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The impact of atrial flow regulator implantation on hemodynamic parameters in patients with heart failure

Background	Left atrial decompression has emerged a new option to treat patients with heart failure and dyspnea at rest or during exercise. Here we report the impact of atrial flow regulator (AFR) implantation on hemodynamic parameters in patients at our center with heart failure and with reduced (HFrEF) or with preserved left ventricular ejection fraction (HFpEF).
Material and methods	The PRELIEVE trial is designed to assess the safety and efficacy of the AFR in patients with HFrEF or HFpEF. Patients with left ventricular end-diastolic pressure ≥15 mmHg at rest or ≥25 mmHg during exercise and with an ejection fraction ≥15% were enrolled. Echocardiographic data, 6-min walking distance, Kansas City Cardiomyopathy Questionnaire, and brain natriuretic peptide levels were assessed pre- and post-AFR implantation and at 3 mos. Invasive hemodynamic assessments were also performed pre- and post-AFR implantation and at 3 mos.
Results	27 (69.2%) patients with HFrEF and 12 (30.8%) patients with HFpEF at our center were enrolled in this study. A significant decrease was observed in pulmonary arterial wedge pressure regardless of EF (p=0.007 for HFrEF and p=0.03 for HFpEF). No significant difference of mean pulmonary arterial pressure, right arterial pressure and cardiac output (CO) existed at 3 months compared with pre-implantation baseline values.
Conclusion	AFR implantation led to decrease in left ventricle filling pressure without the deleterious impact on CO and right heart function regardless of ejection fraction.

Keywords	Atrial flow regulator; diuretics; device; dyspnea; edema; heart failure; interatrial shunt; quality of life
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Introduction

Increased left atrial pressure (LAP) secondary to elevated left ventricular end-diastolic pressure (LVEDP) leads to pulmonary congestion that is responsible for dyspnea at rest or during exercise in patients with heart failure and with reduced (HFrEF) or preserved left ventricular ejection fraction (HFpEF) [1]. Decreased left ventricular ejection fraction (LVEF) in HFrEF and impaired myocardial relaxation in HFpEF cause elevated LVEDP and LAP [2, 3]. Diuretics and vasodilators are used to reduce LVEDP and LAP [4], but as heart failure progresses, the effects of medical therapy abate. The prevalence of HF is 1–2% in the general population and reaches >10% in persons aged 70 and older [5]. Given the high prevalence of HF in the older population, drug-resistant scenarios are inevitable.

Recently, several novel device implants to treat heart failure symptoms using left atrial decompression have been tested successfully. They include the Ventura device (V-Wave Ltd., Or Akiva, Israel), the IASD (Corvia Inc., Tewksbury, MA, USA), the AFR (Occlutech, Schaffhausen, Switzerland), and the Transcatheter Atrial Shunt System (a left atrium-to-coronary sinus shunt device by Edwards Lifesciences, Irvine, California). The latter device is placed by atriotomy, whereas the other three devices are deployed in the interatrial septum. The IASD has been investigated in HFpEF patients [6, 7], and the Ventura device was tested in patients with HFrEF [8]. Both devices were proven to be safe and showed initial beneficial hemodynamic and clinical outcomes. Last year, 3-mos results of the PRELIEVE trial in both HFrEF and HFpEF patients were published in Eurointervention [9]. All three interatrial shunting devices are approved (CE-marked) for use in patients with HF.

These devices create passive left atrial decompression. In a computer simulation study, an 8-mm interatrial shunt, which was identical to the bAFR device shunt, shifted the left atrial pressure-volume loop leftward and downward [10]. This caused a minimal decrease in left ventricle output while mildly increasing right ventricle output. These results were coupled with a marked reduction in pulmonary artery wedge pressure (PAWP) (~3 mmHg at rest and ~11 mmHg at peak exercise). Right atrial and pulmonary artery pressures did not significantly increase. The effects of interatrial shunt on pulmonary hemodynamics have been investigated in a preclinical study [11]. That study

demonstrated the favorable effects of creating an interatrial shunt on pulmonary hemodynamics in rats with HFpEF.

Here we report the hemodynamic changes following AFR implantation at 3 mos in patients with HFrEF and HFpEF.

Material and methods

PRELIEVE is a non-randomized, prospective, multi-center, open label pilot study of the AFR. PRELIEVE has been approved by local and national ethics committees, and 19 clinical centers in Turkey, Belgium and Germany are part of the study. Prior to patient recruitement study protocol was approved by sponsor and local ethic committee in Bezmialem Vakif University (Date:29/03/2017, No: 71306642–050.01.04).

Quality of life (QoL, assessed by the Kansas City Cardiomyopathy Questionnaire (KCQQ)), New York Heart Association (NYHA) class, 6-min walking distance (6MWD), and transthoracic echocardiography (TTE) parameters are assessed during follow-up according to the protocol (Figure 1).

HFrEF and HFpEF patients were enrolled in the study. Patients with left ventricular ejection fraction (LVEF) equal to or greater than 15% and less than 40%, and with documented elevated left ventricular filling pressure (PAWP ≥15 mmHg at rest or ≥25 mmHg during exercise) were included in the HFrEF group. Patients with LVEF equal to or greater than 40% and with documented elevated left ventricular filling pressure were included in the HFpEF group. Inclusion and exclusion criteria are summarized in Table 1.

The study follow-up period was planned to be completed in 12 m and consisted of eight clinical visits, i.e., screening, implantation, and six follow-up visits. 6MWD performance and QoL (KCCQ) were assessed after 1, 3, 6, and 12 mos. Transesophageal echocardiography (TEE) and right heart catheterization were performed at the 3-mon follow up visit. The study is ongoing. We reported here 3-month data.

The primary safety endpoint was the presence of serious adverse device effects (SADEs) at 3 mos, SADEs were defined as device dislocation or embolization, device-related injury of mitral or tricuspid valve, device-related intractable

Figure 1. Brief review of the study protocol

Physical examination	(Day 7, 30, 90, 180, 360)
Vital signs	(Day 1, 7, 30, 90, 180, 360)
Laboratory testing, included BNP	(Day 7, 30, 90, 180, 360)
Electrocardiography	(Day 7 and 90)
6-minutes walking test	(Day 30, 90, 180, 360)
Transthoracic echocardiography	(Day 1, 7, 30, 180, 360)
Transesophageal echocardiography	(Day 90)
KCCQ	(Day 30, 90, 180, 360)
Right and Left Heart Catheterization	(Day 90)

Table 1. Inclusion and exclusion criteria

Inclusion criteria (All criteria had to be fulfilled)	
1	Age ≥18 yrs
2	NYHA class III/IV
3	Under medical treatment (according to ESC guidelines) at least 6 mos
4	History of hospitalization due to symptomatic heart failure in the last 12 mos
5	Non-significant (moderate-to-severe) valvular heart diseases (aortic stenosis, mitral regurgitation and stenosis)
6	Controlled arrhythmia with heart rate ≤110 bpm
7	Life expectancy ≥1 yr
8	Undergone successful balloon atrial septostomy and patient in stable condition
9	Left ventricular ejection fraction≥15% and ≤70% – for LVEF≥40%: NT-pro-BNP≥125 pg/ml
10	Elevated left ventricular filling pressures; – PCWP/LVEDP≥15 mmHg and greater than CVP, at rest or – PCWP≥25 mmHg, CVP<20 mmHg during exercise
11	Transseptal catheterization and transfemoral vein procedure determined to be accessible
Exclusion criteria	
1	Sepsis or any acute infections
2	History of allergic reaction to titanium/nickel, anticoagulation or antiaggregant
3	Contrast media intolerance
4	Pregnancy and lactation
5	Occluded inferior vein cava
6	History of ASD and/or ASD repair or closure device in place
7	Intracardiac thrombus
8	Unstable and intractable angina pectoris
9	Right ventricular dysfunction, described as following: – TAPSE<14 mm – RV volume ≥LV volume – PASP >70 mmHg
10	Severe valve disease or mechanical valve prosthesis
11	Congenital heart defect, large PFO with significant atrial septal aneurysm
12	Mitral valve stenosis
13	Resting heart rate>110 bpm
14	Clinically relevant thrombocytopenia, thrombocytosis, leucopenia, anemia
15	Unable to perform 6MWD test
16	Active malignancy
17	Symptomatic carotid artery disease
18	Uncontrolled systolic blood pressure>170 mmHg
19	Severe lung disease
20	History of TIA or stroke within 6 mos
21	Candidates to heart transplantation
22	Bleeding disorders (INR>2.0, thrombocytes <100 000, hemoglobin <8.0 g/dl)
23	History of MI or PCI or CABG in last 3 mos or indication for coronary intervention
24	CRT implantation within last 6 mos
25	Septic aneurysm
26	Atrial septal thickness >10 mm
27	HF due to hypertrophic or infiltrative cardiomyopathy
28	Thromboembolic events within last 6 mos
29	Dialysis or renal insufficiency requiring dialysis

6MWD, 6-min walking distance; ASD, atrial septal defect; CABG, coronary artery bypass grafting; CRT, cardiac resynchronization therapy; CVP, central venous pressure; HF, heart failure; LVEDP, left ventricular end-diastolic pressure; MI, myocardial infarction; PASP, pulmonary arterial systolic pressure; PCI, percutaneous coronary intervention; PCWP, pulmonary capillary wedge pressure; PFO, patent foramen ovale; RV, right ventricular; TAPSE, tricuspid annular plane systolic excursion.

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Figure 2. AFR device ex vivo in face (a) and side view (b)

arrhythmia, or any circumstance that required device removal. The secondary safety endpoints were the rate of all serious device events (SAE) and the presence of SADEs during 12 mos after implantation.

AFR device description

The AFR device is a self-expanding, double-disc, circular device made of nitinol wire mesh with «superelastic properties» (Figure 2). A waist with a central shunt connects the discs. A welded ball structure located on the proximal disc surface serves as an adapter for the pusher cable during implantation. The AFR is available with different waist-shunt diameters, waist heights and disc diameters to provide shunts of different diameters and to accommodate varying atrial septal anatomy. Depending on the size of the AFR, the manufacturer recommends using the Occlutech Delivery System (ODS) with sizes ranging from 8F to 14F.

Procedural details

The procedure began with local anesthesia and sedation. Right and left cardiac catheterizations were performed. PAWP, pulmonary artery and right heart chamber pressures, central venous, and aortic and left ventricular pressures were recorded. Blood samples for gas analysis were obtained. Cardiac output (CO), pulmonary and systemic vascular resistance were calculated. Hemodynamic findings were

Figure 3. Fluoroscopic view of the implantation procedure (a-c). Color Doppler view of implanted AFR device on TEE (d)

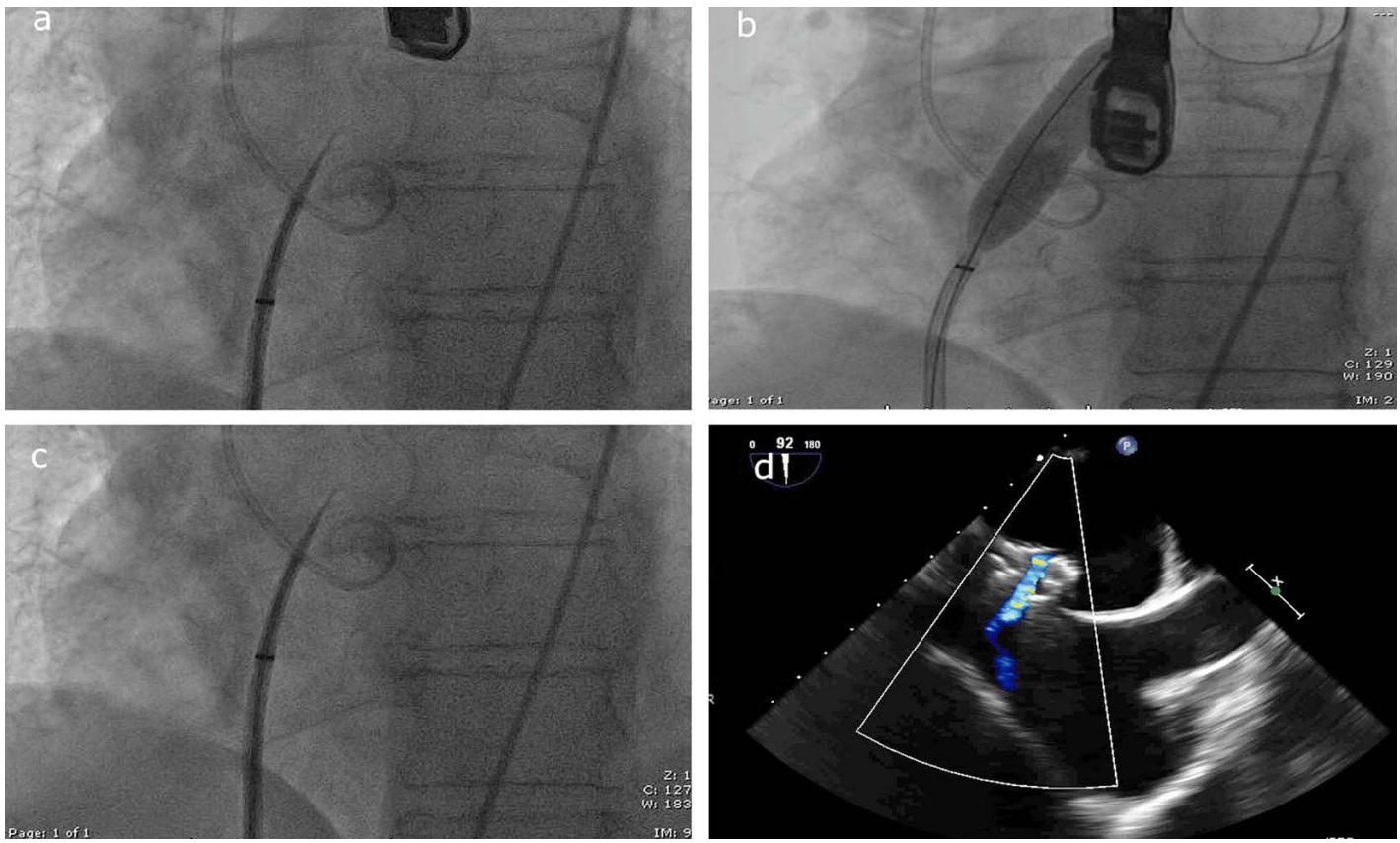

Table 2. Baseline characteristics of study population

Variable	HFrEF patients, n=27	HFpEF patients, n=12
Demographic features		
Age, yrs	68.3±7.1	70.6±7.2
Gender, males	18 (66.7)	7 (58.3)
BMI, kg/m^2, IQR	26.61 (23.30–28.98)	29.07 (26.17–32.38)
Medical History		
Hypertension	18 (67)	9 (75)
Dyslipidemia	8 (30)	2 (17)
Diabetes mellitus	10 (37)	7 (58)
CAD	13 (48)	7 (58)
CABG	1 (4)	2 (17)
AF	11 (41)	4 (33)
COPD	2 (7)	0 (0)
Stroke	0 (0)	0 (0)
Thyroid disease	4 (15)	3 (25)
Medications		
Beta- blockers	24 (89)	12 (100)
MRA	19 (70)	4 (33)
ACEI/ARB	15 (56)	10 (83)
ARNI	1 (4)	0 (0)
Ivabradine	3 (11)	0 (0)
Digoxin	7 (26)	2 (17)
Statin	7 (26)	4 (33)
Oral nitrate	6 (22)	4 (33)
Warfarin	2 (7)	0 (0)
DOAC	7 (26)	7 (58)
Amiodarone	8 (30)	4 (33)
SSRI	5 (19)	2 (17)

Data are mean±SD, median with 25th –75th interquartile range, or n (%). ACEI, angiotensin convertase enzyme inhibitory; AF- atrial fibrillation; ARB;angiotensin receptor blocker; ARNI-angiotensin receptor neprilysin inhibition; BMI;body mass index; CABG;coronary artery bypass grafting; CAD– coronary artery disease; COPD; chronic obstructive pulmonary disease; DOAC; direct oral anticoagulation; MRA; mineralocorticoid receptor antagonist; SSRI- selective serotonin receptor inhibition.

Table 3. Baseline clinical, laboratory and echocardiographic characteristics

Variable	HFrEF patients, n=27	HFpEF patients, n=12
Clinical features		
NYHA III, n (%)	25 (93)	11 (92)
NYHA IV, n (%)	2 (7)	1 (8)
6MWTD, m	165 (982-31)	175 (105-280)
KCCQ-OS	59.53 (51.72–72.60)	54.96 (38.35–74.69)
SBP, mmHg	119 (106-130)	131 (112-154)
DBP, mmHg	72 (60-82)	70 (62-76)
Echocardiographic findings		
LVEF	27.0 (21.0–31.3)	48.6 (40.5–55.8)
LVED diameter, mm	62.23 (53.93–70.25)	56.61 (51.50–61.00)
LVES diameter, mm	51.83 (43.53–57.88)	40.19 (33.72–48.30)
Left atrial diameter, mm	41.0 (36.8–44.0)	42.0 (40.0–45.0)
Mitral valve E/E` ratio	9.61 (5.98–11.84)	13.44 (8.81–17.44)
TAPSE, cm	2.24 (1.60–2.77)	2.17 (1.83–2.44)
Laboratory findings		
Hemoglobin, g/dl	13.45 (11.32–15.20)	12.61 (11.62–13.59)
Serum creatinine, mg/dl	1.15 (092–1.45)	0.97 (0.82–1.08)
eGFR, ml/min	65.24 (43.50–81.37)	72.25 (64.00–82.74)
BUN, mg/dl	26.01 (19.40–30.89)	21.28 (14.49–26.64)
Bilirubin, total, mg/dl	0.57 (0.26–0.95)	0.39 (0.22–0.67)
BNP, pg/mL	921 (147.85–1329.30)	334 (117.10–239.4)

Data are median with 25th – 75th interquartile range or n (%). 6MWTD, 6 min walking test distance; BNP, brain natriuretic peptide; DBP, diastolic blood pressure; BUN, blood urine nitrogen; eGFR, estimated glomerular filtration rate; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire Overall Score; LVEF, left ventricular ejection fraction; LVED, left ventricular end-diastolic; LVES, left ventricular end-systolic; NYHA, New York Heart Association; SBP, systolic blood pressure; TAPSE, tricuspid annular plane systolic excursion.

used to confirm subjects' study eligibility. Device sizing was performed according to hemodynamic and clinical data as well as atrial septal thickness (Figure 3). Transseptal puncture was performed with TEE guidance and under general anesthesia. After the transseptal puncture, unfractionated heparin was given intravenously to achieve an activated clotting time (ACT) >250 sec, and a stiff wire was placed in the left upper pulmonary vein. The puncture site in the septum was predilated by balloon inflation to a diameter 2 mm larger than the intended shunt, i.e., the AFR device diameter. After the AFR device was loaded onto the pusher, the AFR was advanced through the delivery sheath into the left atrium. Following appropriate positioning of the left atrial disc, the right atrial disc was deployed. Before releasing the device from its pusher, the Minnesota maneuver [10] was used to test device stability, and TEE was performed to confirm correct device position and patency. Following device placement, right and left heart catheterizations were repeated.

During the first 3 mos after implantation, patients received oral clopidogrel 75 mg and acetylsalicylic acid 100 mg OD. Thereafter, acetylsalicylic acid 100 mg OD was recommended for patients not on anticoagulation. If a patient needed anticoagulation for any reason, daily clopidogrel 75 mg was added. Standard endocarditis prophylaxis was administered during the procedure and for a minimum of 6 mos following implantation.

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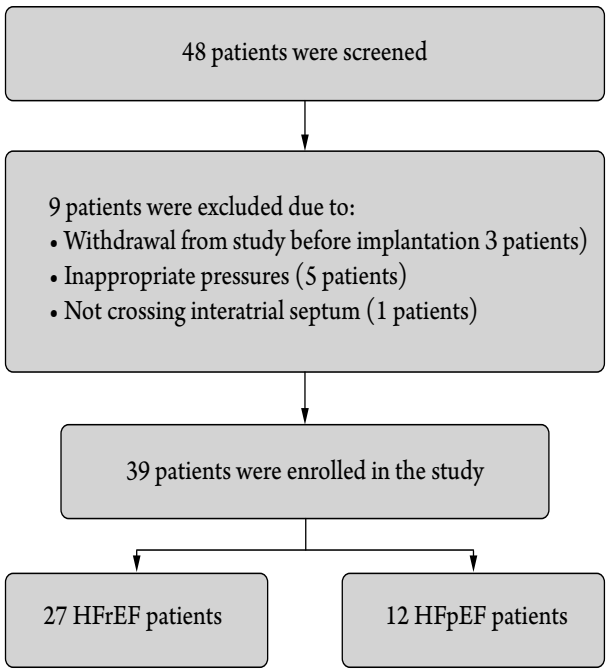
Table 4. Procedural characteristics

Variable	HFrEF patients	HFpEF patients
Implantation success, n (%)		
Device fenestration diameter		
8 mm	22 (82)	11 (92)
10 mm	5 (19)	1 (8)
Device waist height		
5 mm	27 (100)	10 (83)
10 mm	0 (0)	2 (17)
Procedural duration		
Balloon atrial septostomy duration, min	10 (4-14)	9 (4-14)
Device implantation duration, min	4 (3-5)	4 (3-6)
Overall catheterization duration, min	86 (70-103)	89 (71-105)
Fluoroscopy time, min	23 (18-27)	21 (16-27)
Qp/Qs ratio immediately after implantation of AFR	1.23±0.29, n=22	1.18±0.37, n=10
Qp/Qs ratio at 3 mos	1.32±0.39, n=22	1.12±0.32, n=10
Left-to-right shunt flow at 3 mos	22 (100)	10 (100)
Periprocedural TEE	25 (100)	12 (100)

Data are mean±SD, median with 25th –75th interquartile range, or n (%). AFR, atrial flow regulator; TEE, transesophageal echocardiog raphy.

Figure 4. Flowchart of study population



Statistical methods

Normally distributed continuous variables are reported as mean±standard deviation, skewed continuous variables are presented as median with interquartile ranges (25th–75th), and categorical variables are expressed as percentiles. Paired t-tests were used for group comparisons if the paired means distribute normally, otherwise the Wilcoxon Signed Rank test was used. All statistical analyses were 2-tailed and $p<0.05$ was considered statistically significant. All statistical analyses were performed with SPSS version 22.

Results

Study Populations and Baseline Characteristics

A flowchart showing patient enrollment is shown in Figure 4. A total of 48 patients were screened and 39 patients were enrolled in the study at our center. Twenty-seven (69.2%) patients were in the HFrEF group and 12 (30.8%) patients were in the HFpEF group. Eighteen (66.7%) HFrEF patients and 7 (58.3%) HFpEF patients were male. The median age of the HFrEF population was 68.3±7.1 yrs and 70.6±7.2 yrs in the HFpEF population. Additional study population information and characteristics are listed in Table 2.

Procedural results

Procedural data are summarized in Table 3. Overall catheterization times were similar in both groups (HFrEF: 86 (70–103) min and HFpEF: 89 (71–105) min. The AFR device with an inner fenestration diameter of 8 mm (HFrEF: 81% and HFpEF: 92%) and a height of 5 mm (HFrEF: 100% and HFpEF: 83%) was used in most of the study population (Table 4). The final opening size was assessed by intra-procedural TEE in terms of device recoiling. We did not observe any recoiling of the devices. Left-to-right shunting through the device was documented immediately after deployment in all patients, and device patency was 100% at the 3-mo follow up, as assessed by TEE or TTE.

Safety events at the 3-mo follow up examination

Safety data are summarized in Table 5. Adverse device effects were seen in two HFrEF patients (injection site reaction and paresthesia) and all had resolved. No adverse device events and deaths were seen in the HFpEF patients. One HFrEF patient died within 1 wk after device implantation due to pneumonia and septicemia. SAEs were observed in 12 (44.4%) HFrEF and 4 (33.3%) HFpEF patients. Worsening heart failure was observed in 3 (11.1%) patients, all in the HFrEF group. Iliac vein thrombosis occurred in one HFrEF patient. Acute arterial deoxygenation was not reported, and all patients were discharged after implantation. Procedure related serious adverse effects (SAEs) were observed in 2 patients (5.1%), all in the HFrEF group. No strokes/transient ischemic attacks (TIA), myocardial infarctions, or complications requiring device removal were seen in either group. Device patency was maintained in all patients at the 3-mo follow-up examination.

Table 5. Adverse events during 3-month follow-up

Event	HFrEF patients, n=27	HFpEF patients, n=12	All patients, n=39
Hospitalization for worsening HF	3 (11.1)	0 (0)	3 (7.7)
Death	1 (3.7)	0	1 (2.6)
Stroke or TIA	0	0	0
Myocardial infarction	0	0	0
Device removal	0	0	0
Procedure-related SAE	2	0	2
SADE	0	0	0
SAE rate, total numbers of events	30	10	1
Patients with SAE	12 (44.4)	4 (33.3)	16 (41.0)
AE rates, total number of events,	23	43	66
Patients with AE	4 (14.8)	11 (91.7)	15 (38.5)
ADE total number	2	0	2
Patients with ADE	2 (7.4)	0	2 (5.1)

Data are n (%). ADE, adverse device event (s); AE, adverse event (s); HF, heart failure; SADE, serious adverse device event (s); SAE, serious adverse event (s); TIA, transient ischemic attack.

Impact on hemodynamic parameters. HFrEF population

Detailed hemodynamic variables are summarized in Table 6. Compared with pre-implantation, PAWP and LVEDP were significantly reduced at 3 mos (p=0.007 and p=0.01, respectively). There was no difference between pre-implantation and 3-mos cardiac output (p=0.45). No significant difference existed between post-implantation Qp/Qs and Qp/Qs calculated at 3 mos (1.23±0.29 vs. 1.32±0.39, respectively). Mean pulmonary pressure decreased mildly but not significantly (p>0.99). There was no increased in RA pressure at 3 mos compared with baseline (median 10.00 vs. 9.33, respectively, p=0.70) (Figure 5).

HFpEF population

PAWP was significantly improved at 3 mos, from median 18 to 10 mmHg (p=0.03). There was no change in cardiac output at 3 mos compared with baseline, median 4.67 vs 4.99 l/min, respectively (p=0.67). Median mean pulmonary arterial pressure decreased from 28 to 23 mmHg, but it was not statistically significant (p=0.39). No significant difference was observed between pre-implantation and 3-month mean right arterial pressure (p=0.80) (Figure 6).

Discussion

We assessed the impact of AFR device implantation on hemodynamic parameters in both HFrEF and HFpEF patients. Device implantation were performed without any complications in either group. No events requiring device removal occurred after implantation. At 3 mos, device patency was present in all assessed cases. A left-to right shunt was seen immediately after device placement and at 3 mos. No acute or chronic arterial deoxygenation was observed after AFR device deployment nor during the 3-mo follow up period.

Two different situations show that left atrial decompression may be effective in heart failure. The first is Lutembacher's syndrome, which is defined as the concomitant rheumatic mitral stenosis and atrial septal defect [11]. This combination is associated with a relatively small increase in left atrial pressure during rest and effort, and a delay in the onset of dyspnea compared to isolated mitral

Table 6. Invasive measurements

Variable	HFrEF patients, baseline, n=24	HFrEF patients, at 3 mos, n=24	p, value	HFpEF patients, baseline, n=10	HFpEF patients, at 3 mos, n=10	p
RAP, mmHg	9.33 (5.25-12.75)	10.00 (4.50-12.75)	0.70	10.90 (7.25-14.25)	10.80 (3.25-19.50)	0.80
PAP, mmHg	29 (18-33)	24 (16-29)	1.00	28 (20-36)	23 (11-33)	0.39
Systolic PAP, mmHg	43 (29-54)	41 (35-47)	0.91	45 (30-56)	43 (32-56)	0.96
CO, l/min	4.45 (3.48-4.79)	4.91 (3.80 -5.05)	0.45	4.67 (3.86-5.44)	4.99 (4.01-5.55)	0.65
PCWP, mmHg	19 (16-24)	14 (8-18)	0.007	18 (17-21)	10 (4-17)	0.037
LVEDP, mmHg	18 (14-22)	14 (8-18)	0.01	16 (14-21)	11 (4-17)	0.10
Systolic aortic pressure, mmHg	136 (124-151)	140 (119 – 155)	0.88	154 (135-173)	152 (132-173)	0.88
Diastolic aortic pressure, mmHg	74 (64-82)	76 (64 – 88)	0.91	74 (56-88)	75 (59-93)	0.88

Data are median with 25th – 75th interquartile range, CO, cardiac output; LVEDP, left ventricular end-diastolic pressure; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure.

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НОРМАЛИЗАЦИЯ ЛИПИДНОГО СПЕКТРА[3,4]

СНИЖЕНИЕ РИСКА СЕРДЕЧНО-СОСУДИСТЫХ СОБЫТИЙ[5,6]

Супрозафен. **Регистрационный номер:** ЛП-006619. **Группировочное наименование:** розувастатин + фенофибрат. **Лекарственная форма:** таблетки, покрытые пленочной оболочкой, 5 мг +145 мг, 10 мг + 145 мг. **Показания к применению:** лекарственный препарат Супрозафен предназначен для применения у взрослых пациентов, которым показан одновременный прием розувастатина и фенофибрата в соответствующих дозах, при наличии следующих дислипидемий: – первичная гиперхолестеринемия (тип IIa по классификации Фредриксона) или смешанная гиперхолестеринемия (тип IIb по классификации Фредриксона) в качестве дополнения к диете, когда диета и другие немедикаментозные методы лечения (например, снижение массы тела, физические упражнения) оказываются недостаточными; – гипертриглицеридемия (тип IV по классификации Фредриксона) в качестве дополнения к диете. Лекарственный препарат Супрозафен не должен применяться для стартовой терапии у пациентов, ранее не получавших гиполипидемические лекарственные средства. **Противопоказания:** гиперчувствительность к розувастатину, фенофибрату или любому компоненту препарата; возраст до 18 лет (эффективность и безопасность не установлены); тяжелые нарушения функции печени: класс С по классификации Чайлд-Пью (10-15 баллов по шкале Чайлд-Пью), включая билиарный цирроз и персистирующее нарушение функции печени неясной этиологии; заболевания печени в активной фазе, включая стойкое повышение сывороточной активности трансаминаз и любое повышение активности трансаминаз в сыворотке крови (> 3 раза по сравнению с верхней границей нормы (ВГН)); тяжелое и умеренное нарушение функции почек (КК ниже 60 мл/мин); миопатия; предрасположенность к развитию миотоксических осложнений; миотоксичность на фоне применения ингибиторов ГМГ-КоА-редуктазы или фибратов в анамнезе; наличие в анамнезе фотосенсибилизации или фототоксичности при лечении фибратами или кетопрофеном; заболевания желчного пузыря в анамнезе; хронический или острый панкреатит, за исключением случаев острого панкреатита, обусловленного выраженной гипертриглицеридемией; одновременный прием лекарственного препарата Супрозафен и циклоспорина, других фибратов или других ингибиторов ГМГ-КоА-редуктазы (правастатин, аторвастатин, симвастатин и т.д.); у женщин: беременность, период грудного вскармливания, отсутствие адекватных методов контрацепции; врожденная галактоземия, непереносимость лактозы, недостаточность лактазы, нарушение всасывания глюкозы и галактозы (препарат содержит лактозу); врожденная фруктоземия, недостаточность сахаразы-изомальтазы, синдром глюкозо-галактозной мальабсорбции (препарат содержит сахарозу). **С осторожностью:** почечная недостаточность легкой степени тяжести, одновременный прием пероральных антикоагулянтов, возраст старше 65 лет, состояния, при которых отмечено повышение плазменной концентрации розувастатина, расовая принадлежность (азиатская раса), заболевания печени в анамнезе, сепсис, артериальная гипотензия, обширные хирургические вмешательства, травмы, тяжелые метаболические, эндокринные или электролитные нарушения или неконтролируемые судорожные припадки. **Применение при беременности и в период грудного вскармливания:** прием Супрозафена противопоказан при беременности и в период лактации. Фертильность: Клинические данные по влиянию препарата на фертильность у людей отсутствуют. Беременность: нет достаточных данных о применении фенофибрата у беременных. В случае возникновения беременности в процессе терапии, прием препарата Супрозафен должен быть прекращен немедленно. Период грудного вскармливания: Прием препарата Супрозафен в период грудного вскармливания противопоказан. При необходимости применения при лактации, грудное вскармливание необходимо прекратить. **Способ применения и дозы*:** внутрь, в любое время суток, независимо от времени приема пищи. Таблетку проглатывают целиком, не разжевывая и не измельчая, запивая водой. До начала терапии препаратом Супрозафен пациент должен начать соблюдать стандартную гипохолестеринемическую диету и продолжать соблюдать ее во время лечения. Препарат Супрозафен принимают по 1 таблетке один раз в сутки. Рекомендуемая начальная доза препарата Супрозафен составляет 5 мг + 145 мг 1 раз в сутки. В случае необходимости доза препарата может быть увеличена через 4 недели до максимальной дозы 10 мг +145 мг 1 раз в сутки. Пожилые пациенты. Коррекции дозы не требуется. Необходим мониторинг функции почек данной категории пациентов. Пациенты с нарушением функции почек. У пациентов с почечной недостаточностью легкой степени тяжести коррекция дозы не требуется. Препарат Супрозафен следует применять с осторожностью у пациентов с почечной недостаточностью легкой степени тяжести. У пациентов с умеренной и тяжелой почечной недостаточностью применение препарата Супрозафен противопоказано. Пациенты с нарушением функции печени. Препарат Супрозафен противопоказан пациентам с заболеваниями печени в активной фазе и с тяжелыми нарушениями функции печени. Этнические группы. При изучении фармакокинетических параметров розувастатина у пациентов разных этнических групп отмечено увеличение системной концентрации розувастатина у японцев и китайцев. Генетический полиморфизм. Для носителей генотипов с.521CC или с.421AA рекомендуемая максимальная доза розувастатина составляет 20 мг один раз в сутки. Сопутствующая терапия. При одновременном применении препарата Супрозафен с лекарственными препаратами, повышающими концентрацию розувастатина в плазме крови, может повышаться риск миопатии, включая рабдомиолиз. В таких случаях следует оценить возможность назначения альтернативной терапии или временного прекращения применения препарата Супрозафен. Дети. Препарат Супрозафен противопоказан к применению у детей в возрасте до 18 лет. **Побочное действие*:** со стороны эндокринной системы: сахарный диабет 2 типа; со стороны нервной системы: головная боль, головокружение; со стороны желудочно-кишечного тракта: боль в животе, рвота, диарея, метеоризм, тошнота, запор; со стороны печени и желчевыводящих путей: повышение активности сывороточных трансаминаз; со стороны скелетно-мышечной и соединительной ткани: миалгия; общие расстройства и нарушения в месте введения: астенический синдром; лабораторные и инструментальные данные: повышение уровня гомоцистеина крови. При приеме ингибиторов ГМГ-КоА-редуктазы сообщалось о побочных эффектах: депрессия, нарушения сна, включая бессонницу и «кошмарные» сновидения, сексуальная дисфункция, гипергликемия, повышение уровня гликированного гемоглобина. Описание отдельных нежелательных реакций при применении розувастатина: со стороны почек и мочевыводящей системы: протеинурия; со стороны скелетно-мышечной системы и соединительной ткани: миалгия, миопатия (включая миозит); лабораторные показатели: при приеме розувастатина отмечали изменения лабораторных показателей: повышение концентрации глюкозы, билирубина, активности гамма-глютамилтранспептидазы, щелочной фосфатазы, нарушения функции щитовидной железы. Перечень всех побочных действий представлен в инструкции по медицинскому применению. **Передозировка*:** Информация о передозировке для лекарственного препарата Супрозафен отсутствует. Розувастатин: при одновременном приеме нескольких суточных доз фармакокинетические параметры розувастатина не изменяются. Лечение: симптоматическое. Фенофибрат: есть единичные сообщения о передозировке, о симптомах не сообщалось. Лечение: симптоматическое. **Взаимодействие с другими лекарственными средствами*:** при приеме фенофибрата одновременно со статинами (правастатин, симвастатин, аторвастатин) или другими фибратами повышается риск серьезного токсического воздействия на мышцы. Дозу розувастатина корректируют при необходимости его совместного применения с лекарственными средствами, увеличивающими экспозицию к розувастатину. Требуется соблюдать особую осторожность при применении с антацидами, гемфиброзилом и другими гиполипидемическими средствами, ингибиторами транспортных белков, ингибиторами протеазы вируса иммунодефицита человека (ВИЧ), изоферментами цитохрома Р450, фузидовой кислотой, циклоспорином, эзетимибом, эритромицином, антагонистами витамина К, пероральными контрацептивами/гормон заместительной терапией, пероральными антикоагулянтами, производными тиазолидиндиона (глитазонами), секвестрантами желчных кислот, эстрогенами. **Особые указания*:** перед назначением препарата Супрозафен следует провести лечение для устранения причины вторичной гиперхолестеринемии. Розувастатин. Почечные эффекты: у пациентов, получавших высокие дозы розувастатина (в основном 40 мг), наблюдалась канальцевая протеинурия. Определение креатинфосфокиназы: терапия должна быть прекращена, если уровень КФК значительно увеличен (> 5 раз по сравнению с ВГН) или если симптомы со стороны мышц резко выражены и вызывают ежедневный дискомфорт. Печень: прием розувастатина прекратить или уменьшить дозу, если активность трансаминаз в сыворотке крови в 3 раза превышает ВГН. Ингибиторы протеаз: не рекомендуется совместное применение с ингибиторами протеаз. Интерстициальное заболевание легких: при подозрении на интерстициальное заболевание легких следует прекратить терапию препаратом Супрозафен. Сахарный диабет 2-го типа: при концентрации глюкозы от 5,6 до 6,9 ммоль/л терапия розувастатина ассоциировалась с повышенным риском развития СД 2-го типа. Фенофибрат. Функция печени: пациенты, у которых на фоне лечения повысилась активность «печеночных» трансаминаз, требуют внимания, и в случае повышения активности АЛТ и АСТ >3 раза по сравнению с ВГН прием препарата прекращают. При появлении симптомов гепатита (желтуха, кожный зуд) следует провести лабораторные исследования и, в случае подтверждения диагноза гепатит, отменить препарат. Панкреатит: описаны случаи развития панкреатита в период лечения фенофибратом. Мышцы: токсическое влияние на мышечную ткань может быть заподозрено на основании жалоб пациента на слабость, диффузную миалгию, миозит, мышечные спазмы и судороги и/или выраженного повышения активности КФК (более чем в 5 раз выше ВГН). В этих случаях лечение препаратом Супрозафен необходимо прекратить. Почечная функция: при повышении концентрации креатинина > 50 % выше ВГН лечение следует приостановить. Гематологические нарушения: после начала терапии фенофибратом наблюдалось легкое или умеренное снижение уровня гемоглобина, снижение гематокрита и уменьшение числа лейкоцитов. Сообщалось о возникновении тромбоцитопении и агранулоцитоза у отдельных пациентов, получавших фенофибрат. Гиперчувствительность немедленного типа: в случае, если наблюдаются признаки или симптомы гиперчувствительности немедленного типа, необходимо немедленно обратиться к врачу и прекратить применение препарата. Гиперчувствительность замедленного типа: при подозрении на серьезные нежелательные реакции со стороны кожи необходимо прекратить прием и проводить специфическое лечение. Парадоксальное снижение ЛВП: при выраженном снижении содержания ЛВП следует отменить препарат и контролировать содержание ЛВП до возвращения к исходным значениям. Вспомогательные вещества: препарат Супрозафен содержит лактозу и сахарозу, его не следует применять при лактазной недостаточности, непереносимости галактозы и глюкозо-галактозной мальабсорбции, врожденной фруктоземии, недостаточности сахаразы-изомальтазы, синдроме глюкозо-галактозной мальабсорбции. **Влияние на способность управлять транспортными средствами, механизмами:** следует соблюдать осторожность при управлении автотранспортом или работе, связанной с повышенной концентрацией внимания и психомоторной реакцией (риск развития головокружения). **Условия отпуска:** отпускают по рецепту. ***Полная информация представлена в инструкции по медицинскому применению.** СИП от 19.03.2021 на основании ИМП ЛП-006619 от 04.12.2020

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stenosis. The same volume of blood may lead to lower pressure in the right atrium compared to the left atrium due to greater right atrial distensibility [12]. This theory was supported by Little's anatomical study in isolated canine hearts [13]. Similar results were reported in post-MitraClip (Abbott, Chicago, USA) cases performed by the transseptal route. Recent publications demonstrated that hemodynamic and clinical results may be effective in selected MitraClip cases with persistent iatrogenic septal defects. In a study by Ikenaga et al., although left atrial pressure was higher in post-MitraClip patients with persistent iatrogenic atrial septal defect (iASD) compared to those without iASD, the lack of difference between NYHA FC and brain natriuretic peptide (BNP) values indicated that left atrial decompression may be beneficial [14]. In the MITHRAS study, percutaneous closure of the iASD following transcatheter mitral valve repair was compared with conservative treatment. Patients with Qp/Qs >1.3 were included in the study. At 5-mo follow-up, there were no differences in terms of 6MWDT, NHYA class and peripheral edema between groups [15]. The second situation is the effect of atrial septal defect (ASD) closure on left ventricular and atrial hemodynamics in adults [16], where it was shown that ASD closure triggers left heart failure in patients with high left ventricular end-diastolic pressures. In light of the data obtained from these two contrasting situations but with similar results, it can be postulated that interatrial shunt devices may be effective in treating isolated left heart failure [17].

The main concerns regarding left atrial decompression with interatrial shunt devices are:

1) successful implantation and stability of the device;
2) long-term shunt patency;
3) the risk of paradoxical embolism;
4) right heart volume overload and increased pulmonary pressure at the long-term follow-up;
5) decrease in left ventricle output.

The shunt diameter of the Ventura V-Wave device is 5 mm. The first generation version of this device contained a bioprosthetic valve, and stenosis or occlusion of the shunt was seen in 50% of subjects at 1-yr follow up [18]. After examination of an explanted heart, it was found that the occlusion/stenosis was associated with the bioprosthetic valve rather than due to thrombus. V-Wave designed a second generation device without a bioprosthetic valve. Shunt patency was maintained with this device for up to 1 yr [19].

The InterAtrial Shunt Device (IASD) has a shunt diameter of 8 mm. This device has been studied in HFpEF patients [20]. Shah et al. could not find any evidence of shunt stenosis/shunt occlusion at 12 mos [21].

To date, no cases of paradoxical embolism have been reported in post-MitraClip patients despite having relatively

Figure 5. Temporal changes in PAP (a), mean RAP (b), CO (c) and mean PAWP (d) in HFrEF patients

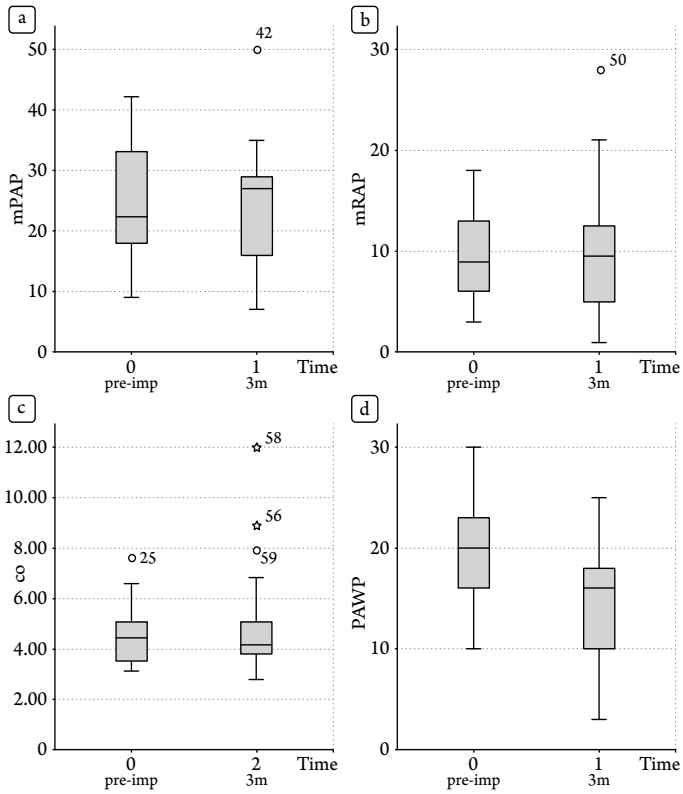
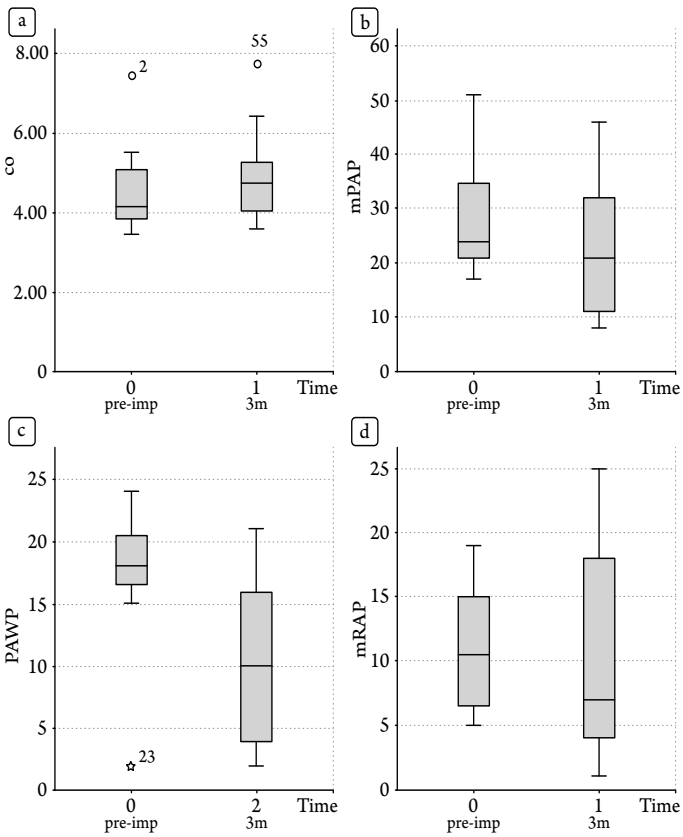


Figure 6. Temporal changes in CO (a), mean PAP (b), PAWP (c) and mean RAP (d) in HFpEF patients



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larger iASD [22]. In studies of two different interatrial shunt devices, Del Trigo et al. [8] and Feldman et al. [23] reported no events associated with paradoxical embolism or device thrombus.

An increase in pulmonary artery pressure as a result of volume overload created by the left-right shunt is another concern. However, as known from congenital heart disease patients, small defects, e.g., an ASD of 10 mm, are not associated with deleterious hemodynamic effects during a long-term follow-up period [24]. These data were confirmed in a simulation study by Kaye et al. [25]. They observed that the interatrial shunt with a diameter of 8–9 mm provided a significant decrease in PAWP without serious volume loading in the right ventricle or a serious decrease in left ventricular output [25]. The lumen diameters of the AFR device are 8 and 10 mm. In the present study, 33 (85%) patients were implanted with an AFR device with a diameter of 8 mm. An AFR with a diameter of 10 mm was implanted in patients whose resting left ventricular end-diastolic pressure was less than 15 mmHg but with exercise LVEDP equal to or greater than 25 mmHg. The Qp/Qs ratio was 1.32±0.39 in the HFrEF group and 1.12±0.32 in the HFpEF group at the end of 3 mos. There was no significant decrease in resting cardiac output in either group at the end of 3 mos (HFrEF: 4.45 (3.48–4.79) vs 4.91 (3.80–5.05) p=0.45; HFpEF: 4.67 (3.86–5.44) vs 4.99 (4.01–5.55), p=0.65). Compared to the basal value, a significant decrease was observed in PAWP at the end of 3 mos in both groups (HFrEF: 19 (16-24) mmHg vs 14 (8-18) mmHg, p=0.007; HFpEF: 18 (17-21) mmHg vs. 10 (4-17) mmHg, p=0.037).

Study limitations

This study has several limitations. First, this was an open label, non-randomized trial. The results are limited by being conducted at one center and with a small sample size. Second, the follow-up period was restricted to 3 mos after the procedure. The PRELIEVE study is ongoing, and further results will be available in the future. Third, the study was a single-arm trial, and we could not compare these results with placebo therapy.

Conclusion

Regardless of left ventricular ejection fraction, AFR implantation decreased left ventricle filling pressure without a deleterious impact on cardiac output or on right heart function.

No conflict of interest is reported.

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