]

Currently, the fields of application of this device can be summarized into 5 clusters (Table 3):

1. Advanced left HF due to reduced left ventricular EF. The AFR device promotes the unloading of the left chambers by creating a left-to-right shunt, relieving pulmonary congestion, improving subendocardial perfusion, and reducing oxygen consumption.[14,15]
2. Cardiomyopathies with preserved EF (restrictive cardiomyopathies and HFpEF or diastolic HF). In these conditions, the interatrial communication leads to left atrial unloading and subsequent reduction of pulmonary hypertension. In addition, the device helps to preserve cardiac output in case of a sudden pulmonary hypertensive crisis or acute right ventricular dysfunction by maintaining a stable cardiac output through a transient right-to-left shunt.[10]
3. Severe pulmonary hypertension. In end-stage settings, the creation of an ASD might preserve the cardiac output, improve the quality of life, and reduce the risk of stress-induced syncope.[16]
4. Fontan failure. In the context of Fontan circulation, the AFR has been used to create or calibrate a fenestration in the Fontan circuit. The creation of a right-to-left shunt at the Fontan conduit level allows for a reduction in pressures within the Fontan circuit at the expense of systemic desaturation.[17,18] In addition, some authors have used the device to reduce preexisting fenestration.[19,20] The choice to implant an AFR device in the Fontan conduit appears to be a reasonable alternative compared with a surgical approach or other devices (stent implantation, custom-made fenestrated atrial septal devices, vascular plugs), with a higher risk of occlusion (up to 63%) or systemic or pulmonary venous flow obstruction.[21]
5. Finally, AFR might be used to vent the left atrium during ECMO support. This maneuver has been demonstrated to have benefits in terms of shorter support duration and a higher rate of recovery.[22,23] On the other hand, several techniques are available for these purposes, due to the brief duration of ECMO treatment (eg, surgical apical venting, percutaneous left ventricular venting by using a percutaneous intravascular device, perforation and balloon dilatation of the atrial septum, and stent implantation through the atrial septum). The choice depends on various factors including underlying pathology, chances of recovery, need for further cardiac surgeries, patient age, and specific indication/contraindication in each setting. Therefore, other cost-effective techniques such as atrial septal dilation with angioplasty balloon or atrial septal stent implantation can be considered (Table 4). Nevertheless, the AFR offers advantages in terms of defect calibration, durability (it might improve the chances of ECMO weaning), easy closure when no longer needed (by using an 18 mm PFO device), and low risk of injury in case of further maneuvers on ECMO cannulas.

The use of the AFR device in pediatric patients is not standardized, and the evidence is somewhat limited, primarily consisting of case reports and short case series. The most common indications in patients of this age were: complex congenital heart diseases (particularly to fenestrate failing Fontan circulations),[17–20] palliation of end-stage pulmonary arterial hypertension,[6,10] and left atrial venting during ECMO support.[24] The device size depends on patient weight, anatomy, and clinical indication for implantation. Similar to adult patients, the most commonly used size is 8 mm. To create a smaller communication, 2 options are available: a smaller device (a 6-mm AFR device is available in the US but not in Europe), or predilatation with a smaller balloon catheter (diameter 5-7 mm instead of 8-10 mm).

To the best of our knowledge, this is the first study reporting the use of AFR in HF in pediatric patients. We demonstrated that percutaneous creation of an interatrial shunt by AFR implantation is a low-risk and well-tolerated procedure, even in pediatric patients. While we observed a relatively high mortality rate in our patients (3/10), these events were attributed to a very advanced disease stage and the presence of multiple organ dysfunction at the time of implantation. In the remaining patients, the procedure improved symptoms and quality of life. Although the creation of an ASD cannot be considered strictly a therapy

Table 4. Comparison between Atrial Flow Regulator and other techniques.

	Fr needed	Durability	Size control	Easy to implant	Protrusion	Crossability	Obliteration
Balloon	5-8	+	+	+++	–	++	++
Stent	5-10	++	++	+	+++	+	+
Atrial Flow Regulator	10-12	+++	+++	+++	–	+++	+++

for HF, in patients with high left ventricular filling pressures and high parietal stress, the partial (and dynamic) unloading of the left chambers might improve the myocardial perfusion, reduce the risk of arrhythmias, and have an adjuvant effect on medical therapy. This is the first pediatric study evaluating the efficacy of AFR implantation through echocardiographic parameters. Serial echocardiographic follow-up showed significant improvement in EF. In patients who underwent the procedure in critical settings and on inotropic support, we observed a significant reduction of vasoactive-inotropic score 48 hours after AFR implantation for all patients.

These findings demonstrate how early atrial fenestration can modify patient hemodynamics and lead to an immediate benefit in reducing the duration of ICU stay. In our opinion, the device should be considered in symptomatic HF despite optimal medical therapy, with invasive measurement of left atrial pressure >15 mm Hg in children and >20 mm Hg in adolescents, and 2 or more admissions due to HF in the last 12 months. In patients admitted to the ICU with signs of multiorgan failure, AFR might be used to vent the left atrium; however, the mortality rate in these patients remains high. An 8 mm device is usually sufficient to create an adequate shunt in pediatric patients. In addition, the atrial septum is usually compliant in these patients, so balloon oversizing or progressive balloon dilatation is usually unnecessary in pediatric cases. A 6 mm device might be helpful for children and for Fontan fenestration. Unfortunately, it is still not available in the EU market. Finally, our study demonstrated that the percutaneous approach is feasible for patients weighing at least 15 kg, even when the patient is under ECMO support. The presence of the cannulas might render the procedure more challenging but still feasible.

All patients should be on aspirin after device implantation. In Fontan patients, or when EF is <20%, anticoagulation should be considered.

This study has several limitations. First, it was a retrospective study, and patient characteristics were heterogeneous in terms of underlying pathophysiology and comorbidities. We observed a high mortality rate in our cohort, which can be attributed to the selection criteria of the studied patients (end-stage disease despite full medical therapy); however, in survivors, the analysis of paired data demonstrated a progressive improvement in signs and symptoms of HF. Furthermore, the number of treated subjects is relatively small, and the follow-up duration is relatively short. A larger, multicenter study focused on pediatric patients with HF may improve patient selection and determine the optimal timing for AFR implantation.

In conclusion, the creation of an interatrial defect using an AFR device is safe and effective in pediatric HF. The procedure should be considered for symptomatic patients with recurrent admissions for cardiovascular events despite optimal medical therapy. This device might be also considered in rescue or emergent settings; however, in these cases, the mortality rate remains high.

Declaration of competing interest

Biagio Castaldi was a proctor for Occlutech (2022). The remaining authors have no conflicts to disclose.

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Ethics statement and patient consent

This is a retrospective study. All the implants were performed by a skilled interventional cardiology team after written consent from the parents.

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