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Novel percutaneous interventional therapies in heart failure with preserved ejection fraction: an integrative review

Alexandru Burlacu[1,2] · Paul Simion[1,2] · Ionut Nistor[2,3] · Adrian Covic[2,4] · Grigore Tinica[2,5]

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Abstract

Heart failure with preserved ejection fraction (HFpEF) is a common disorder generating high mortality and important morbidity prevalence, with a very limited medical treatment available. Studies have shown that the pathophysiological hallmark of this condition is an elevated left intra-atrial pressure (LAP), exertional dyspnea being its clinical manifestation. The increasing pressure from LA is not based on volume overload (such as in heart failure with reduced ejection fraction) but on a diastolic left ventricular (LV) dysfunction combined with an inter-atrial dyssynchrony mimicking a pseudo-pacemaker syndrome. In this review, we aimed to summarize current knowledge and discuss future directions of the newest interventional percutaneous therapies of HFpEF. Novel interventional approaches developed to counter these mechanisms are as follows: LA decompression (inter-atrial shunt devices), enhancement of LV compliance (LV expanders), and inter-atrial resynchronization therapy (LA permanent pacing). To date, inter-atrial shunt devices (IASD) are the most studied, being the only devices currently tested in a phase 3 trial. Recent data showed that IASD are feasible, safe, and have a short-term clinical benefit in HFpEF patients. LV expanders and LA pacing therapy present with a smaller clinical benefit compared with IASD, but they are safe, without any major adverse outcomes currently noted. With further development and improvement of these mechanism-specific devices, it will be interesting to determine in the future whether a complex intervention of multiple HFpEF device implantation will be safe and have further benefits in HFpEF patients.

Keywords HFpEF · Interventions · Therapy · Devices

Introduction

Heart failure with preserved ejection fraction (HFpEF) is a clinical syndrome of heart failure in a patient with left ventricular ejection fraction (LVEF) of > 40–50% [1]. Although the incidence is accounting for more than 50% of HF patients, (with a devastating 5-year survival rate of < 50% [2], high rehospitalization rate > 50% and debilitating symptoms), no efficient medical treatment is available [3].

In fact, the last European Society of Cardiology guidelines for the diagnosis and treatment of HF state that "no treatment has yet been shown, convincingly, to reduce morbidity or mortality in patients with HFpEF." Actually, these guidelines merely recommend diuretics for fluid removal and symptom relief [4]. To date, all trials evaluating beta-blockers, ACE inhibitors, ARBs, or MRAs in patients with HFpEF showed no benefit in terms of mortality [4].

So, "why have we failed to develop effective treatments for HFpEF?" [5] This lack of success for the pharmacological treatment may be due to the multifactorial nature of HFpEF pathophysiology and the imprecise diagnostic criteria [5]. HFpEF incorporates a complex network of multiple pathways throughout the body. These involve not only diastolic function, but also "cardiac reserves, systemic and pulmonary vascular function, renal function, oxygen carrying capacity, and peripheral oxygen extraction" [6]. Actually, all systemic comorbidities involved in HFpEF pathogenesis seem to induce structural cardiac changes (molecular alteration in

✉ Paul Simion
simion_alexis@yahoo.com

1 Department of Interventional Cardiology, Cardiovascular Diseases Institute, Bucharest, Romania

2 'Grigore T. Popa' University of Medicine, Iasi, Romania

3 Methods Support Team ERBP, Ghent University, Ghent, Belgium

4 Nephrology Clinic, Dialysis and Renal Transplant Center, 'C.I. Parhon' University Hospital, Iasi, Romania

5 Department of Cardiovascular Surgery, Cardiovascular Diseases Institute, Bucharest, Romania

cardiomyocytes [7], myocardial and endothelial inflammation [8], collagen modification, increased systemic and diastolic ventricular passive stiffness [9, 10], loss of nitric oxide bioavailability [8]).

These molecular and cellular changes translate into biomechanical alterations of cardiac chambers configuration and functioning: changes in left ventricular (LV) geometry and function leading to relaxation and filling impairment, left atrial (LA) remodeling with increase in intra-atrial pressure, inter-atrial dyssynchrony, and changes in systemic and pulmonary vascular compliance [8]. In this context of lack of medical treatment benefits, novel interventional devices and techniques emerged in HFpEF. In each situation, the interventional approach is rather mechanicist, the technique does not target molecular/structural modifications but rather the consequences of those alterations: increased LA pressure (inter-atrial shunt devices), compromised LV relaxation (LV expanders), or inter-atrial mechanical dyssyncrony (LA pacing).

Methods

Search strategy

We conducted an electronic search of PUBMED and SCOPUS from earliest dates until November 2018, for studies that evaluated the efficacy, safety, and feasibility of interventional devices in HFpEF. The terms used for searching were "heart failure with preserved ejection fraction," "HFpEF," "diastolic heart failure," "heart failure," "diastolic dysfunction," "preserved ejection fraction," "therapy," "intervention," "interventional therapy," "interventional techniques," "percutaneous devices," "devices," "device therapy," "left atrial pressure," "IASD," "V-Wave." The reference sections of relevant articles were searched for additional publications. Journals, conference proceedings, and case reports were hand-searched. Two independent reviewers screened the articles for title, abstract, and full text to identify publications that fulfilled the inclusion criteria.

Results

Study selection

Of 225 articles identified, 18 met the inclusion criteria and additional 3 hand-searched articles were included (Fig. 1). Duplicates were excluded manually. In each article, we assessed interventional technique and all endpoints related to HFpEF.

Novel available interventional treatment options in HFpEF include: inter-atrial shunt devices (IASD), left ventricular expanders (LVE), and left permanent atrial pacing (Fig. 2).

Inter-atrial shunt devices

This concept of creating an iatrogenic inter-atrial shunt was derived from the observation that patients with mitral stenosis and inter-atrial septal defect (IASD) (Lutembacher syndrome) manifest fewer symptoms compared with patients with mitral stenosis alone [11]. The low prevalence of exertional dyspnea in Lutembacher patients seems to originate from the reduction of left atrial pressure (LAP) by shunting blood volume into the right cavities. The same concept applies to the acute development of pulmonary edema from a sudden increase in LAP in patients with IASD closure and non-diagnosticated LV diastolic dysfunction [12, 13].

The clinical hallmark of HFpEF patients is exercise intolerance (exertional dyspnea) [14]. Progressive decrease of LV relaxation/compliance gradually leads to an increase in LAP and subsequently pulmonary capillary wedge pressure (PCWP) mainly during exercise [15]. The volume depletion from LA into the right cavities by creating an artificial inter-atrial shunt will reduce the LAP at rest and during exercises, leading to symptoms relief and improved clinical outcomes (an increase in quality of life) [15].

Currently, there are three devices designed for iatrogenic inter-atrial shunting: V-Wave® (V-Wave Ltd., Or Akiva, Israel), IASD® (DC Devices Inc., Tewksbury, MA, USA), and Atrial flow regulator (Occlutech, Istanbul, Turkey) (AFR).

V-Wave device

Interventional procedure The V-Wave device is an hourglass-shaped nitinol frame covered on the left side with polytetrafluoroethylene polymer and with a trileaflet porcine pericardium valve on the right side to prevent paradoxical embolism and early device closure [16] (Fig. 3).

This device is implanted through venous femoral access with general anesthesia and transesophageal echocardiography guidance (TEE). A transseptal puncture is performed with a radiofrequency ablation catheter in the middle of the foramen ovalis fossa. Following the puncture, a 14 Fr Transseptal Mullins™ introducer sheath (Cook Medical, Inc., Bloomington, IN, USA) is inserted and the device is advanced through a delivery catheter [17]. After positioning of the left side of the device in the middle of the LA, the system is pulled back into the inter-atrial septum where the device is detached and released by pulling back the delivery catheter. After delivery, immediate left-to-right shunt is assessed through TEE [17].

It is designed to maintain a left-to-right shunt as long as the inter-atrial pressure difference is above 5 mmHg [16]. The valve will close if the right atrial pressure (RAP) exceeds 2 mmHg preventing right-to-left shunting [16]. Following implantation of the device, 3-month oral anticoagulation is needed with vitamin K antagonists or direct antithrombin inhibitors and low-dose aspirin indefinitely [17].

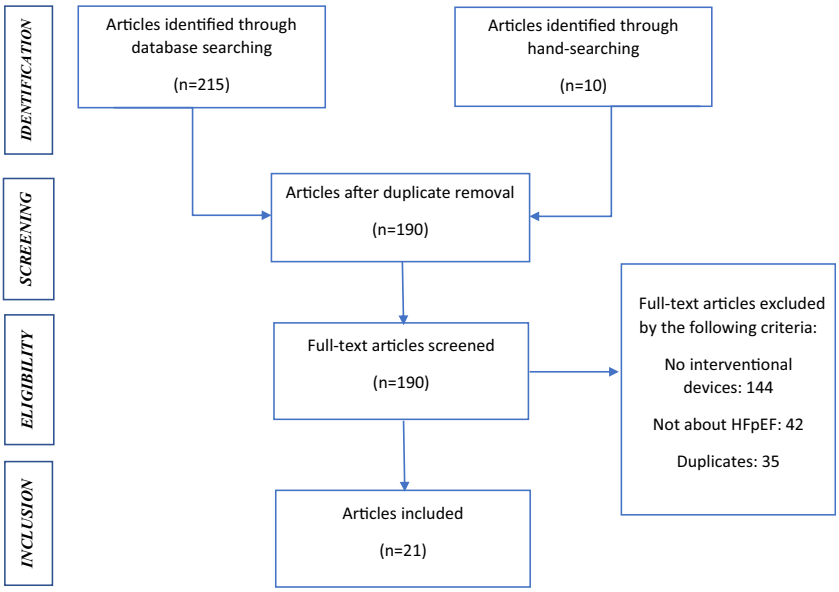

Fig. 1 Inclusion and exclusion criteria flow diagram. HFpEF heart failure with preserved ejection fraction

Trials A first-in-human prospective multicenter single-arm open-label trial assessed the feasibility, safety, and exploratory efficacy of the V-Wave device [18]. The study enrolled eight patients with HF with reduced ejection fraction (HFrEF) and 30 patients with HfpEF, NYHA class III/IV, on guidelines-driven maximally tolerated medical and device therapy, with ≥ 1 HF hospitalization in the prior 12 months or elevated NT-proBNP. All patients had the device successfully implanted and 1–2 hospitalization days.

After 1 year, there was significant improvement in the functional status with a decrease in NYHA class in 61% patients ($p < 0.001$), increase in quality of life assessed by KCCQ/MLHFQ (increase with ≥ 5 points) in 74% patients ($p < 0.001$), and an increase in 6-min walk test (6MWT) with 34 min ($p = 0.012$). Also, at 12 months, there was a 2 mmHg decrease in PCWP and a minor increase in cardiac index without significant changes in the right-sided cardiac function [18].

Shunt occlusion occurred in 14% of patients ($n = 5$) after 1 year and 36% of patients had shunt restenosis ($n = 13$) due to pannus formation in the valve of the device. Patients with permeable shunt were older, had lower glomerular filtration rate, higher PCWP, and had lower exercise tolerance. Also, the patency of the shunt was correlated with a reduced HF hospitalization rate (HR ca. 0.5 vs 2% $p = 0.008$), a decrease in death, ventricular assist-device implantation, and transplant rate (HR ca. 0.3% vs 0.6% $p = 0.001$) compared with occluded shunts [18].

Importantly, the primary outcome was device/procedure-related major adverse cardiovascular and neurological events (MACNE), defined as death, stroke device embolization, pericardial effusion requiring intervention, re-intervention or

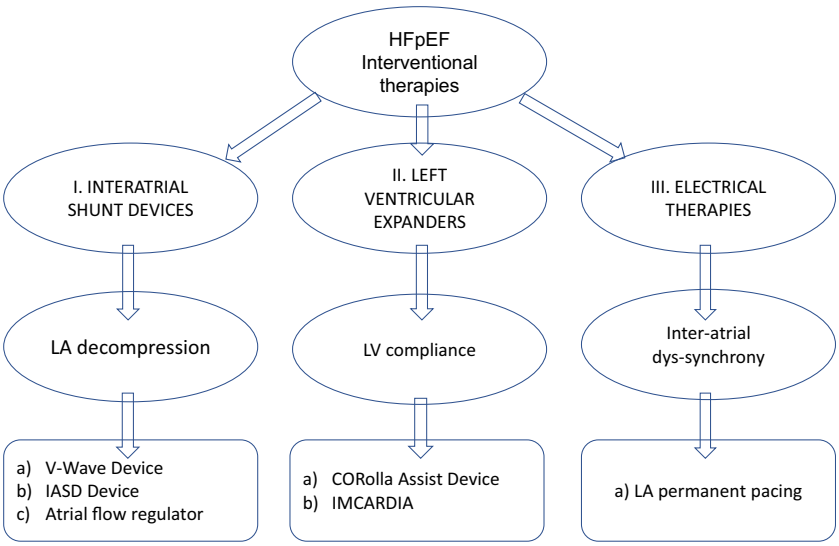

Fig. 2 Physiopathological classification of novel interventional therapies in HFpEF. HFpEF heart failure with preserved ejection fraction, LV left ventricle, LA left atrium

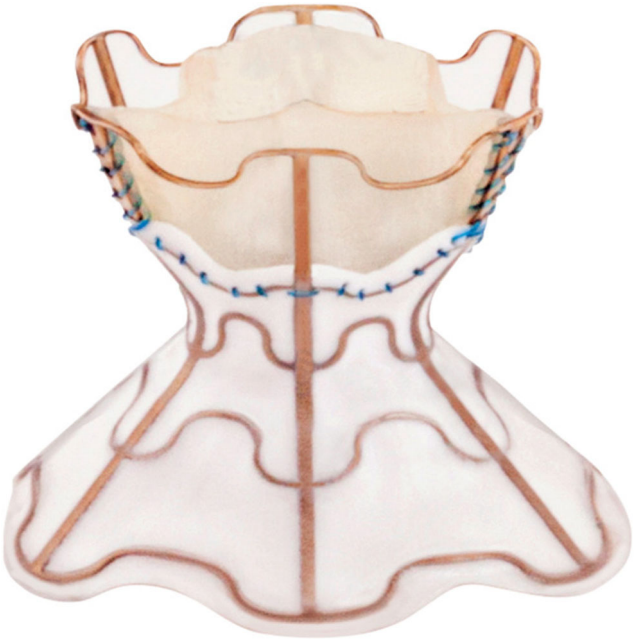

Fig. 3 V-Wave device

surgery at 3 and 12 months follow-up. At both 3 and 12 months, the rate of MACNE was 2.6% [18]. At 12 months, the rate of all-cause MACNE was 7.9%, with one patient experiencing non-fatal cardiac tamponade, concluding that the V-Wave system was feasible and safe for HF patients [18].

Another study enrolled 10 patients with HFrEF NYHA III/IV with LVEF< 40% on optimal medical and device therapy with no evidence of severe right ventricular dysfunction and PCWP > 15 mmHg [19]. The V-Wave device was successfully implanted in all patients with no procedural complications. At 3 months, NYHA class improved from III to II in 89% of patients and PCWP decreased from 23 to 17 mmHg with no increase in RAP and mean pulmonary arterial pressure (p = 0.035) [19].

A novel trial, RELIEVE-HF, with an estimated enrollment of 500 participants has recently started in September 2018 and is estimated to be completed in 2021 (NCT03499236). It was designed to provide reasonable assurance of safety and effectiveness of the V-Wave device by improving meaningful clinical outcomes in patients with NYHA III/IV irrespective of LVEF, who at baseline are treated with guidelines-directed drug or device therapy [20] (Table 1).

To note, all trials designed for V-Wave device were single-arm open-label studies.

IASD device

Interventional procedure The IASD device (IASD II, Corvia Medical Inc.) is a bare-metal nitinol frame with an outer diameter of 19 mm which is inserted percutaneously and implanted through atrial transseptal puncture creating an 8-mm shunt (Fig. 4). The diameter of the shunt was determined based on predictive hemodynamic modeling which evaluated the relationship between LAP and inter-atrial shunt in humans. The device is flat on the LA side to prevent thrombus formation and curved on the right atrial side to accommodate septal deformations. It is inserted via the femoral vein, with a classic atrial transseptal puncture, under general anesthesia/conscious sedation [21].

After the transseptal puncture is performed, a stiff guide wire (super-stiff Amplatzer guide wire) is positioned in the left upper pulmonary vein [22]. The delivery catheter is positioned through the transseptal puncture, and the left atrial part of the device is expanded. With slight traction, the left atrial side is accommodated at the septum, and the right atrial side is expanded with complete fixation of the device. The position is checked with transesophageal echocardiography and with contrast injection through the delivery system. Post-procedural double antiplatelet regimen is required with clopidogrel and aspirin for a non-standardized period of time, with life-long low dose of aspirin afterwards. In patients with atrial fibrillation, oral anticoagulation and clopidogrel are recommended [22].

Trials The first feasibility study of IASD II device was a prospective single-arm single-center study which enrolled 11 patients with HFpEF NYHA III/IV, baseline PCWP ≥ 15 mmHg at rest, or ≥ 25 mmHg during exercise and ≥ 1 hospitalization for HF within the past 12 months [22]. The device was successfully implanted in all patients with no embolization at echocardiographic evaluation at 1 month. The device was permeable at 1 month in nine patients. The NYHA class improved in seven patients, was worse in one patient and stationary in the remaining. A 50 m increase in 6-MWD (330 vs 387m, p = 0.025) and a better performance in MLWHF score (56 vs 30, p = 0.005) was detected at 1 month. The PCWP decreased significantly (19 vs 14mmHg, baseline vs 30 days, p = 0.005) with no increase in RAP (12 vs 11mmHg, p = NS) and mean pulmonary arterial pressure (30 vs 27mmHg, p = NS) [22].

The Reduce Elevated Left Atrial Pressure in Patients with Heart Failure (REDUCE LAP-HF) study is a multicenter, prospective, non-randomized, single-arm phase 1 study designed to assess the safety and performance of the IASD in patients with HFpEF with NYHA II-IV despite optimal medical or device therapy [23]. The study enrolled 64 patients with HFpEF, without severe right ventricular dysfunction or pulmonary hypertension to receive device insertion after a period of 45 days of screening, and to be reassessed at 6 months. The device was implanted successfully in 97% of patients, in three patients initially being removed because of unsuitable position (n = 2) or a suspected small mobile thrombus in the right atrium (n = 1). However, a second device was deployed in all three patients without incident. No peri-procedural or major adverse cardiac or cerebrovascular event, including death,

Table 1 Future trials of novel interventional devices for HFpEF

Device	Manufacturer	Condition	Title	Primary outcome	No. of patients	Design	NCT number
V-Wave	V-Wave Ltd., Or Akiva, Israel	HFpEF, HFrEF	RELIEVE-HF	1. Safety—percentage of treatment patients experiencing MACNE during the first 30 days 2. Effectiveness—hierarchical composite of death, heart transplant or LVAD, HF hospitalizations, and changes in 6MWDT	500	Prospective, multicenter randomized, patient and observer blinded clinical study	NCT03499236
IASD II	Corvia Medical Inc	HFpEF	REDUCE LAP II	Composite of: 1. Incidence of and time to cardiovascular mortality or first non-fatal, ischemic stroke in 12 months 2. Total rate per patient year of HF Changes in baseline KCCQ total summary score	608	Prospective, multicenter, randomized, blinded trial with a non-implant control group	NCT03088033
IASD II	Corvia Medical Inc	HFrEF, EF 20–30%	REDUCE LAP HF-RED	1. Percent of patients who experience MACCE peri-procedural and at 6 month 2. Percent of patients with successful device implantation 3. Percent of patients with left-to-right flow through the device	10	Prospective, single-center, non-randomized, single-arm feasibility trial	NCT03093961
AFR	Occlutech, Istanbul, Turkey	HFpEF, HFrEF	PRELIEVE	Incidence of SADE: - device dislocation/embolization - damage to the tricuspid or mitral valve - intractable arrhythmias caused by the device - any circumstance that requires device removal	30	Prospective, non-randomized, pilot study	NCT03030274
Corolla	CorAssist Cadriovascular Ltd.	HFpEF	CORolla® TAA for heart failure with preserved ejection fraction (HFpEF) and diastolic dysfunction (DD)	1. All-cause mortality and SAEA after months 2. Implantation Rating Questionnaire	10	Prospective, single-group, non-randomized	NCT02499601

HFpEF, heart failure with preserved ejection fraction; *HFrEF*, heart failure with reduced ejection fraction; *MACNE*, major adverse cardiovascular and neurological events; *LVAD*, left ventricular assist device; *HF*, heart failure; *6MWDT*, 6-min walking distance test; *KCCQ*, Kansas city cardiomyopathy questionnaire score; *MACCE*, major adverse cardiac and cerebrovascular events rate; *SADE*, serious adverse device effects; *SAEA*, serious adverse events

Fig. 4 IASD II device

stroke, myocardial infarction, pulmonary or systemic embolism, or need for cardiac surgical intervention for device-related complications were noted during the months of follow-up. At follow-up, all patients with adequate echocardiographic image quality ($n = 50$) had evidence of left-to-right flow through the device with no right-to-left flow observed [23].

At 6 months, the quality of life and symptoms of patients improved: median functional NYHA class decreased by one class in 75% of patients ($p = 0.0001$), mean MLWHF score decreased from 49 to 36 ($p = <0.0001$), mean 6-MWD increased from 313 to 345 m ($p = 0.0023$), and supine exercise duration at the time of right heart catheterization increased from 7.3 to 8.2min ($p = 0.0275$). Also, there was a consistent improvement in hemodynamic parameters: reduction of PCWP at rest in 52% of patients ($n = 32$) and reduced PCWP measured by right heart catheterization during supine bicycle exercise in 58% of patients ($n = 34$), and 39% ($n = 23$) fulfilled both of these criteria, with no significant increase in RAP (9 vs 11mmHg, $p = 0.0270$), or deterioration of right ventricular function (TAPSE at baseline 20 vs 6 months 20mm, $p = 0.97$). It was also noted a consistent reduction of heart failure rehospitalization from 20% ($n = 13$) to 14% ($n = 9$), with no mean reduction of diuretic dose (mean difference between baseline and 6 months of 0 mg) during the 6 months follow-up. Because there was no difference in the treatment regimen, it was unlikely that medical treatment accounted for the recorded reduction of HF rehospitalization [23].

In 2016, David M. Kaye et al. published 1-year outcomes after REDUCE LAP-HF study with particular regard to device safety and performance, and the persistence of clinical and hemodynamic effects [24]. The exercise protocol was as previously used, and to account the hemodynamic effect of differences in workload, corrected workload PCWP was calculated as previously described. Echocardiographic evaluation revealed the presence of left-to-right shunting at 12 months post-device implantation in all patients with adequate image quality ($n = 48$), with unchanged EF, minor increase in right ventricle ejection fraction (59 to 65%), modest reduction in left ventricular end-diastolic volume index (69 to 60 ml/m^2) with concomitant rise in right ventricle end-diastolic index (23 to 30 ml/^{2}). Serial hemodynamic measurements from right side catheterization at 12 months revealed: no improvement in PCWP at rest ($16 \pm$ vs 17 ± 6mmHg), and during exercise (33 ± 9 vs 33 ± 10mmHg) with minor increase in right-sided cardiac output at rest (6.3 ± 1.4 L/min vs 6.7 ± 1.8L/min), and increase in left-sided cardiac output at rest (4.9 ± 1.5L/min vs 5.8 ± 1.5L/min) compared with the 6 months follow-up. Also at 12 months, there was sustained significant improvement in NYHA class, MLWHF score and 6-MWD test compared with baseline, but no improvement compared with the 6 months follow-up [24].

Recently, REDUCE LAP-HF I, a phase 2 randomized, parallel-group, blinded multicenter sham-controlled trial to evaluate de IASD in patients with HFpEF, published the short-term results [25]. Ninety-four patients with HF NYHA III/IV were enrolled under optimal medical or device treatment with LVEF > 40%, exercise PCWP > 25mmHg, and PCWP-right atrial pressure gradient > 5 mmHg to be randomized 1:1 to implantation of IASD device vs a sham procedure (femoral venous access with intracardiac echocardiography but no IASD placement). The device was successfully implanted in 21 patients of 22 (in one patient, the device could not be placed due to an occluded inferior vena cava filter) [25]. No subsequent adverse cardiac, cerebrovascular, and renal events occurred at 1 month. There was no significant decrease in NYHA class or rehospitalization for HF in the IASD group compared with the sham group and baseline after 1 month. There was a significant decrease in exercise PCWP in the IASD group compared with baseline (-3.2 ± 5.2 mmHg at low workload—20 W and -2.3 ± 4.9 mmHg at high workload—60 W) and no significant improvement in exercise PCWP in the sham group (0.9 ± 5.1 mmHg at 20 W and -1.3 ± 4.9 mmHg at 60 W). There was no significant increase in right atrial pressure at rest and mean pulmonary arterial pressure at rest in the IASD group compared with baseline and control group ($p = 0.0673$ and $p = 0.111$). The major limitation of the study is the small period of follow-up and was not powered up to assess clinical endpoints [25].

Three novel trials evaluating IASD device are being planned: Reduce LAP-HF II, Reduce LAP-HF III, and Reduce LAP-HFrEF (Table 1). The first one is a randomized, controlled, blinded trial with a non-implant control group with 1:1 randomization which will enroll almost 600 patients with HF NYHA III/IV with LVEF over 40% on guideline medical or device therapy [26]. The primary outcome is cardiovascular mortality, ischemic stroke, total rate per patient year of heart failure admissions, and change in baseline KCCQ total summary score at 12 months. The trial is due to be completed in 2024.

Fig. 5 Atrial flow regulator

Reduce LAP HFrEF is a non-randomized feasibility trial which will enroll 10 patients with HF with EF < 40% with elevated LAP who remain symptomatic despite guideline medical or device therapy [27]. The study will assess the successful device implantation, the permeability of the device at 6 months, and the incidence of major adverse cardiac and cerebrovascular events at 6 months, and is due to be completed in 2024.

Atrial flow regulator

Interventional procedure The AFR (Fig. 5) is a self-expandable double-disc wired mesh with a central penetration that enables inter-atrial shunting. The device is implanted percutaneously via the femoral vein with standard transseptal punction and positioned similarly to atrial septal defect occluder devices. It is available in 6, 8, 10-mm fenestration diameters and 1, 24, 30-mm total device diameter [28, 29]. The first use of AFR was for severe pulmonary hypertension based on the fact that atrial septostomy relieves syncope, improves heart filling, cardiac output, and systemic oxygen transport despite hypoxia [29].

Trials A recent trial included 12 patients with severe pulmonary hypertension undergoing AFR implantation [30]. The device was feasible and safely implanted in all patients, with significant improvement of symptoms, 6 min walk distance (377.3 ± 33.2 to 423 ± 31.32), cardiac index (2.36 ± 0.52 to 2.89 ± 0.56 L/min/m2), and systemic oxygen transport (367.5 ± 75.5 to 428.0 ± 67.1 ml/min/m2). Being a bidirectional flow device, AFR can be used as a left-to-right shunt also. Due to the success of the IASD devices in the past decade, the spectrum of indications for AFR extended to HFpEF patients [28].

Currently, PRELIEVE trial aims to investigate the safety and efficacy of the AFR in patients with HFrEF and HFpEF, with an estimated completion date in 2019 (Table 1) [31].

Left ventricular expanders

Left ventricular expanders are devices that aim to improve LV compliance through direct internal or external expansion forces distributed on the left ventricular walls during diastole [28]. Currently, there are three devices made: CORolla® and ImCardia®.

COROlla assist device

Interventional procedure CORolla (CorAssist Inc., Haifa, Israel) is an elastic self-expanding device inserted percutaneously (or transfemural) and attached to the endocardium (Fig. 6). The device enhances LV diastolic expansion, improves LV filling, and lowers LVEDP and LAP [32].

Trials Preclinical studies demonstrated safety and efficacy [33]. The first-in-man procedure was performed in 2013 in a patient with severe aortic stenosis requiring surgery and type IV diastolic dysfunction [34]. The device was surgically implanted. At 6 months follow-up, there was a significant improvement in LV mass, LA indexed volume, and a consistent regression of diastolic dysfunction (from type IV to type I) suggesting a good hemodynamic performance and safety of the device. In 2017, the device was percutaneously inserted (transapical) at RAMBAM Medical Center with the same consistent LV remodeling improvement at 6 months. An ongoing trial (NCT02499601) enrolling 10 patients aims to demonstrate the safety and feasibility of the device during 12 months follow-up in patients with HFpEF with NYHA III/IV (Table 1) [35].

ImCardia

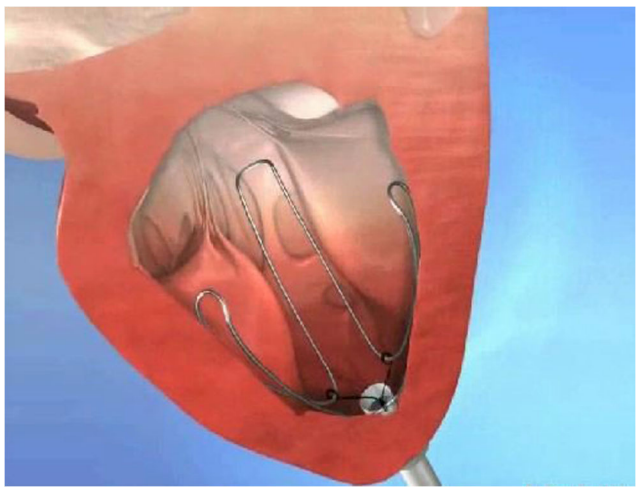

Fig. 6 COROlla device

Interventional procedure ImCardia (CorAssist Inc., Haifa, Israel) is an elastic self-expanding device attached on the epicardial surface of the left ventricle. The device is inserted surgically through an off-pump procedure in patients undergoing surgery for aortic valvular disease [36].

Trials Krucoff et al. conducted a study in which 10 patients with severe aortic stenosis underwent surgical treatment concomitant with ImCardia insertion [36]. There were no improvements in NYHA class and 6-MWT at 1 year, but there was a significant LV mass regression (− 126 g ± 33 g) and LA area decrease (− 2.29 cm^2 ± 3.09 cm^2). The trial was terminated with the conclusion that the device needs further improvement.

Electrical therapy in HFpEF

Left atrial permanent pacing for atrial dyssynchrony syndrome

Interventional procedure A novel theory suggests that atrial electrical dyssynchrony and left atrial dysfunction may be the missing "key" in the physiopathology of HFpEF [37]. Left atrial pacing (coronary sinus pacing) was firstly developed for the management of atrial tachyarrhythmias and it was recently developed for atrial resynchronization in HFpEF patients [38]. The procedure requires a specially designed coronary sinus (CS) lead, with a double 45° angulation at its distal end, ensuring very close contact with the upper wall of the CS [39]. For optimal threshold pacing voltage, the lead can be positioned from the middle to the distal part of CS.

Trials Recent echocardiographic studies suggest that HFpEF patients present with an increased intra-atrial dyssynchrony and reduced LA diastolic and systolic function compared with normal patients [40]. Furthermore, there is an independent correlation between the severity of the dyssynchrony and reduced LA systolic function with NYHA class >II in patients with HFpEF [41, 42].

A study conducted in 2013 by Laurent et al. presented atrial dyssynchrony syndrome as inter-atrial conduction delay (ADS) (P wave duration > 120ms in D II), short left atrioventricular interval (< 70 ms), and increased left atrial stiffness [43]. The study evaluated the implantation of a lead put inside the coronary sinus for active vs. inactive LA pacing in six patients with HFpEF NYHA III/IV under optimal medical treatment. After 3 months of pacing, there was significant improvement in 6-MWDT (240 ± 25 m vs. 190 ± 15m, $P < 0.05$), mitral A wave duration was longer (104 ± 8 vs. 158 ± 25 ms, $P = 0.002$) and E/A and E/e' ratio was smaller (3.4 ± 1.3 vs. 1.8 ± 0.9, $P = 0.009$, and 22.6 ± 4.6 vs. 15.3 ± 4.3, $P = 0.006$, respectively). Importantly, after the inactivation of pacing for 1 week, there was a significant reduction in 6-MWDT with an on/off response. This novel beneficial effects of LA permanent pacing opens a new perspective for the electrical therapy in HfpEF [43].

Cardiac contractility modulation

Interventional procedure Cardiac contraction modulation (CCM) is a pacemaker-like therapy that applies non-excitatory electrical signals (biphasic high-voltage bipolar) to the right ventricular septum during the absolute refractory period. This concept was developed for symptomatic patients with HFrEF with slightly prolonged QRS interval not eligible for CRT therapy [44]. Currently, there are nearly 3000 devices (Optimizer Smart, Optimizer III, Optimizer IV from Impulse Dynamics) implanted worldwide [45].

Trials The benefits of CCM therapy were mostly studied in HFrEF patients [46]. Few studies promise good safety and feasibility with increasing exercise tolerance and symptoms improvement in HFpEF [47, 48]. An ongoing trial evaluates the efficacy and safety of CCM therapy in HFpEF patients who have NYHA Class II or III symptoms despite appropriate medication (for potential expansion of the CE Mark indication for use in the HFpEF population) [49].

Limitations and future directions

The failure of medical therapy to improve symptoms in HFpEF gave rise to interventional approaches, based on the subsequent pathophysiology of the disease. Given the recently approached strategies, artificial inter-atrial shunting developed the most, being the only devices tested in a phase 3 trial [25]. Although IASD devices are recently introduced, long-term safety needs to be proven.

The exact duration of *antithrombotic therapy* needs to be established. Currently, IASD II requires 1-year double antiplatelet therapy, V-Wave requires oral anticoagulation and aspirin for 3 months and AFR requires 6–12 months double antiplatelet therapy. A low dose of aspirin is required in all the devices indefinitely [19, 25, 29].

Another long-term consideration should be the development of *atrial tachyarrhythmias*. Atrial electrical vulnerability is presented in atrial septal defects with left-to-right shunting due to the hemodynamic derangements causing atrial stretch and RV dilatation [50]. Although computer models suggested that a 5–8-mm shunt will be non-hemodynamic significant, long-term monitorization for the incidence of atrial tachyarrhythmias is required [25].

Another important follow-up parameter in IASD implanted patients will be the *incidence of cryptogenic stroke*, considering the high incidence of this condition in patients with patent foramen ovale [51].

The most important concern in IASD devices remain the *volume overload* of right-sided chambers. Recent studies involving all the types of devices concluded that there is no significant hemodynamic stress on the right heart, with and improvement in symptoms, but long-term outcomes need to be established. Also, the clinical improvement may be due to the Hawthorne effect, which appears after receiving a procedure [52]. Left ventricular expanders are a novel approach on HFpEF with positive short-term results but the devices need to be further refined to a standardized technical approach.

Two mechanical assist devices were used in HFpEF setting to pump blood from either LA [53] or LV [54] into arterial system. Both studies showed (at least in theory) that these devices could improve hemodynamics in HFpEF patients by increasing the total stroke volume and decompressing LA/LV cavities.

Conclusions

HFpEF is a common and severe condition, with devastating mortality and morbidity rate [2]. Due to the lack of optimal medical management, new interventional approaches are being implemented and evaluated with good early clinical outcomes. New long-term trials are required in order to prove the benefits, safety, and feasibility of these devices.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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