



Update on Devices for Diastolic Dysfunction: Options for a No Option Condition?

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Published online: 15 August 2018
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Abstract

Purpose of Review This article provides an update on percutaneous devices to treat diastolic dysfunction, current clinical experience, and actively enrolling trials. We also discuss potential complications and limitations of devices.

Recent Findings Exertional symptoms including exertional dyspnea and exercise intolerance are common features of heart failure that are driven by left ventricular and left atrial non-compliance that results in pulmonary vascular congestion. Multiple studies that have shown that reducing total body volume and intravascular pressure, using pharmacologic therapies, are associated with improved outcomes among patients who have heart failure with reduced ejection fraction (HFrEF) (ejection fraction [EF] < 40%), but not heart failure with preserved ejection fraction (HFpEF) (EF > 55%). This is related to the fact that HFpEF is associated with altered diastolic compliance but not volume overload, which presents as exertional increases in left atrial pressure. Exercise assessment of LA and pulmonary pressures are not commonly assessed today in the clinic or in the catheterization laboratory. As elevated left atrial pressure mediates these symptoms, selective reduction in left atrial pressure may provide improvement in symptoms without complications of pharmacologic therapy such as diuresis and aggressive blood pressure reduction. Mechanical devices that aim to reduce left atrial pressure have been developed and evaluated in HFpEF and HFrEF patients.

Summary The current data from the small number of patients who have undergone treatment with left atrial decompression devices indicate that they have a high rate of success and may improve patient's exercise capacity. Larger, controlled trials are underway to better understand the role of these devices in patients with diastolic dysfunction.

Keywords Heart failure · Diastolic dysfunction · HFpEF · Left atrial pressure · Percutaneous device · Atrial septum

Abbreviations

LA	Left atrium
LV	Left ventricle
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
LVEF	Left ventricular ejection fraction
IASD	The Inter Atrial Shunt Device

Introduction

The prevalence of heart failure with preserved ejection fraction (HFpEF) is estimated to represent 50% of all clinical heart failure (HF) patients. Left ventricular diastolic dysfunction resulting from abnormal relaxation and increased passive stiffness impairs diastolic reserve. While many patients with HFpEF may have normal resting pressures, they typically develop marked elevations in LA pressure followed by pulmonary vein hypertension with exercise due to the altered diastolic compliance. This is typically manifest as exertional dyspnea. Therapies that aim to reduce total body volume and consequently intravascular pressure have been associated with improved outcomes among patients who have heart failure with reduced ejection fraction (HFrEF) (ejection fraction [EF] < 40%), but not heart failure with preserved ejection fraction (HFpEF) (EF > 50%). Diuretics may be effective in bringing symptomatic relief but their use is frequently complicated

This article is part of the Topical Collection on *Interventional Cardiology*

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by hypovolemia and azotemia as many patients are not volume overloaded. In recent years, innovative devices in clinical trials have shown promise and this article is intended to review current status of progress made.

Diastolic Heart Failure (HFpEF)

Heart failure is a clinical diagnosis and several criteria have been proposed to define HFpEF such as (a) clinical signs or symptoms of heart failure, (b) evidence of preserved or normal left ventricular ejection fraction (LVEF) (variably classified as EF > 40%, > 50%, or > 55%), and (c) evidence of left ventricular (LV) diastolic dysfunction by echocardiographic or cardiac catheterization criteria [1•]. The pathophysiologic basis of diastolic dysfunction is impaired LV relaxation (which primarily affects early diastole) and increased myocardial stiffness (which primarily affects late diastole). The pathophysiologic basis of diastolic dysfunction is impaired active LV relaxation (which primarily affects early diastole) and increased myocardial stiffness (which primarily affects late diastole). The rate and extent of the active relaxation influence LV relaxation during the early filling phase. Both abnormalities lead to elevation of diastolic pressures which are transmitted eventually to left atrium (LA) and pulmonary veins leading to exercise intolerance and dyspnea [2]. Both abnormalities lead to elevation of diastolic pressures which are transmitted eventually to the left atrium (LA) and pulmonary veins leading to increased pulmonary interstitial fluid, increased work of breathing, exercise intolerance, and dyspnea on exertion.

In the USA, the prevalence of heart failure (HF) cases is estimated to exceed 5.8 million patient with > 650,000 new HF cases diagnosed annually. Of these, based on community studies, nearly half of the patients have preserved ejection fraction (HFpEF) [3]. HF is characterized by periodic exacerbations that require treatment intensification most often in the hospital and is the single most frequent primary diagnosis at the time of hospitalization in persons aged ≥ 65 years. Nearly 1 million hospitalizations for HF occur each year, with rates of hospitalization that continue to rise [4]. With aging population and expected increasing prevalence of HF, there is unmet need for exploring therapies to decrease morbidity and mortality from HFpEF.

Role of Left Atrial Pressure

Hemodynamics obtained with invasive catheterization during rest and exercise have shed more light on HFpEF patients, all of which demonstrate (1) marked increase in LA/pulmonary capillary wedge pressure (PCWP) with increasing exercise workload compared to normal subjects even though corresponding measurements are comparable at rest, (2) rapid decrease in PCWP within a few minutes of cessation of exercise which emphasizes that these patients are not hypervolemic,

and (3) volume sensitivity with as little as 600 ml intravenous fluid administration resulting in marked increase in pulmonary wedge pressure which is a surrogate of LA pressure [5••]. Higher peak PCWP corrected for workload during exercise has been associated with reduced exercise capacity and worse outcomes in the setting of HFpEF [6••, 7•]. In addition, intrinsic LA mechanical dysfunction is associated with an increased incidence of atrial fibrillation and is recognized as a driver of poor outcomes in HFpEF [8–10, 11••].

Strict control of LA pressure by invasive monitoring and physician-directed self-management have been associated with significant improvement in NYHA class as well as with a major reduction in rehospitalizations and mortality at mid-term follow-up [12]. The closure of congenital atrial septal defects in patients with diastolic dysfunction have been associated with a rise in LA pressures and decompensated HF [13].

None of the medical therapies other than diuretics have been able to show any decrease in morbidity, which themselves have side effects due to decrease in intravascular volume. Hence device-based therapies which can decrease LA pressure selectively with exercise would seem to promise decreasing morbidity with fewer side effects than medical therapy alone.

Rationale of Interatrial Septostomy

Left atrium is an elastic chamber receiving blood from pulmonary vein passively which modulates LV filling by acting as active booster during atrial systole. The LA buffers pressure and flow coupling between the LV and the pulmonary circulation due to the cyclic nature of cardiac hemodynamics [14]. At identical mean LA pressure in patients with heart failure, HFrEF patients had larger LA volumes while HFpEF patients had higher LA peak pressures and higher LA stiffness. LA function has been related to mortality in HFpEF patients but not in HFrEF patients [9].

LA pressure itself may be prognostically important. In patients undergoing paravalvular leakage closure ($n = 134$) with invasive LA pressure monitoring, the LA pressure post closure was found to be related to mortality in over next 3 years of follow-up. Each 10% reduction in post procedural LA pressure was associated with a significant 9% decrease in risk of death after adjustment for age, gender, and residual MR over the next 3 years [15]. It has been reported that patients with Lutembacher syndrome which is a combination of mitral stenosis and atrial septal defect (ASD) did better than patients with mitral stenosis alone [16]. There have been case reports of iatrogenic ASD made to decompress LV in case of fulminant myocarditis with pulmonary hemorrhage which was shown to decrease LA hypertension [17]. Also, in patients with restrictive LV physiology who have ASD, case reports suggest improved outcomes by closing them with fenestrated

ASD closure devices [18]. In patients with severe pulmonary hypertension and right ventricular dysfunction, creation of interatrial shunt already has been shown to improve symptoms and hemodynamics [19]. So, creation of unidirectional left to right shunt in patient with HFpEF should provide relief during episodes of acute elevation of LA pressure, reduce LA pressure overtime, improve functional class, and eventually reduce rehospitalizations.

Computer simulation study performed with exercise-associated hemodynamics has shown the theoretical effects of such a shunt (diameter up to 12 mm) on acute rest and exercise hemodynamic data (including changes in PCWP) in patients with HFpEF. The interatrial shunt was predicted to lower PCWP acutely by ~3 mmHg under simulated resting conditions (from 10 to 7 mmHg) and by ~11 mmHg during simulated peak exercise (from 28 to 17 mmHg). Left ventricular cardiac output was predicted to decrease ~0.5 L/min at rest and ~1.3 L/min at peak exercise, with corresponding increases in right ventricular cardiac output. The authors also studied effect on rest and exercise hemodynamics of varying the shunt diameter from 0 to 12 mm [20•]. As expected, shunt flow increases with increasing shunt size at rest and during exercise [20•]. Under resting conditions, as shunt flow size was increased, there was a progressive decrease in PCWP and a lesser increase in RA pressure with corresponding increase in right ventricular cardiac output (CO) and a decrease in left ventricular CO [20•]. All of these effects reach a plateau at a shunt diameter of 8–9 mm. During exercise, the effects were significantly more pronounced because of the larger LA-RA pressure gradient under this condition; however, the effect on shunt flow still plateaus at approximately 10 mm [20•]. Direction of flow in shunt was left to right in all case scenarios tested. Authors concluded that this approach may reduce the propensity for heart failure exacerbations and allow patients to exercise longer, thus attaining higher heart rates and cardiac outputs with the shunt compared with no shunt [20•].

There are multiple established techniques for creating large interatrial communication like percutaneous perforation, balloon dilation, and stent implantation. However, complications of these procedures include excessive desaturation, spontaneous fenestration closure, stent occlusion or migration, difficulties in adjusting shunt size to achieve the desired hemodynamic effect, and the inability to remove or close the shunt [21]. Now, there are three percutaneously deployed innovative devices which avoid these complications and are currently undergoing clinical trials. The trials of percutaneous device therapies are summarized in Table 1.

Inter Atrial Shunt Devices

The Inter Atrial Shunt Device (IASD) (Corvia Medical Inc., Tewkesbury, MA, USA) (Fig. 1a) is a nitinol device (outer diameter 19.4 mm) inserted percutaneously in the interatrial

Table 1 Current HFpEF device trials

Device	Manufacturer	Etiology	Title	1° endpoint	No. of patients	Design	NCT number
IASD	Corvia Medical	HFpEF	REDUCELAPHF II	Cardiovascular mortality or non-fatal, ischemic stroke through 6 months; 2. Change in baseline KCCR at 6 months	380	Triple blind with sham arm	NCT03088033
V wave	V-Wave Ltd	Heart failure	Relieve HF	Freedom from study-related major adverse cardiac and neurological events (MACNE) at 6 months	Not specified	Single arm <i>withdrawn</i>	NCT02511912
CORolla	Cor-Assist Cardiovascular Ltd.	HFpEF	CORolla® TAA for heart failure with preserved ejection fraction (HFpEF) and diastolic dysfunction (DD)	All-cause mortality and serious adverse events (SAE/As) at 6 months	10	Single-arm study design including with patients with isolated HFpEF, in NYHA f. Cl. III-IV	NCT02499601

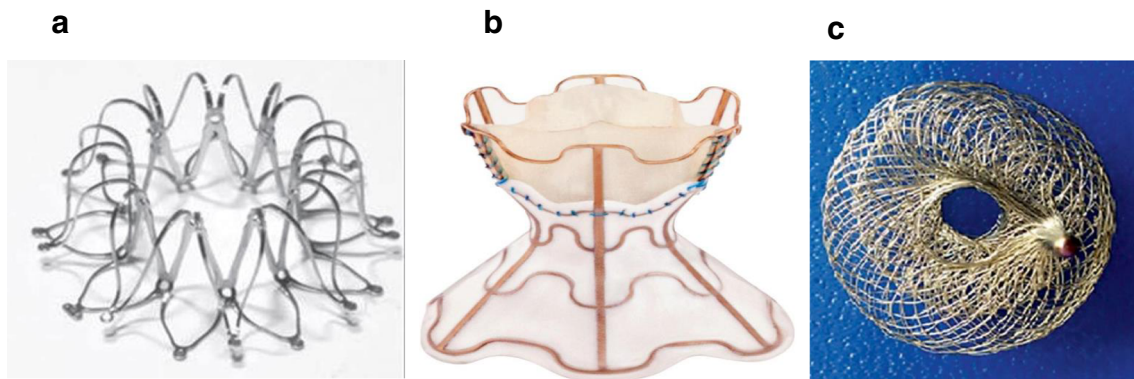


Fig. 1 Devices that are currently in evaluation for HFpEF. Current devices in research trials: **a** Corvia, **b** V wave, and **c** atrial flow regulator

septum to produce a permanent 8-mm atrial septal communication. It is delivered through a 16-F sheath via transfemoral vein access. The device is deployed after trans-septal puncture of the mid-fossa ovalis, positioning the delivery catheter into the left atrium and deploying the left atrial disc, retracting and apposing this disc to the atrial septum, verifying the right atrial location of the delivery catheter, and then deploying the right atrial disc such that the device is secured across the atrial septum and sits flush on the left atrial side. The device achieves bidirectional flow with a Qp:Qs ratio of 1.3:1. Antiplatelets recommended for 12 months and aspirin indefinitely.

The initial human experience was published in 2014 by Sondergaard et al. Eleven patients (EF > 45%, all with New York Heart Association [NYHA] III/IV heart failure and PCWP > 15 mmHg at rest or > 25 mmHg with exercise) were treated in a pilot study. At 30 days, PCWP had decreased in 10 of 11 patients (mean, 19.7 ± 3.4 mmHg at baseline and 14.2 ± 2.7 mmHg at 30 days; $p < .01$), most patients had improved by at least one NYHA class, and there was significant increase in 6-min walk distance [22].

This initial experience resulted in the larger open-label study “reduce elevated left atrial pressure in patients with heart failure (REDUCE LAP-HF)” which was a single-arm, phase 1 study designed to assess the performance and safety of IASD in patients older than 40 years with HFpEF symptoms uncontrolled with pharmacotherapy, EF > 40%, PCWP > 15 mmHg at rest, and > 25 mmHg during exercise. REDUCE LAP-HF enrolled patients in 21 centers in multiple countries and patients followed up for 6 months. Sixty-six patients had implantation attempted with 64 devices successfully implanted and no periprocedural complications. At 6 months, hemodynamic data was available for 59 patients with exercise. It showed 52% patients had a reduction in PCWP at rest and 58% had a lower PCWP during exertion with 39% fulfilling both these criteria. Mean exercise PCWP was lower at 6 months than at baseline, both at 20-W workload (mean 32 mmHg [SD 8] at baseline vs 29 mmHg [SD 9] at 6 months, $p = 0.0124$) and at peak exercise (34 mmHg [SD 8] vs 32 [SD 8], $p = 0.0255$),

despite increased supine mean exercise duration (baseline vs 6 months: 7.3 min [SD 3.1] vs 8.2 min [SD 3.4], $p = 0.03$). Sustained device patency at 6 months was confirmed with shunt ratio of 1.3:1. Using this data IASD received CE mark approval in May 2016 [23••].

One-year data follow-up of these patients by exercise hemodynamics showed there were no significant changes in the RA pressure, pulmonary artery pressure, or PCWP at rest or during exercise [24]. Implantation of the shunt device reduced the pressure gradient between the left and right atrium, as assessed by the PCWP to RA pressure gradient and this reduction was sustained through to 12 months [24]. There was a significant increase in total right-sided cardiac output after IASD implantation, as measured by thermodilution, and this continued through 12 months but LV cardiac output remained same [24]. The Qp:Qs ratio in patients undergoing cardiac catheterization at 12 months was 1.25 ± 0.25 , which was unchanged from that at 6 months (1.27 ± 0.24) [24]. However, exercise time increased significantly from baseline to 6 months (8.2 ± 3.4 versus 9.7 ± 3.2 min; $p < 0.05$), and this increase was sustained at 12 months (10.4 ± 4.2 min; $p < 0.05$ versus baseline) [24]. Similarly, there was an increase in the supine cycling peak work capacity from baseline to 6 months (48 ± 19 versus 60 ± 16 W; $p < 0.01$; $n = 17$), and this increase was sustained at 12 months (55 ± 15 W; $p < 0.01$ versus baseline) [24]. This led to sustained significant reduction in workload indexed PCWP > 12 months [24]. During the period 6 months to 1 year, 3 patients died representing an overall 1-year survival of 95% [24]. There was a total of 17 HF hospitalizations, occurring in 13 patients over the first year [24]. Of these, 10 HF hospitalizations events occurred within the first 6 months, in 10 patients. At 12 months, there were sustained significant improvements in New York Heart Association class and quality of life (Minnesota Living with Heart Failure) score [24].

To rigorously test the efficacy of next generation IASD system II, REDUCE Cardiac Output LAP-HF I trial was designed which was multi-center, prospective, randomized, parallel group, double-blinded as well as sham-controlled study [25]. IASD System II consists of a 1-piece, self-expanding

metal cage that has a double-disc design with an opening in the center and is echogenic and radiopaque. Key inclusion criteria included documented chronic symptomatic HF and (1) prior hospitalization for HF (or acute care facility/emergency room intensification of diuretic therapy) within the prior 12 months, or (2) elevated B-type natriuretic peptide (BNP) or N-terminal pro-BNP (NTproBNP) within the past 6 months with defined criteria in patients >40 years of age with EF > 40%, no right ventricular dysfunction, no pulmonary hypertension (< 4 Woods unit), and elevated LA pressure documented invasively by end-expiratory PCWP during supine bike exercise ≥ 25 mmHg, and PCWP-RA pressure (RAP) gradient ≥ 5 mmHg [25].

Patients were randomized 1:1 ratio between device and sham-controlled arms. Both patients and physicians who followed them were blinded to treatment assignment and hemodynamic findings. Both treatment and control arm patients underwent femoral venous access after randomization. Patients randomized to the treatment arm underwent a trans-septal puncture and IASD System II implantation guided by fluoroscopy and intracardiac or transesophageal echocardiography whereas control arm underwent all procedures except trans-septal puncture. The primary effectiveness endpoint was exercise PCWP at 1 month. The primary safety endpoint was major adverse cardiac, cerebrovascular, and renal events (MACCRE) at 1 month.

Ninety patients were enrolled, of which 44 met criteria and were randomized to the IASD ($N = 22$) and control ($N = 22$) groups. Mean age was 70 ± 9 years and 50% were female. Device was implanted successfully in 20/22 patients. At 1 month, the IASD resulted in a greater reduction in PCWP compared to sham-control ($p = 0.028$) meeting predefined primary efficacy endpoint. Peak PCWP decreased by 3.5 ± 6.4 mmHg in the treatment group vs. 0.5 ± 5.0 mmHg in the control group ($p = 0.14$) which was similar as seen previously in REDUCE LAP-HF trial at 6 months and 12 months. There were no periprocedural complications and 1 MACCRE event with worsening renal function. No patient from treatment arm was admitted for HF during this period whereas 9.1% (2/22) patients in sham-control arm were admitted. The lowering of PCWP during exercise and improvements in workload-corrected PCWP, exercise duration, and peak exercise workload compared to sham control were numerically better in the treatment group but the differences did not achieve statistical significance, as the trial was not powered to demonstrate effectiveness in these endpoints.

V Wave

The V wave device (V-Wave Ltd., Or Akiva, Israel), Fig. 1b, in the first generation consisted of an hourglass shaped, self-expanding nitinol frame that contains a tri-leaflet porcine pericardium tissue valve sutured inside which allowed

unidirectional flow from the LA to the right atrium if the pressure gradient exceeded 2 mmHg achieving a Qp:Qs of 1.1–2:1. The valve prevents reverse shunting of blood and prevents paradoxical embolism. The stent is deployed under fluoroscopic and transesophageal echo guidance with a 14-French sheath so that the neck of the hourglass is placed across the fossa ovalis and secured in place by its geometry with the wider entry funnel deployed in the left atrium and the wider exit funnel in the right atrium. The entry funnel and the central neck are encapsulated with expanded polytetrafluoroethylene (ePTFE) to facilitate laminar flow and limit tissue ingrowth during device healing. Three months of anticoagulation with coumadin or DOAC is recommended by the device manufacturer along with aspirin for life.

The V wave device was evaluated in 10 HF rEF patients in a single center in Canada using the special access process to prove the concept. The patients averaged 62 years of age and notably had an average LVEF of 25%, and NYHA class III or greater symptoms; the average PCWP at cath was 23 mmHg without right ventricular dysfunction. The average NTproBNP at baseline was 2712 pg/mL. The patients were evaluated at 3 months after the index procedure and in this small population, there was a reduction in NYHA class, improved their 6-min walk distance, and reported improved quality of life (QoL) and physical function. Echo cardiograms at 3 months showed a small decrease in LV volumes but importantly, there was a decrease in PCWP from 23 mmHg at baseline to 17 mmHg at 3-month follow-up; $p = 0.035$. Neither the RAP (9 vs 8 mmHg) nor the mean pulmonary artery pressure (29 vs 26 mmHg) showed a significant change [26].

At 1-year follow-up, resting shunt fraction had declined from a mean of 1.2:1 to 1.1:1, with 14% of patients having no interatrial flow. This occurred in conjunction with pannus thickening of the bioprosthetic leaflets and lumen loss, which prompted the creation of a second-generation device with extended ePTFE coating and without unidirectional valve and included a hood to prevent potential thromboemboli from opposing the right atrial side of the implant. This version of the device has not shown late lumen loss at 6 months in animal studies [26].

Cabau presented a larger series including of 22 patients from the original single center and 16 additional patients from the First in Man Multi-Center Feasibility Study performed in Israel and Italy [27]. The population included 30 patients with reduced LVEF (26%) and eight with preserved LVEF (50%). There was 100% implant success (38/38) but at 1 year, 5/36 (14%) of devices were occluded or stenotic. Stenosis conveyed a worse outcome. A further single-arm prospective, nonrandomized, open-label, multi-center study of the device was planned in patients with both HF rEF and HF pEF (NCT02511912) but was withdrawn in September 8, 2017.

Atrial Flow Regulator

The atrial flow regulator (AFR) (Occlutech, Istanbul, Turkey), Fig. 1c, is a self-expandable double-disc wire mesh device constructed from 0.004–0.0075-in. nitinol braided into two flat discs connected by a waist of 1–2 mm and central fenestration which enables bidirectional flow. A welded ball connector located on the device's proximal disc serves as an adapter to connect the delivery system for deployment. After implantation, the AFR conforms completely to the atrial septum leaving an interatrial communication with a preselected fixed diameter. The device is easy to handle, self-centers following deployment, and is retrievable prior to release. The device is available in 6, 8, and 10 mm fenestration diameters with a total device diameter of 18, 24, and 30 mm delivered via 10- to 12-F sheath.

The first clinical utilization of the device followed a compassionate use approval from the US Food and Drug Administration. The patient was a 54-year-old woman with severe and irreversible pulmonary artery hypertension. Implantation was associated with immediate right-to-left shunting and a corresponding decrease in arterial saturation (from 95 to 89%). She reported functional improvement at 6 weeks [28•]. This experience was later extended to 12 patients (mean age 28.3 ± 8.5 years) with severe irreversible pulmonary arterial hypertension [29]. All the patients were receiving optimal doses of two oral pulmonary vasodilators of which one belonged to endothelin receptor antagonists and the other belonged to phosphodiesterase-5 inhibitors. All procedures were successful without any major complications and antiplatelets were given to maintain patency of device. All patients had relief of syncope and 6-min walk distance improved significantly from 377.3 ± 33.2 to 423 ± 31.32 m. The 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) also showed a significant improvement [29]. Even though echocardiographic parameters of right ventricular function did not show significant change, inferior caval vein congestion and pericardial effusion were reduced due to improvement in heart failure. The device was patent in all patients at a median follow-up of 189 days (range 10–296 days) resulting in a significant reduction of oxygen saturations from 98 ± 0.18 to $85.2 \pm 62.86\%$ after exercise [29]. Complete endothelialization of nitinol atrial septal occluders was demonstrated within a few months after implantation, permitting withdrawal of antiplatelets after 6–12 months.

In patients with diastolic dysfunction and left to right atrial gradient, the shunt direction will be left to right and is expected to get results similar to other interatrial septostomy devices with shunt ratio based on device size. An international clinical trial PRELIEVE to study AFR device is currently recruiting. It is an open-label, nonrandomized trial including up to 30 patients with symptomatic heart failure (HFpEF or HFrEF) and a heart failure admission in the past 12 months (NCT03030274).

CoRolla

CoRolla (CorAssist Inc., Haifa, Israel) is an intraventricular device invented by Dr. Yair Field which is designed to be implanted by minimally invasive transapical approach off pump. It is elastic self-expanding internal spring like device which is based on mechanical principles of energy transfer from systole to diastole. The device applies direct internal expansion forces distributed on the left ventricle wall and septum to directly improve diastolic function. The device improves filling performance and diastolic dynamics without needing an external power source. Preclinical studies have showed safety over 24-month duration and first in human implantation was carried out in RAMBAM medical center, Haifa, Israel, in July 2017. There is registered clinical trial NCT01956526 which is an open-label study to evaluate CoRolla in HFpEF patients with NYHA III-IV and in patients with Aortic stenosis who are undergoing aortic valve replacement as add on procedure. Primary aim of trial is to assess safety over 12 months post procedure and assess for efficacy over 36 months with clinical and echocardiographic endpoints.

Long-term Considerations

Biggest concern for interatrial septostomy devices is an increased volume loading of right-sided circulation from shunting causing pulmonary hypertension and leading to RV dysfunction. Such hemodynamic changes might affect other organs already compromised in HFpEF, such as the kidneys, with a subsequent negative impact on long-term outcome [30]. Although the literature from congenital heart disease patients suggest small shunts (< 1.3:1) are generally tolerable for decades [28•], the adult heart failure phenotype, especially with hypertension, may be different. Reported experience with the IASD system in heart failure patients has revealed nonsignificant increases in right atrial and ventricular volumes at 6 months after implantation, which did not progress at 12-month follow-up and have not been associated with depressed right ventricular function or pulmonary hypertension [24].

Another factor that may influence long-term outcome is the use of anticoagulation: IASD implantation required 1-year dual antiplatelet therapy, AFR required 6–12 months whereas V wave required warfarin or DOAC for 3 months following implantation. All devices require indefinite, low-dose aspirin. Additionally, because atrial arrhythmias are a common manifestation of unrepaired congenital atrial septal defects and are observed with greater frequency in the months after implantation of other atrial septal devices [29], ongoing surveillance is warranted post IASD implantation. As atrial arrhythmias are also common in heart failure patients, it will be interesting to see if the incidence of atrial arrhythmias in interatrial septostomy devices is even higher or lower than anticipated.

The anticoagulation required for atrial fibrillation or Flutter when concurrent with DAPT may also increase bleeding risk.

Recently, closure of PFO has been shown to be beneficial in long-term management of cryptogenic stroke likely due to preventing paradoxical embolism [31, 32]. It will be important to follow the IASD patients long term to assess if incidence of strokes is found to be higher than general population and needs to be included in any risk versus benefit discussion.

Sham-controlled trial for renal nerve denervation has shown that invasive treatment trials for devices may be subject to bias. Also, changing patient behavior due to study involvement, known as the “Hawthorne effect,” could have influenced the study results [32], possibly by increasing medication compliance during follow-up. In view of these concerns, it is important that future randomized trials include an active sham procedure or blinded readers with larger sample size and for longer duration to get definitive evidence of efficacy.

Conclusion

Diastolic heart failure patients still do not have effective pharmacological therapies other than managing underlying comorbidities including hypertension, diabetes, and CKD. Innovative approaches to lower left atrial pressure with devices or increase compliance of LV offer options for this unmet need. Early clinical studies have provided evidence of efficacy of these devices with most robust evidence base for IASD. Ongoing clinical trials are needed to provide more evidence of efficacy as well as longevity of therapeutic effect for other devices.

Compliance with Ethical Standards

Conflict of Interest Amit Gupta and Steven R. Bailey declare that they have no conflict of interest.

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

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