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STRUCTURAL HEART DISEASE (RJ SIEGEL AND NC WUNDERLICH, SECTION EDITORS)

The Creation of an Interatrial Right-To-Left Shunt in Patients with Severe, Irreversible Pulmonary Hypertension: Rationale, Devices, Outcomes

Anja Lehner[1] · Ingram Schulze-Neick[1] · Marcus Fischer[1] · Silvia Fernandez-Rodriguez[1] · Sarah Ulrich[1] · Nikolaus A. Haas[1] · André Jakob[1]

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Abstract

Purpose of the Review Targeted pharmacotherapies did improve survival rates, exercise capacity, and quality of life (QoL) of PAH patients. However, these pharmacological interventions are expensive and not always accessible. In addition, not all patients do respond similarly to these medications and many will continue to deteriorate. This review aims to discuss the beneficial role of an artificial right-to-left shunt and highlights current interventional devices and outcomes.

Recent Findings Since patients with preexisting atrial shunts or patients with Eisenmenger's disease show better survival rates, improved exercise capacity, and QoL, PAH patients clinically do benefit from an atrial septostomy by reducing signs of right heart failure, improving left heart filling, cardiac output, and systemic oxygen transport despite hypoxia. However, an uncontrolled septostomy with unrestricted right-to-left shunt bears the risk of acute severe desaturation and death. The Atrial Flow Regulator (AFR device, Occlutech®, Sweden) provides an adjustable shunt size with restricted flow and excellent short-term outcomes.

Summary Interventional strategies for PAH palliation are on the rise. The novel AFR device provides a durable and safe option for a controlled right-to-left shunting, thus enabling an individualized management.

Keywords Pulmonary hypertension · Interatrial shunt · Septostomy · Atrial flow regulator · AFR device · Right-to-left shunt

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✉ Nikolaus A. Haas
nikolaus.haas@med.uni-muenchen.de

Anja Lehner
anja.lehner@med.uni-muenchen.de

Ingram Schulze-Neick
ingram.schulze-neick@med.uni-muenchen.de

Marcus Fischer
marcus.fischer@med.uni-muenchen.de

Silvia Fernandez-Rodriguez
sylvia.fernandez_rodriguez@med.uni-muenchen.de

Sarah Ulrich
sarah.ulrich@med.uni-muenchen.de

André Jakob
andre.Jakob@med.uni-mnuenchen.de

[1] Department for Pediatric Cardiology and Intensive Care, Ludwig Maximilians University, Marchioninistrasse 15, D-80137 Munich, Germany

Introduction

Pulmonary arterial hypertension (PAH) is a severe, irreversible, progressive, and fatal disease characterized by a progressive destruction of the pulmonary vascular bed, secondary by increase in right ventricular (RV) pressures, and finally by right ventricular failure, low cardiac output, and death [1, 2].

Despite excellent recent advances in medical therapy targeting different pathogenic pathways, many patients continue to deteriorate while on optimal medical therapy with a decline in quality of life, a high rate of hospitalizations, and increased medical costs [3]. The annual mortality rates are about 10% in idiopathic PAH and even more with certain adverse types like scleroderma-related PAH [4, 5]. Therefore, there is a need for additional, innovative, and perhaps cost-effective therapies and interventions to improve long-term outcomes.

The creation of an interatrial right-to-left shunt in patients with PAH may reduce the clinical signs of acute or chronic right heart failure and enhance systemic ventricular output by

promoting right-to-left shunt via atrial fenestration at the expense of desaturation. Increasing systemic ventricular output may improve effective systemic oxygen transport and delivery despite arterial oxygen desaturation—especially if the desaturation is well titrated and not excessive [6, 7].

Creating a sustainable interatrial communication with adequate restriction is however challenging; stent implantation and balloon dilatation of the interatrial septum (IAS) are well-established techniques to create or enlarge an atrial communication in a variety of conditions in order to improve cardiac output [7]. Today, atrial septostomy is recommended in the current guidelines as a bridge to transplantation or as a destination therapy in patients with limited access to such therapy [1, 8].

Clinical symptoms of PAH such as dizziness and fainting in pulmonary hypertensive crisis and especially the incidence of syncope improve after septostomy not only in idiopathic PAH but also in corrected congenital heart diseases, connective tissue diseases, and distal chronic thromboembolic PAH [9, 10••]. The right-to-left shunt through the iatrogenic atrial septal defect (ASD) improves cardiac index and systemic oxygen transport despite hypoxia [11]. The reduced preload and secondary RV decompression improves RV function and reduces the sympathetic overactivity, and B-type natriuretic peptide (BNP) levels [12].

Early spontaneous closure of the fenestration is common after static balloon septostomy and leads to recurrence of symptoms. A large defect may circumvent the problems of spontaneous closure but carries the risk of acute severe hypoxia and death [6]. Therefore, there is a need for a balanced restrictive device to create an adjustable interatrial shunt to avoid both problems named above.

Congenital Heart Defects

The presence of an atrial septal defect (ASD) or any interatrial shunt is essential for the survival or optimization of hemodynamics in some congenital heart defects such as severe pulmonary stenosis and reduced right ventricular volume either for RV hypoplasia or massive RV hypertrophy, as well as in some forms of Ebstein's anomaly and in patients with tricuspid atresia [13, 14]. In addition, the benefit of an ASD is well used to optimize hemodynamics after interventional treatment of pulmonary atresia, surgical correction of Tetralogy of Fallot with hypoplastic pulmonary arteries, and after completion of the Fontan circulation [15].

Protective Effect of a PFO in PAH

Whereas the life expectancy of patients with severe PAH is poor, the patency of the foramen ovale (PFO) has been associated with longer survival irrespective of the actual pressure in the pulmonary arteries [16]. The PFO leads to typical gas exchange variations especially under exercise by the right-to-left shunt thereby undermining the positive effect of a PFO especially under exercise conditions [17]. Patients with a PFO tend to have less elevated right atrial pressures and a higher cardiac output [18].

Patients with Eisenmenger's Syndrome

It has been shown by many authors that patients with Eisenmenger's syndrome (ES) have a more favorable hemodynamic profile and prognosis than adults with primary pulmonary hypertension even in the setting of higher pulmonary artery pressures [19–21]. The right ventricle in patients with ES provides better performance indicated by a lower right atrial pressure and better cardiac index [19]. When analyzing additional groups of patients with PAH, survival from diagnosis was longer in ES compared to other causes of PAH and similar between closed-shunt with PAH and other causes of PH ([22, 23].

First Animal Experiments

The concept of creating a right-to-left shunt for the management of pulmonary hypertension has first been described by Austen et al. in 1964. They showed in a dog model with progressive pulmonary banding and a surgical shunt between the superior vena cava and the left atrium an improved cardiac index and systemic blood pressure while opening the shunt [24]. In addition, those animals with a pulmonary band and a surgically created ASD could run on a lead whereas those without died during or after exercise. The authors concluded that surgical creation of an ASD may be useful for the management for severe PAH.

Interventional Creation of an Atrial Septal Defect

The first interventional creation of an ASD was performed by William Rashkind in 1966 using a balloon catheter followed by Sang C Park using blade septostomy in 1978 and 1982 [25–27]. In 1983, Rich and Lam performed the first septostomy in a patient with severe PAH; the patient initially did benefit from the procedure but died the subsequent day in deep hypoxia. Autopsy revealed an atrial septal defect of 9 mm [28]. Successful case reports followed thereafter [29]. The first patient series were reported by Nihill et al. in 14 patients with terminal cor pulmonale; there were two early deaths and 9 long-term survivors with beneficial outcome so that the authors concluded that atrial septostomy can improve

Table 1 Interventional approaches to create a right-to-left shunt in patients with PAH (selected articles)

Author	Interventional approach	Patients (*n*)	Results
Rich et al. 1983	Blade balloon atrial septostomy	1	Initial clinical improvement, early death due to deep hypoxia
Nihill et al. 1991	Balloon dilatation and blade balloon atrial septostomy	14	9 long-term survivors with beneficial outcome
Kerstein et al. 1995	Blade balloon atrial septostomy	15	Improved survival of 13 patients
Sandoval et al. 1998	Balloon dilatation atrial septostomy	15	Step-wise dilatation, 14 patients with clinical improvement, 4 repeat procedures for spontaneous closure
Allcock et al. 2003	Balloon dilatation atrial septostomy	12	3 with repeat procedures
Kurzyna et al. 2007	Balloon dilatation atrial septostomy	14	Increase in NYHA stage, 6 with decreasing orifice sizes, 3 repeat procedures
Micheletti et al. 2006	Customized Amplatzer device	20	All with clinical improvement, 2 spontaneous closures
Prieto et al. 2006	Butterfly stent	1	Clinical improvement
Roy et al. 2013	Butterfly stent	1	Clinical improvement
Fraisse et al. 2006	Modified Amplatzer device	1	Patient stable during 42-month follow-up
O'Loughlin et al. 2006	Modified Amplatzer device	1	Clinical improvement
Lammers et al. 2007	Modified Amplatzer device	10	Clinical improvement in all, 4 spontaneous closures
Stumper O et al. 2003	Stent fenestration (diabolo shape)	6 with PHT	No stent occlusion up to 1.75 years of follow-up
Troost et al. 2009	Stent fenestration (diabolo shape)	15	No stent occlusion up to 2.3 years of follow-up

symptoms and may serve as a palliative bridge to heart and/or lung transplantation [30]. Kerstein et al. performed blade balloon atrial septostomy in 15 children and young adults with severe primary pulmonary hypertension that resulted in clinical and hemodynamic improvement and were the first to show improved survival in these selected patients with severe primary pulmonary hypertension [31]. In order to reduce the procedure-related mortality caused by severe desaturation, static balloon dilatation of the septum was changed to a step-wise approach with increasing balloon diameters [32]. This procedure showed however a significant closure rate leading to repeat maneuvers. This technique is nowadays used in most centers [33].

For a literature overview on interventional approaches for creation of an atrial septal defect in patients with PAH, see Table 1.

Hemodynamics of an ASD in PAH

The creation of an ASD in PAH patients has some significant hemodynamic effects in patients with various degrees of pulmonary hypertension.

Severe right heart failure and congestive dilatation of the right atrium leads to secondary organ failure (ascites, edema, liver congestion, secondary renal failure). Decompression of the RA leads to a relief of these secondary signs. Besides enlarged and distended right heart structures, a reduced filling of the left side due to significantly reduced transpulmonary blood flow may be additionally present in PAH patient. A right-to-left shunt across the IAS improves LV blood supply and thereby cardiac output despite systemic desaturation.

Recurrent syncope in PAH is best explained by an acute and significant increase in pulmonary vascular resistance and thereby acutely diminished left-sided filling, loss in blood pressure, and impaired organ perfusion. In those patients, an ASD provides the possibility of acute right-to-left shunting and thereby maintains the filling of the left side—thus preventing syncope.

In those patients with *PAH and reduced exercise capacity*, a similar effect like in patients with syncope is provided under physical exercise; the impaired transpulmonary blood flow can be compensated up to a certain limit; persistent exercise load will lead to a situation comparable to syncope resulting in an inadequate transpulmonary blood flow, increase of RV pressure and RV enlargement, and finally secondary RA enlargement. In this situation, the right-to-left shunt restores left-sided filling with the hemodynamic consequences outlined above.

These hemodynamics are shown in various publications [9, 10••, 11, 33, 34]. After creation of an ASD, the functional status of patients with PAH usually improves significantly. Kurzyna et al. showed an increase in NYHA classification for about 1 grade, an increase in cardiac index, and a trend in improved oxygen transport [35]. In general, there is a substantial improvement in the 6-min walk test exceeding the benefits of most modern pharmaceutical approaches. Sandoval showed an increase from 105 to 210 m, Vachiery from 220 to 380 m, Allcock from 200 to 250 m, and Troost from 305 to 370 m [32, 36–38]. In addition, the overall

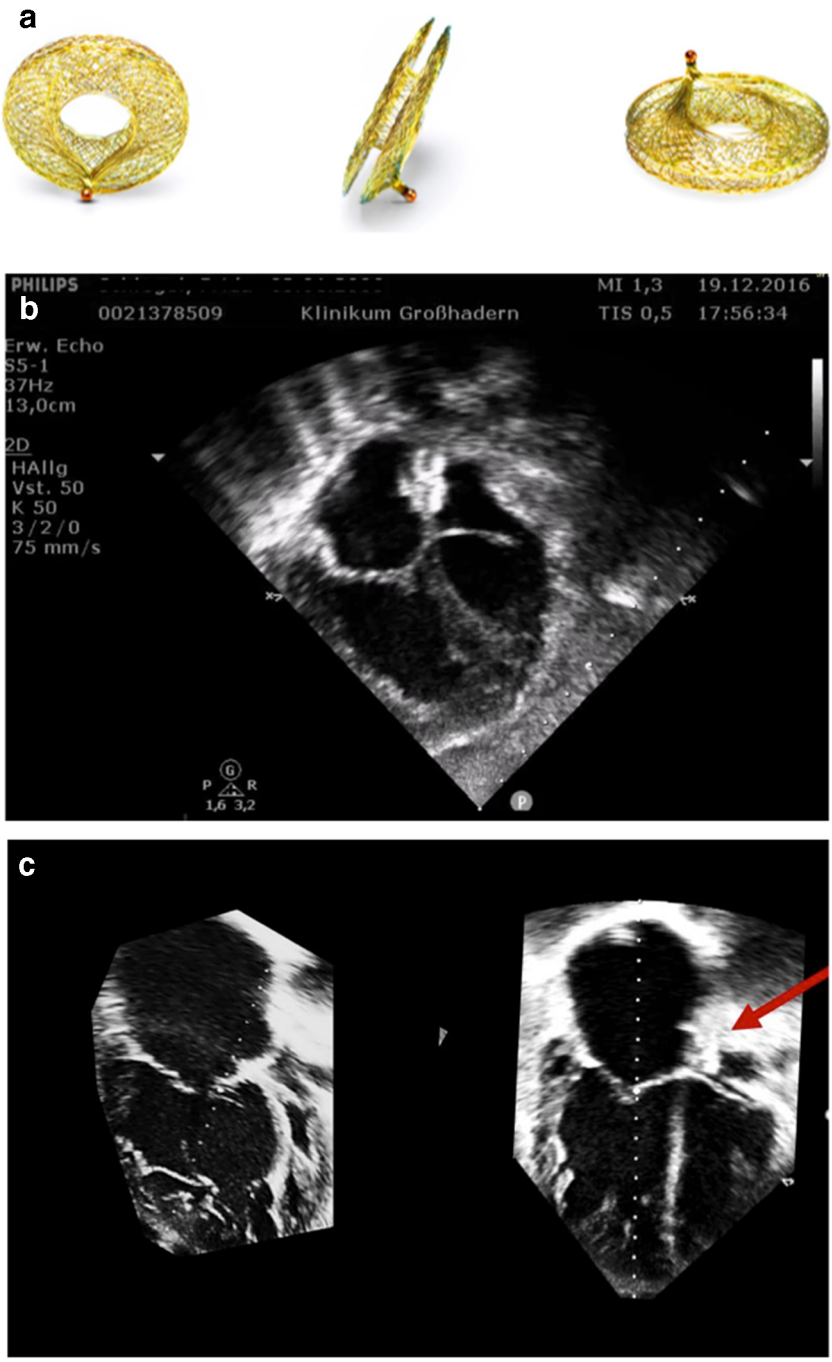

Fig. 1 **a** The Occlutech Atrial Flow Regulator (AFR®) device. A classical nitinol double-disk occluder with central fenestration of sizes from 4 to 10 mm. Fully retrievable up to 1 month postimplantation; balloon dilatation is possible for further shunt adjustment (used with permission from Occlutech). **b** Echocardiography showing a 4-chamber view with AFR® occluder within the interatrial septum. **c** Echocardiography showing a 4-chamber view pre- and postimplantation of an AFR® device (*arrow*). Note the remarkable left ventricular filling due to right-to-left shunting

survival of patients with PAH is poor [39]. Based on the established survival curves, the benefit of BAS can be estimated and compared. Sandoval showed a dramatically improved survival in PAH patients after BAS [11]. Additional beneficial effects have been demonstrated such as an improved echocardiographic right heart function, mainly induced by reduced filling pressures and a shift in the Frank Starling curve of the RV, indicated by reduced right atrial size [40]. In many studies, decompression of the RA results in a reduction of BNP levels [12, 41••]. A reduction of atrial arrhythmias after BAS has been reported [42].

The major side effects reported are a significant hypoxemia mainly induced by an uncontrolled size of the atrial septal defect. Sandoval has reviewed numerous reports of BAS in PAH; he could nicely demonstrate that, out of 372 patients reported, the rate of immediate death was 7.2% with an additional rate of 5.2% at 1 month [10••]. A significant predictor of death was an RA pressure > 20 mmHg with an odds ratio of 11.4 resulting in significant desaturation. The mortality increased from 0% in patients with an RA pressure < 10 to 4% in a RA pressure of 10–20 and to 43% in those patients with an RA pressure > 20 mmHg. The desaturation was closely

correlated to an increase in cardiac index where a desaturation of 10% and 20% correlated to an increase in CI of 50 and 100% respectively.

Devices Used to Maintain Patency of the Atrial Septal Defect

Certain palliative transcatheter atrial septal interventions have shown symptom relief in PAH [11]. To avoid the problem of early closure of ASDs created by static balloon dilatation, Micheletti et al. implanted a custom-made atrial septal device at the end of the septostomy in order to maintain patency [43]. In 7 out of 20 children, a short-term closure could be successfully avoided. This approach has been followed by other investigators [44, 45]. Modified Amplatzer septal occluders with custom-made fenestrations have been associated with high closure rates previously [46].

Another well-described technique is the insertion of a stent in the interatrial septum named as "diabolo stent" or "butterfly stent" [47, 48]. Diabolo atrial stents have shown improved patency but need an experienced operator to avoid stent occlusion, embolization, cardiac injury, and difficulties in adjusting shunt size to achieve the desired hemodynamic effects [49–52].

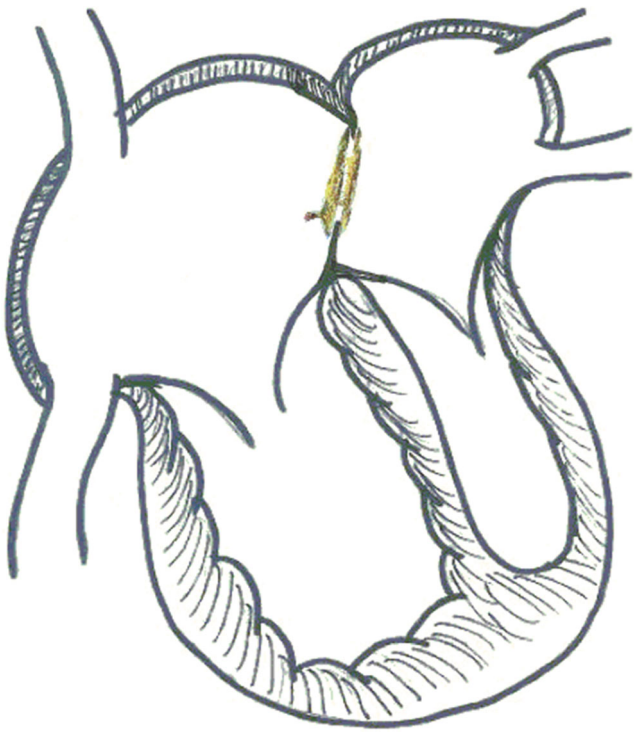

Fig. 2 Schematic implantation of an AFR® device in a patient with PHT and congested right heart. After transseptal puncture, the device is placed within the interatrial septum in a similar way like a standard ASD occluder

The Occlutech AFR® Occluder

The first factory-made specific fenestrated device for the creation of a well-defined ASD is offered by the Occlutech company. The Atrial Flow Regulator (AFR® device) is a self-expandable double-disk wire mesh device without fabric. It is constructed from 0.004–0.0075 in. nitinol (51% nickel, 49% titanium) tightly braided into two flat discs, dedicated to create a defined fenestration and to allow blood flow across the interatrial septum (Fig. 1). There are 4 different fenestrations available from 4,6,8 and 10 mm; the discs range from 16 to 30 mm requiring a delivery system of 10, 11, and 12 Fr, respectively. The device is available in 3 different waists of 2, 5, and 8 mm according to the thickness of the atrial septum. The device has high flexibility and adaptability with unique braiding. It is responsible and fully retrievable [53]. The predominant advantage of the AFR® will be a controlled and predictable orifice and continued patency due to endothelialization of the shunt orifice, which prevents thrombotic occlusion of the shunt.

Implantation Technique

The implantation of the AFR® device does not differ significantly from any other device application used for interventional ASD closure using nitinol-based double disk devices. The crucial part of the procedure is the transseptal puncture; as the anatomy in patients may vary substantially, mainly due to an underfilled small left atrium, echocardiographic guidance (if feasible by TTE) is essential to avoid pericardial perforation and tamponade. After access to the LA is achieved, a stiff exchange wire is placed in the left upper pulmonary vein. Thereafter, a static balloon dilatation of the septum is performed. The balloon diameter should be at minimum 6 to 8 mm bigger than the finally planned communication of the AFR® device (i.e., a 16-mm balloon for a 8-mm device). Thereafter, the long implantation sheath is advanced to the LA and the left side of the device deployed. Under echo and fluoroscopic guidance, the device is retracted until firm contact to the septum is established. Then, the right side of the device is released by retracting the sheath. A careful hemodynamic evaluation is performed before the release of the device. This includes especially a close monitoring of the saturations and right-and left-sided pressures. If the desaturation exceeds 15% of reached values below 75%, the device should be exchanged to a smaller device or the procedure aborted. After adequate hemodynamic monitoring, the device can be released. Retrieval of the device is possible until 4 weeks after implantation by snaring the delivery site and retracting the device. Secondary device closure is possible by using a standard PFO occluder. Reducing the device size may be possible by implanting a smaller device inside the original device.

Table 2 Creation of a right-to-left shunt with the Occlutech Atrial Flow Regulator (AFR®)

Author	Diagnosis	Patients (*n*)	Fenestration diameter of AFR® device	Results
Patel et al. 2015	PAH	1	6 mm	Clinical improvement
Rajeshkumar et al. 2017	PAH	12	3 × 8 mm 9 × 10 mm	Clinical improvement of all patients, patency of right-to-left-shunting during follow-up
Manuri et al. 2018	Failing Fontan	1	4 mm	Reduction of shunting via Fontan fenestration, clinical improvement
Lehner et al. 2018	Failing Fontan	1	6 mm	Creation of a Fontan fenestration, clinical improvement

First Clinical Experience

The first in-human use was performed by Vettukattils group in January 2015 [54•]. They implanted a 6-mm AFR® device in a 54-year-old lady with moderate PAH after surgical ASD® closure some years ago but clinical signs of severe right heart failure despite anti-PAH medication and catecholamine therapy. The patient's RA pressure was 19/14 (12) mmHg and PA pressure was 72/18 (34) with systemic blood pressure of 99/46 (62) mmHg. The patient's oxygen saturation measured prior to dilatation dropped from 95 to 89% immediately after the procedure. After implantation, the patient improved significantly. At her 6-week follow-up visit, the patient reported that she had more energy with recorded resting saturation of 98%. The 6-minute walk test distance doubled and she remained without ascites and pedal edema without any increase in her diuretic therapy. The next patient series was reported by Sivakumar's group in 2017 [41••]. The AFR® device was implanted in 12 patients with severe PAH presenting with syncope and right heart failure.

All procedures were successful without any major complications. All patients had complete relief of syncope, and 6-min walk distance improved significantly from 377 to 423 m [41••]. The cardiac index (2.3 to 2.8 l/min/m^2) and systemic oxygen transport (367 to 428 ml/min/m^2) also showed a significant improvement [41••]. The device was patent in all patients at a median follow-up of 189 days (range 10–296 days) resulting in a significant reduction of oxygen saturations from 98 to 85% after exercise [41••]. The reduction in BNP levels also did not reach statistical significance [41••].

The AFR® device was used in addition in patients with Fontan circulation. Lehner et al. reported a GUCH patient with failing Fontan hemodynamics caused by an elevated transpulmonary pressure gradient—hence a situation similar to reduced transpulmonary blood flow in PAH [55•]. For a schematic AFR implantation, see Fig. 2.

After the implantation of a 6-mm AFR® device, the clinical symptoms relieved and the AFR® device stayed open for at least 2 years. In a similar way, an AFR® device was implanted to reduce an oversized 9-mm Fontan fenestration to a more favorable 4-mm fenestration in a 5-year-old child [56]. For a literature overview, see Table 2.

Current World Wide Experience

The AFR® device is currently in the registration process for CE registration. There are two CE registration studies initiated, the PROPHET trial for its use in pulmonary hypertension and the PRELIEVE trial for diastolic and systolic heart failure. In addition, compassionate use cases may be enabled upon special application. To date, the AFR® device has been used in about 80 patients, the majority for PAH, 5 patients with Fontan circulation, and the remainder in diastolic heart failure. Follow-up time was 2 years for 5 patients, 12 months for 35, 6 months for 55, and 3 months for the remainder with excellent patency and no procedure-related complications.

Future Application of the AFR® Device

Besides its use in PAH patients [57], the application of the AFR® device may well be extended to other heart failure populations, especially those with severe restrictive cardiomyopathy or severe diastolic dysfunction of the LV and end-stage systolic dysfunction awaiting left ventricular assist device (LVAD), and in patients who remain symptomatic despite ambulatory inotropes with elevated LA pressures. Elevated LA pressure in chronic heart failure may permit left heart decompression via the atrial fenestration and recovery of LV function over time. In addition, in patients with a Fontan circulation, the device may be useful in creating or reducing the size of a fenestration.

Conclusion

Survival in patients with PAH with an atrial septal communication is longer as it leads to preserved cardiac index. Classical or static balloon atrial septostomy creates this communication, but it often closes spontaneously or may lead to severe desaturation and death when the communication is too large. In symptomatic patients with PAH, transcatheter creation of a palliative restricted atrial septal defect by implantation of an

AFR® device is an alternative approach to increase systemic ventricular output and treat clinical signs of PAH such as reduced exercise capacity, syncope, or overt right heart failure. The use of AFR® as a device-based approach to treat PAH provides a unique alternative to improve hemodynamics and symptomatic status. Implantation was simple, safe, tolerated well, and feasible. The device retained patency on medium-term follow-up.

The application of this device may well be extended to patients with chronic refractory right-and left-sided heart failure with elevated atrial pressures. However, further long-term multicenter clinical trials will be required to evaluate its efficacy and long-term outcomes.

Impact on Daily Practice

The AFR® device is designed to decompress the RA or LA chambers by creation of a defined and restrictive interatrial communication. Thereby, in PAH patients, cardiac output is enhanced or maintained, signs of right heart failure reduced. AFR® implantation early in the course of the disease may show an improved survival in patients who have a predictable septal communication. An early AFR® therapy could also favorably remodel the right ventricle. The device may also be useful in systolic and diastolic left heart failure of the RV or LV, in Fontan patients, and provide access to the LA when repeated procedures are expected.

Compliance with Ethical Standards

Conflict of Interest Nikolaus A. Haas works as consultant and proctor for Occlutech. Anja Lehner, Ingram Schulze-Neick, Marcus Fischer, Silvia Fernandez Rodriguez, Sarah Ulrich, and André Jakob declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with animals or human participants performed by any of the authors.

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