Results of atrial flow regulator implantation in pulmonary arterial hypertension patients with severe heart failure despite maximal medical therapy

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INTRODUCTION

Pulmonary arterial hypertension (PAH) is a rare severe progressive disease that leads to right heart failure and, ultimately, death [1]. Failure of medical therapy is an indication for referral for lung transplantation.

Balloon atrial septostomy has been proposed as a palliative measure or a bridge to transplant procedures in patients with PAH and severe heart failure, resistant ascites, and recurrent syncope despite maximal medical therapy.

The main disadvantages of this procedure are restenosis of the interatrial opening and unpredictable shunt size [2]. Recently, an atrial flow regulator (AFR) has been introduced to overcome these problems. The device allows for adjustment of fenestration diameter to interatrial pressure gradient, arterial oxygen saturation (SaO_2), and long-term maintenance of the interatrial shunt.

So far, 2 observational studies have presented the efficacy and safety of the AFR in patients with PAH treated with a combination of an endothelin receptor antagonist and a phosphodiesterase-5 inhibitor [3, 4]. The role of AFR in patients on maximal medical therapy has been reported only in single case descriptions.

In this study, we present the experience of 3 tertiary pulmonary hypertension centers with the use of the AFR in patients with PAH experiencing severe symptoms despite maximal medical therapy.

METHODS

We enrolled all consecutive adult PAH patients referred to 3 pulmonary hypertension tertiary centers in Poland (Krakow, n = 5; Gdansk, n = 2; Poznan, n = 2) for AFR implantation between May 21, 2018 and August 23, 2022 and followed them until September 26, 2022. Eight patients were enrolled in an international prospective clinical trial (THE AFR-PROPHET TRIAL; NCT03022851), and 1 patient received AFR as compassionate treatment outside the trial. We adopted the AFR-PROPHET's inclusion and exclusion criteria (https://clinicaltrials.gov/ct2/show/NCT03022851). In short, patients were eligible if they had recurrent decompensations of heart failure requiring hospital admissions, ascites resistant to treatment, or syncope due to heart failure despite use of conventional treatment.

The following measurements were analyzed: World Health Organization functional class (WHO-FC), N-terminal prohormone of brain natriuretic peptide level, results of 6-minute walk test, transthoracic echocardiography, and right heart catheterization (RHC). The

A

	Visit 0	Visit 1	Visit 2
WHO–FC			
6MWD			
NT-proBNP			
RHC			
HR			
SaO_2			

B

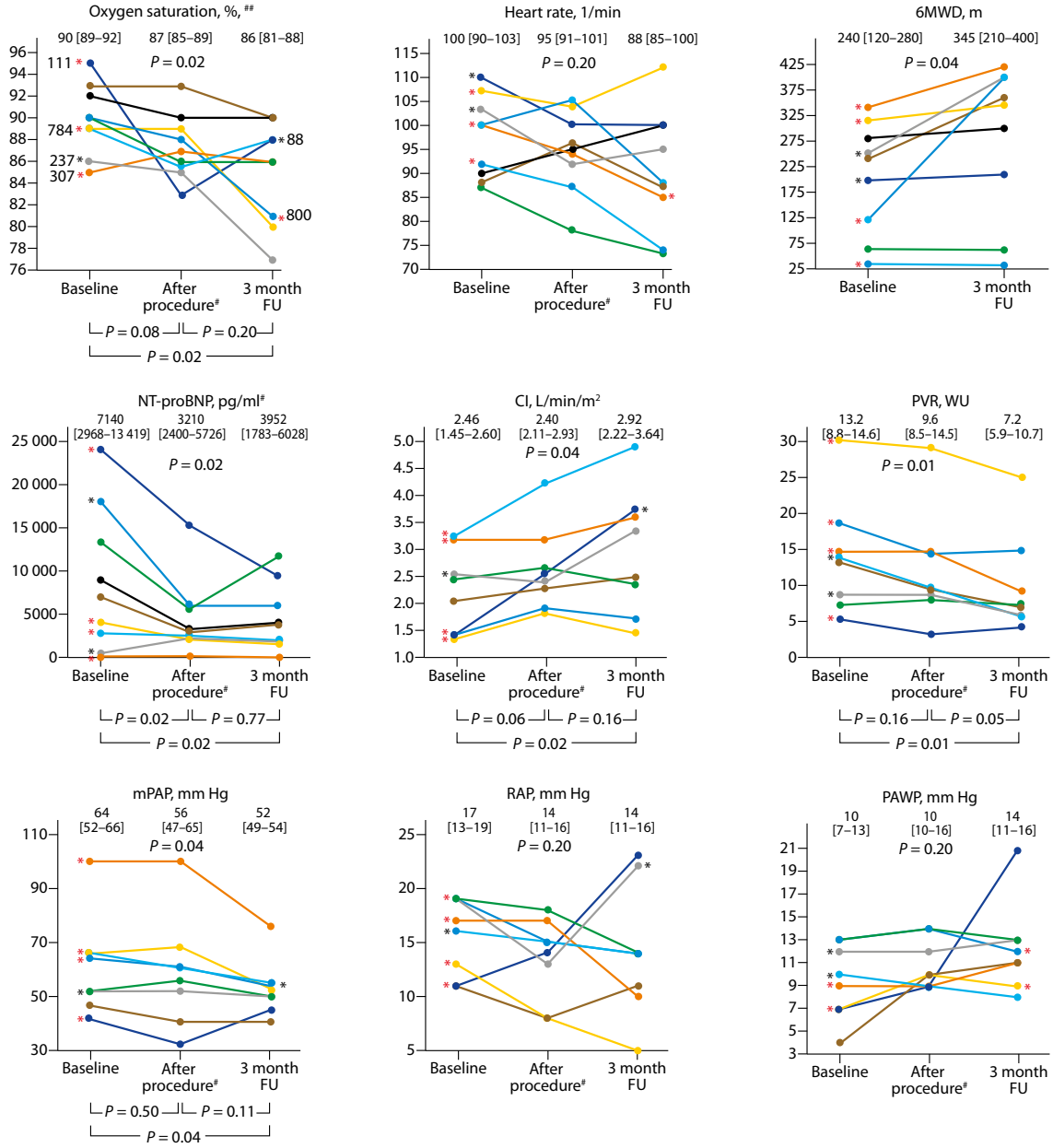

Figure 1. The sequence of measurements (**A**) and the results of atrial flow regulator implantation (**B**). The crossed cells in A denote the tests performed at different time points. The graphs show changes in parameters separately for each patient. Changes in median (interquartile ranges) values are shown above the graphs. Visit 0 denotes the day before AFR implantation; visit 1 is the period from the day of AFR implantation to hospital discharge; visit 2 indicates a follow-up of 3 months after AFR implantation. For variables measured at three time points, the *P* values are presented in red above each graph while the respective *P* values of post-hoc analyses are presented below each graph. Patients who died at follow-up are marked with red * and those who had lung transplantation with black *.
Next to the lines denoting oxygen saturation, we added time to transplantation or death (days).
#Visit 1: NT-proBNP, heart rate, and pulse oximetry were measured on hospital discharge while hemodynamic parameters were measured immediately after AFR implantation; ##Pulse oximetry
Abbreviations: 6MWD, 6-minute walk distance; CI, cardiac index; HR, heart rate; mPAP, mean pulmonary arterial pressure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; RAP, right arterial pressure; RHC, right heart catheterization; SaO_2, arterial blood oxygen saturation; WHO-FC, World Health Organization functional class

schedule of assessments (visits 0, 1, and 2) is presented in Figure 1.

AFR implantation was performed through the femoral vein. The procedure included RHC (before and after implantation of the device), atrial septal puncture, and implantation of the device. The AFR device was described by fenestration diameter (D1), diameters of the discs (D2), and waist (h) height. The protocol for AFR implantation followed the manufacturer's instructions.

The categorical variables were presented as n (%) and the continuous variables as medians (interquartile ranges). To assess differences of repeated measurements of continuous variables we used the Friedman test with a post-hoc Wilcoxon matched-pairs signed-rank test for variables measured 3 times and the Wilcoxon matched-pairs signed-rank test for variables measured twice. Exact McNemar's test was used to assess differences in repeated categorical variables. The significance level was set at $\alpha = 0.05$. The institutional ethics committee approved the study protocol (94/KBL/OIL/2018, NKBBN/247/2018) and written informed consent was obtained from each patient before the study.

RESULTS AND DISCUSSION

We enrolled 9 (6 men and 3 women) consecutive adult PAH patients from 5 PAH tertiary centers in Poland at a median (IQR) age of 48.6 (30.6–50.3) years. Idiopathic PAH was present in 6 patients, 2 patients had PAH associated with congenital heart disease after defect correction, and 1 patient had PAH associated with connective tissue disease. All patients were on the waiting list for lung transplantation. The median (IQR) time between PAH diagnosis and AFR implantation was 4.1 (1.9–7.5) years.

On enrollment, all patients presented advanced stages of PAH. Two (22%) patients were in the WHO-FC III and 7 (78%), in the WHO-FC IV.

All patients were treated with maximal medical therapy for PAH, including a combination of sildenafil (8 patients [89%]), an endothelin receptor antagonist (bosentan, 6 [67%]; macitentan, 3 [33%]), and prostacyclin analogs (epoprostenol 3, [33%]; treprostinil 6 [67%]). One patient did not receive sildenafil due to intolerance.

The indication for AFR implantation in all patients was severe heart failure with recurrent ascites resistant to diuretics. Patients did not report syncope.

Atrial septostomy was performed using balloons with diameters ranging from 8 to 12 mm. Then, the devices with the following characteristics were implanted: D1 of 6 mm and D2 of 18 mm in 7 (78%) patients; D1 of 8 mm and D2 of 21 mm in 2 (22%) patients.; h of 5 mm in 9 (100%) patients. The median (IQR) fluoroscopy time was 22 (18–30) minutes. The median (IQR) time of hospitalization after the procedure was 9 (4–12) days. Immediately after the procedure, a median (IQR) drop in SaO2 of 2 (0–4) percentage points was observed. We did not observe any other significant complications. All patients were prescribed 75 mg/d clopidogrel for 3 months starting from the day of AFR implantation.

On visit 2, echocardiography showed continuous right-to-left flow through AFR in all patients. Ascites reoccurred in 4 patients but only in those who had the smaller fenestration diameter (D1 = 6 mm). Despite significant hypoxia, exercise tolerance was maintained or improved probably due to increased cardiac output. Compared with baseline, the number of patients in WHO-FC IV decreased to 1, and apart from that person, all other patients remained in or improved their WHO-FC III ($P = 0.03$) while the median of 6-minute walk distance increased in the study group (Figure 1). The median (IQR) doses of diuretics tended to decrease as follows: furosemide by 60 (0–20) mg (38% [0%–51%]); ($P = 0.1$), torasemide by 10 (0–35) mg (17% [0%–35%]); ($P = 0.05$), and spironolactone by 50 (0–50) mg (50% [0%–50%]); ($P = 0.05$).

Changes in hemodynamic and clinical parameters from baseline (V0) to visit 2 (V2) in each study participant are presented in Figure 1. In Supplementary material, *Figure S1* presents changes in liver and kidney function parameters.

During the median (IQR) follow-up of 307 (111–413) days, 4 patients (44%) died due to progression of heart failure and 2 (22%) underwent lung transplantation.

To the best of our knowledge, this is the first study to show that implantation of an AFR in patients treated with maximal PAH therapy improves pulmonary hemodynamics and exercise capacity, reduces ascites, and tends to reduce the need for diuretics.

The positive hemodynamic and functional effects were reached at the cost of arterial blood oxygen desaturation, which was observed immediately after AFR implantation and continued at follow-up. To prevent severe hypoxia, fenestration diameter was selected based on the interatrial pressure and SaO_2. As our patients had low resting SaO_2 and high right arterial pressure before the procedure in most of them, only implantation of devices with a small fenestration diameter of 6 mm was possible. This is in contrast to 2 earlier case series studies, in which fenestrations of 10 mm or 8 mm were chosen in most patients [3, 4]. This difference could be explained by lower baseline right arterial pressure (9.4 [5.0] mm Hg and 10.16 [5.8] mm Hg) and higher resting SaO_2 (96.4% [85.5%] and 98.0% [0.18%]) in those 2 populations as compared with our population. Despite using smaller fenestration diameters in our patients, the increase of the cardiac index was similar in our study and the 2 abovementioned studies.

An unexpected result of our study was a drop in mean pulmonary pressure after AFR implantation. We hypothesize that it could be an effect of blood redistribution and a decrease in sympathetic activity due to hemodynamic improvement. In fact, we observed a decrease in the resting heart rate in the 3-month follow-up.

A recent meta-analysis of 16 studies showed that atrial septostomy is a safe procedure with an early mortality

(48 hours) rate of 4.8% [5]. Safety of AFR implantation was also shown in 2 case series studies [3, 4] and confirmed in our study (no periprocedural deaths). Importantly, all shunts were active during the follow-up period as assessed by echocardiography.

Despite AFR implantation, the long-term mortality rate was high. However, only patients with the most severe end-stage PAH were enrolled, and no further treatment options apart from lung transplantation could have been considered in those cases. Notably, 2 patients survived lung transplantation after AFR implantation.

In conclusion, AFR implantation in addition to maximal medical therapy improves symptoms and hemodynamics in patients with PAH and severe heart failure with resistant ascites. As it is also a safe procedure, it should be regarded as a bridge to transplantation, especially in regions with prolonged lung transplantation waiting times.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/kardiologia_polska.

Article information

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