



CASE REPORT

Atrial Flow Regulator: A New Player for the Treatment of Refractory Heart Failure

Vincenzo Rizza, MD^{1,2*}, Giuseppe Uccello, MD², Francesco Federico, MD^{1,2}, Mariano Pellicano, MD, PhD², Maurizio Tespili, MD² and Alfonso Ielasi, MD²



¹Vita-Salute San Raffaele University, Milan, Italy

²Clinical and Interventional Cardiology Unit, Istituto Clinico Sant'Ambrogio, Gruppo Ospedaliero San Donato, Milan, Italy

*Corresponding author: Vincenzo Rizza, MD, Vita-Salute San Raffaele University, Via Olgettina 58, 20132; Clinical and Interventional Cardiology Unit, Istituto Clinico Sant'Ambrogio, Gruppo Ospedaliero San Donato, Milan, Italy, Tel: +393290380627

Abstract

Described herein the case of a 55-year-old man diagnosed with advanced heart failure. He had a history of ischemic heart disease leading to moderate left ventricular systolic dysfunction, symptomatic for effort dyspnoea despite optimal medical therapy. After coronary angiography and right heart catheterization (showing basal pulmonary capillary wedge pressures - PCWP - 20 mmHg), the patient underwent percutaneous inter-atrial shunt therapy (IAST) through the opposition of an Atrial Flow Regulator (AFR) device (Occlutech™) to reduce left atrial pressures (LAP) and theoretically ameliorate his symptoms. LAP was acutely reduced after the procedure and the patient developed a significant clinical and functional improvement at 3 months.

Keywords

Heart failure, Atrial flow regulator, Inter-atrial shunt therapy, Inter-atrial shunt devices, Left atrial pressure

Introduction

Heart failure (HF) is a clinical syndrome characterized by typical symptoms (e.g. dyspnoea, orthopnoea or fatigue) and signs (pulmonary crackles or peripheral oedema) caused by a structural and or functional cardiac abnormalities, resulting in a reduced cardiac output and/or elevated intracardiac pressures [1]. HF is an irreversible, progressive disorder that affects more than 23 million people worldwide, including 1-2% of the whole adult population [2,3]. Coronary artery disease is a common cause of HF and both conditions share several risk factors such as obesity,

arterial hypertension and diabetes mellitus [4]. HF is a leading cause of hospitalization and it confers a substantial burden to the healthcare system: in the U.S. the total medical costs for patients with HF are expected to rise from US\$20.9 billion in 2012 to \$53.1 billion by 2030 [4]. Both, morbidity and mortality are increased and some prognostic models have been proposed in order to predict patients' clinical outcomes [4,5]. Patients with HF and reduced ejection fraction (HFrEF) usually benefit from drug therapy consisting of angiotensin-converting-enzyme inhibitors, angiotensin receptor-neprilysin inhibitors (ARNI), beta-blockers, mineralocorticoid receptor antagonists, inhibitors of sodium-glucose co-transporter-2 (SGLT2) and, in selected cases, from non-pharmacological approaches (e.g. cardiac resynchronization therapy in subjects with left ventricular ejection fraction (LVEF) ≤ 35% and complete left bundle branch block (LBBB) [1,6,7]. Instead, up to nowadays, there is no substantiated effective treatment for HF and preserved ejection fraction (HFpEF). Increased left atrial pressure (LAP) is thought to be the common final pathological way to cause decompensated HF symptoms, even in patients treated with optimal medical management [8]. Dorfs, et al. showed that pulmonary capillary wedge pressure (PCWP) at rest and an excessive rise of this parameter during physical exercise are associated with increased mortality in a group of 355 patients with HFpEF [9]. Inter-atrial shunt therapy (IAST) has been recently proposed

as an innovative strategy to reduce LAP and PCWP in patients with advanced HF in order to ameliorate symptoms and improve functional status [10-12].

Case Report

A 55-year-old man, hypertensive with type 2 insulin-dependent diabetes mellitus, dyslipidaemia and obesity (BMI: 33.96 kg/m²) underwent clinical evaluation because of more-than-3-month effort dyspnoea (NYHA III). His past medical history consisted of prior anterior ST-elevation myocardial infarction (STEMI) treated by percutaneous coronary intervention (PCI) with drug-eluting stent (DES) implantation on the left descending artery (LDA) and on the posterolateral artery (PLA). At follow-up, both DES resulted occluded while another PCI with DES implantation was performed on the obtuse marginal artery (OM1) due to a symptomatic critical CAD. A subsequent stress cardiac magnetic resonance (CMR) showed a moderate LV dysfunction (LVEF 40%) without viability of the left ventricular apex and the anterior wall. The patient was on optimal medical therapy including beta-blockers, ARNI, SGLT-2 inhibitor, diuretic, mineralocorticoid receptor antagonist). According to the recent 2021 ESC Guidelines on HF, the patient was diagnosed with advanced heart failure [1]: he presented typical symptoms of HF with persisting high N-terminal

prohormone of Brain Natriuretic Peptide (NT-proBNP) and evident cardiac structural abnormalities; moreover, he had 4 episodes of pulmonary congestion requiring hospitalization, the last registered 6 months before, and developed a severe inability even to low-grade exercise. Due to this clinical scenario, the patient was admitted to our Cardiology Unit. Baseline transthoracic echocardiography confirmed left ventricle systolic impairment (LVEF 40%), but showed no right heart dysfunction nor severe pulmonary hypertension (e.g. pulmonary artery systolic pressure - PASP - \geq 60 mmHg). Estimated ultrasonographic LAP at rest was 26 mmHg. Coronary angiography confirmed an occlusive in-stent restenosis on the LAD and a critical stenosis in the right coronary artery treated by DES implantation. Right heart catheterization reported mild pulmonary hypertension (PASP: 32 mmHg, diastolic pulmonary artery pressure - PAP: 24 mmHg, mean PAP: 27 mmHg) and increased PCWP at rest which was 20 mmHg. Based on these data the patient was considered a candidate for IAST using an 8-mm-diameter Atrial Flow Regulator device (Occlutech™). The procedure was successfully performed under general anaesthesia, through a hybrid fluoroscopic and transoesophageal echocardiographic guide. Procedural steps are described by Paitazoglou C, et al. [12] and are summarized in Figure 1. No

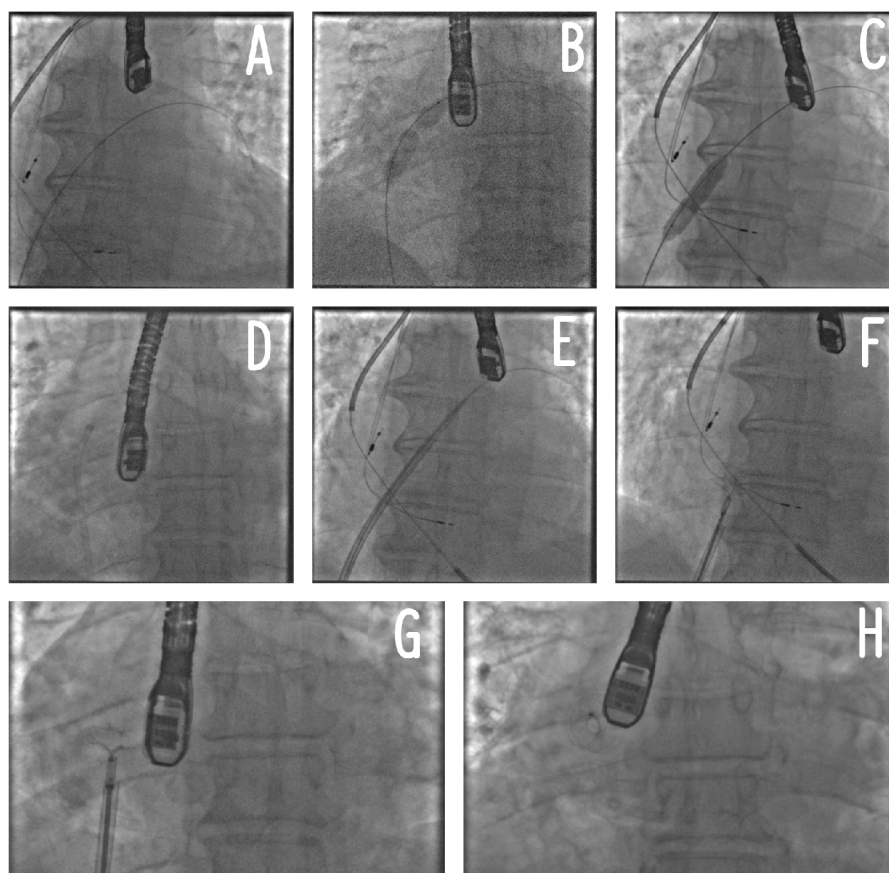


Figure 1: Procedural steps of AFR implantation. Panel A: positioning of a stiff wire in the left superior pulmonary vein; Panel B: atrial septostomy and septal dilatation (part 1); Panel C: septal dilatation (part 2); Panel D: crossing of the AFR delivery system through the septostomy inside the left atrium; Panel E: Advancement of the AFR delivery system inside the left atrium; Panel F: AFR initial release; Panel G: AFR traction test before complete release; Panel H: AFR complete release. AFR: Atrial Flow Regulator.

complications were reported and the LAP has been acutely reduced following the generation of an iatrogenic inter-atrial shunt (final Qp/Qs 1.2) (Figure 2 and Figure 3). Patient was discharged 2 days after the procedures on dual antiplatelet therapy in association with beta-blocker, ARNI, diuretic, mineralocorticoid receptor antagonist, SGLT-2 inhibitor.

At the 6-month follow-up visit, the patient showed an improvement of his own clinical status. He switched from NYHA III to NYHA II functional class. At transthoracic echocardiography, there was a preserved left-to-right atrial shunt without any right heart overload (TAPSE 21 mm, PAPs 30 mmHg). Ultrasonographic LAP has been reduced from 26 to 16 mmHg.

Discussion

HF is a progressive clinical syndrome characterized by reduced cardiac output and/or elevated cardiac pressures [1]. Patients with chronic HF usually present elevated LAP [8], especially at exercise, which leads to excessive rise in PCWP, and subsequently causes HF symptoms, like dyspnoea and reduced tolerance to physical activities [13,14]. Moreover, increased LAP might be the pathophysiological clue to justify the onset of decompensated symptoms in advanced HF. Experience in terms of IAST application in patients with HF is limited, but some scientific evidences indicate that the generation of an inter-atrial shunt is able to improve both clinics and haemodynamics in patients presenting elevated filling pressures. For example, the atrial septal defect (ASD) limits the risk of pulmonary congestion in patients affected by *Lutenbacher syndrome* with mitral

stenosis and, more interestingly, these subjects do not suffer from right HF or an increased risk of stroke at follow-up [15]. On the other hand, early HF onset with acute pulmonary congestion and atrial volume overload was observed in adult patients following transcatheter closure of ASD [16]. Invasive measurement of LAP, guiding medical therapy in patients with HFrEF, was associated with improved symptoms and higher decompensation-free survival [17].

IAST has been proposed as a novel strategy to reduce LAP and PCWP in order to ameliorate symptoms and improve functional status among patients with advanced HF [10-12,18]. Different IASDs (inter-atrial shunt devices) have been investigated in clinical trials: the Corvia Medical device (Corvia Medical Inc., Tewkesbury, MA, USA) produced a significant reduction of PCWP in patients with HFpEF in a small nonrandomized trial [18,19]; the V-Wave device (V-Wave Medical, CA, USA) demonstrated initial safety and early beneficial clinical and hemodynamic outcomes in patients with HFrEF although the benefits were compromised by impaired shunt patency on long-term follow-up [20]; the AFR led to improvement of symptoms and surrogate parameters of HF (NYHA functional class, quality of life assessed with the Minnesota Living With Heart Failure Questionnaire, distance covered at 6MWT) early at 6 months after implantation [21]. Each device was associated with a very low risk of post-procedure side adverse events [22]. Table 1 summarises the main characteristics and the clinical impact of the different percutaneous IASDs [23].

In IAST-based clinical trials, most HF patients

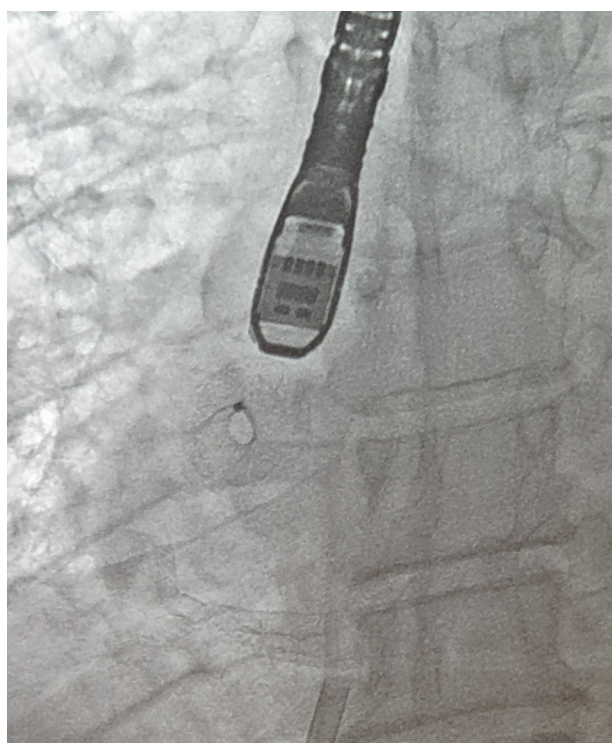


Figure 2: Fluoroscopic view of atrial flow regulator.

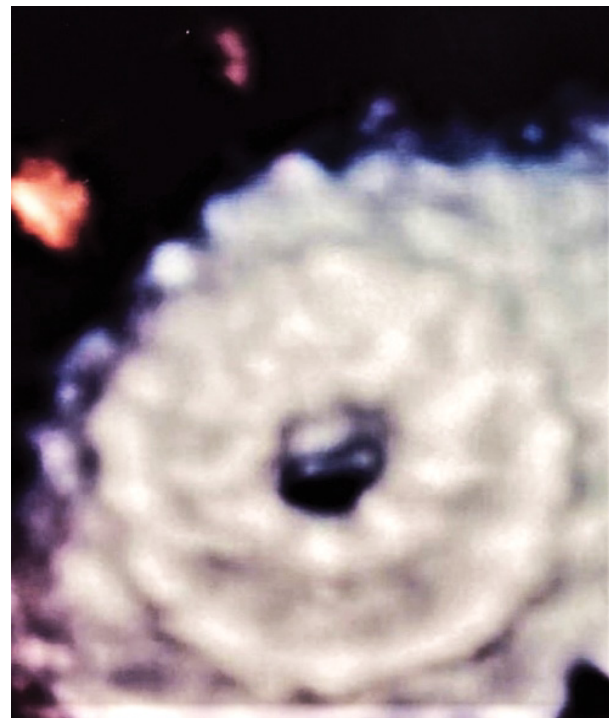


Figure 3: Zoomed 3D-Echocardiographic view of atrial flow regulator.

Table 1: Overview of studies about atrial shunt in patients affected by heart failure.

Reference	IASD	Population	Main inclusion criteria	Endpoints	Results
Sondegaard, et al. [23]	Corvia	n = 11 patients	<ul style="list-style-type: none"> • HFpEF (EF < 45%), • ≥ 1 HF hospitalisation in the last 12 months or persistent NYHA class III/IV for at least 3 months • Baseline PCWP at rest ≥ 15 mmHg or PCWP during exercise ≥ 25 mmHg. 	<p>Primary endpoint: SADEs up to 30 days.</p> <p>Secondary endpoints: procedural success and clinical benefit at 30 days.</p>	<p>No SADEs after 30 days;</p> <p>Procedural success rate: 100%;</p> <p>PCWP reduced by 28% (p = 0.005);</p> <p>NYHA class was improved by two classes in two patients, one class in five patients, and worsened by one class in one patient.</p>
Malek, et al. [19]	Corvia	n = 11 patients	<ul style="list-style-type: none"> • LVEF ≥ 45% and at least one HF hospitalization within the prior year, or with persistent NYHA III class symptoms • PCWP at rest ≥ 15 mmHg or during exercise ≥ 25 mmHg. 	Clinical and functional benefit at 1-year follow-up.	<p>Survival rate: 100%;</p> <p>Decrease of NYHA class (Class III/IV 45%/0% at 1 year vs. 82%/18% at baseline; p = 0.017);</p> <p>NS improvement of 6MWT and QoL.</p>
Hasenfuss, et al. [21]	Corvia	n = 68 patients	<ul style="list-style-type: none"> • Symptomatic (NYHA class II/III/IV) HFpEF (EF > 40%) • PCWP at rest ≥ 15 mmHg or PCWP during exercise ≥ 25 mmHg. 	<p>Primary endpoint: MACCE at 6 months.</p> <p>Secondary endpoint: clinical efficacy at 6 months.</p>	<p>No MACCE and sustained device patency at 6 months;</p> <p>Mean PCWP reduced at 6 months (at rest p = 0.0124, during exercise p = 0.0255).</p>
Del Trigo, et al. [20]	V-Wave	n = 10 patients	<ul style="list-style-type: none"> • HFrEF (LVEF < 40%) or NYHA class III or IV • PCWP at rest ≥ 15 mmHg. 	Safety or the procedure and potential efficacy up to 90 days.	<p>Procedural success rate: 100%;</p> <p>No procedural related SAE;</p> <p>Patency at 30 days: 100%;</p> <p>PCWP at rest reduced from 23 ± 5 to 17 ± 8 (p = 0.035);</p> <p>Improvement of NYHA class (from class III to class II in seven [78%] of nine patients, from class III to class I in one [11%] patient, and no change in one [11%] patient; p = 0.0004);</p> <p>Improvement of QoF, as assessed by the DAS1 (from a mean score of 13 to 24.8; p = 0.016) and the KCCQ (from a mean score of 44.3 to 79.1; p = 0.0001);</p> <p>Increase of 6MWT distance (from a mean of 244 m to 318 m; p = 0.016); one patient died (VT after 2 months)</p>

Feldman T, et al. [11]	Corvia	n = 44 patients (22 IASD, 22 control)	<ul style="list-style-type: none"> Symptomatic (NYHA class III or IV) HFpEF (EF \geq 40%) PCWP during exercise \geq 25 mmHg or RAP gradient \geq 5 mmHg. 	<p>Primary endpoints: ΔPCWP during exercise and at 30 days and MACCRE.</p> <p>Secondary endpoints: ΔPCWP and Δworkload at peak exercise need for explantation, clinical efficacy at 30 days.</p>	Procedural success rate: 95.5%; Δ PCWP during exercise significantly decreased (p = 0.028) and no MACCRE at 30 days; no need for explantation.
Paitazoglou C, et al. [12]	AFR	n = 53 patients	<ul style="list-style-type: none"> Symptomatic chronic HF (NYHA class III or IV) HFrEF (LVEF 15-39%) or HFpEF (LVEF \geq 40%) with elevated BNP ($>$ 125 pg/mL) PCWD or LVEDP \geq 15 mmHg or PCWP \geq 25 mmHg at exercise and CVP $<$ 20 mmHg 	<p>Primary endpoint: incidence of SADEs at 3 months following implantation.</p> <p>Secondary endpoints: SADEs between 3 and 12 months following implantation; left to right shunt through the AFR device at 12 months;</p> <p>Improvement in symptoms and hemodynamic parameters during at 12 months.</p>	<p>1 patient with 2 documented SADEs after the procedure with bleeding at the puncture site and loss of consciousness with prolonged hospitalisation, which resolved without sequelae;</p> <p>100% device patency at 1 year; improvement in terms of NYHA class (-1 ± 0.2 in HFrEF and -0.9 ± 0.2 at 1 year), distance in the 6MWT ($+50.5 \text{ m} \pm 20$ in HFrEF at 1 year), PCWP ($-5 \text{ mmHg} [-12.5, -1.5]$ in HFpEF already at 3 months) and QoL evaluated with the KCCQ ($+21.5 \pm 6.1$ in HFrEF and $+15.3 \pm 4.8$ in HFpEF at 1 year).</p>

6MWT: 6-Minute Walk Test; AFR: Atrial Flow Regulator; BNP: Brain Natriuretic Peptide; CVP: Central Venous Pressure; DASI: Duke Activity Status Index; HFpEF: Heart Failure with Preserved Ejection Fraction; HFrEF: Heart Failure with Reduced Ejection Fraction; IASD: Inter-Atrial Shunt Device; KCCQ: Kansas City Cardiomyopathy Questionnaire; LVEDP: Left Ventricle End-Diastolic Pressure; LVEF: Left Ventricle Ejection Fraction; MACCE: Major Adverse Cardiovascular and Cerebrovascular Events; MACCRE: Major Adverse Cardiac, Cerebrovascular, and Renal Events; NS: Not Significant; NYHA: New York Heart Association; PCWP: Pulmonary Capillary Wedge Pressure; QoL: Quality of Life; SADEs: Sudden Adverse Device-related Events; SAEs: Sudden Adverse Events; VT: Ventricular Tachycardia.

developed a significant improvement in terms of symptoms (evaluated with NYHA classification), haemodynamic parameters (especially in terms of PCWP reduction) and quality of life (evaluated with scores like the Kansas City Cardiomyopathy Questionnaire) [18-22].

The case reported here is a kind of post-ischemic HF with effort dyspnoea resulting refractory to optimal medical therapy. Following adequate clinical evaluation, patient was judged as an optimal candidate to IAST. In fact, he presented elevated PCWP at rest and no right heart overload. An 8-mm-diameter AFR was implanted without any complication. After the procedure, patient developed an important clinical benefit. At 6 months, there were a reduction of LAP and a 1-step-improvement of NYHA functional class.

So, despite it seems to have no prognostic impact, IAST appears a feasible and effective strategy to ameliorate quality of life in advanced HF. Further studies are necessary in order to better define long-term hemodynamic consequences of creating a percutaneous inter-atrial shunt. However, some evidence would highline the idea that IASDs are not noxious to cardiac physiology; in fact, it has been shown that smaller ASDs in adults (diameter $<$ 10 mm and Qp:Qs ratio $<$ 1.5) do not cause right ventricular volume overload, pulmonary hypertension, or right HF [24].

However, whether this interventional treatment is an effective therapeutic option on top of optimal standard medical care for HF patients with elevated filling pressures needs to be proved in randomized phase III trials.

Conclusions

The management of drug-refractory HF is challenging. Elevated LAP and PCWP are typical of this condition and seem to be associated with a worse clinical status. Interatrial shunt therapy through the implantation of an AFR device (Occlutech™) has been showed to be a safe and effective approach in reducing PCWP, ameliorating symptoms and improving functional class in patients affected by refractory HF.

Conflicts of Interest

The authors have no conflicts of interest to declare.

The authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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