

Emerging Technologies for Heart Diseases

Volume 1: Treatments for Heart Failure
and Valvular Disorders

Edited by

Udi Nussinovitch MD PhD

Department of Cardiology and Applicative Cardiovascular Research Center (ACRC),
Meir Medical Center, Kfar Saba, Israel; Sackler Faculty of Medicine, Tel Aviv University,
Tel Aviv, Israel



ACADEMIC PRESS

An imprint of Elsevier

Left atrial decompression devices

Scott M. Lilly^a, Anezi Uzendu^a, Daniel Burkhoff^b

^aDepartment of Cardiology, Ohio State University Wexner Medical Center, Columbus, OH, United States

^bColumbia University Medical Center, and Cardiovascular Research Foundation, New York, NY, United States

5.1 Introduction

Heart failure can be classified based on ejection fraction (EF) into those with preserved (HFpEF; EF \geq 50%), mid-range (HFmrEF; EF 40%–50%), or reduced (HFrEF; EF $<$ 40%) left ventricular systolic function. This separation somewhat correlates with differences in associated risk factors, pathophysiology, and clinical trajectory [1,2]. The clinical burden of HFpEF and HFmrEF combined now exceeds that of HFrEF, a relationship that is anticipated to continue to diverge [3–5]. This may reflect more thorough surveillance, the incorporation of specific indices into imaging and hemodynamic studies, and the increasing prevalence of hypertension, diabetes, obesity, and other comorbidities. In addition to the growing prevalence, mortality among those with relatively preserved ejection fraction is comparable to that of HFrEF. Unfortunately, there is a paucity of effective therapies for this group of patients [4].

5.2 Clinically available solutions

The pharmacologic therapies that are the cornerstones of for treatment of HFrEF have not produced reliably improved outcomes in those with EF $>$ 40%. This is apparent in national and international society guideline documents—there are only two high level recommendations: (1) the use of medications to control hypertension and (2) the use of diuretics in setting of volume overload [2,6]. As left atrial pressure is elevated in patients with heart failure irrespective of ejection fraction, device-based strategies to reduce it have been developed in effort to alleviate symptoms and improve outcomes in heart failure.

5.3 Clinical trials and experimental treatments

The concept of selective left atrial decompression developed in tandem with the realization that many patients with dyspnea had normal resting hemodynamics, though no other clear cause for symptoms. In fact, it was only when patients with unexplained dyspnea were subjected to exercise, that pronounced elevations in left atrial pressure were observed and implicated [7]. In addition to serving as the physiological substrate of dyspnea, elevated left atrial pressures (or surrogate pulmonary capillary wedge pressures) are associated with poorer functional status, a greater incidence of heart-failure hospitalization, and increased long-term mortality [8].

Interatrial shunt therapies have been created in effort to permit left-to-right atrial flow, with the expectation of selective reductions in left atrial pressure and alleviation of pulmonary venous congestion, and dyspnea. The theoretical benefit of an iatrogenic shunt has conceptual roots. For example, there are many reports of patients with left-sided valve disease, and a coincident atrial septal defect that fared better than would be anticipated, presumptively due to the left atrial pressure relief provided by the congenital shunt. In one of these reports, a woman with severe mitral stenosis and an atrial septal defect lived until 74 years old, and survived 11 pregnancies [9]. Others have observed prompt elevations in left atrial pressure after surgical or transcatheter closure of an atrial septal defect, and the onset of clinical heart failure in a subset [10,11].

Percutaneous balloon septostomy has been used with variable success among patients with refractory heart failure and hypoxemia, in effort to decompress the heart and attenuate pulmonary edema [12–15]. In one series, nine patients with severe left ventricular failure requiring extracorporeal membrane oxygenation received blade and balloon interatrial septostomy. The authors observed left atrial decompression with a reduction in left atrial pressure by approximately 50%. Among

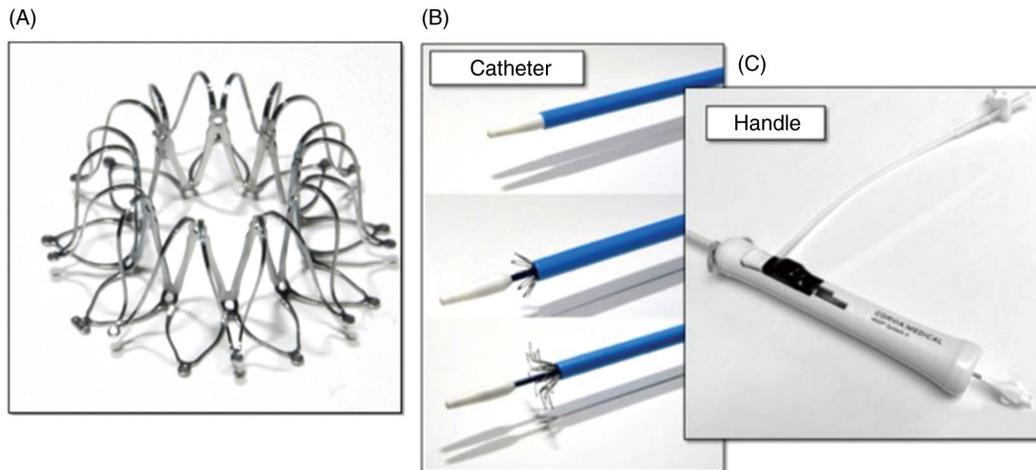


FIGURE 5.1 InterAtrial Shunt Device (IASD®; Corvia Medical Inc., Tewksbury, MA, USA) with delivery system. *Adapted with permission from Corvia.*

the seven survivors, only two of the defects remained patent at 2 months, underscoring the transient nature of balloon atrial septostomy [12]. A larger series ($n = 64$) with refractory pulmonary edema receiving extracorporeal membrane oxygenation also underwent balloon septostomy (mean diameter 22 mm). All patients experienced left atrial decompression, with an average 66% reduction in left atrial pressure and the absence of right-to-left flow [13].

Collectively, these represent an understanding that left atrial pressure is implicated in dyspnea and pulmonary edema, and that in some instances an interatrial communication may be clinically beneficial. To date, two devices have entered clinical trials, and a third device, initially evaluated in pulmonary hypertension, is now undergoing pilot heart failure studies. In the paragraphs that follow, we will review each of these devices, existing data, and ongoing considerations for this class of technologies.

There are three interatrial shunt devices that have been developed and are in clinical trials.

5.3.1 The InterAtrial Shunt

Corvia InterAtrial Shunt Device (IASD; Corvia Medical, Tewksbury, MA, USA) is the most thoroughly and scientifically evaluated interatrial shunt device to date. It is a one-piece nitinol device, with an outer diameter of 19 mm and a central opening that is 8 mm in diameter (Fig. 5.1, top). After femoral venous access (16 Fr) and standard trans-septal puncture, the delivery system (Fig. 5.1, bottom) is placed across the septum, the left atrial disk is exposed and retracted to the septum, and then the right atrial disk is unsheathed creating an interatrial communication (shunt) with pressure-dependent dynamic left-to-right flow (Fig. 5.2). In the heart failure population, this can decompress the left atrium and alleviate pulmonary venous hypertension. The 8 mm shunt diameter was selected based on a computer simulation in which the shunt diameter was varied, and the effects on left-to-right shunt ($Q_p:Q_s$) at rest and with exercise were simulated. At this diameter, the anticipated $Q_p:Q_s$ was 1.3:1, and flow increased dynamically with activity [16]. Among adults with congenital atrial septal defects, shunts $< 1.5:1$ are generally well tolerated, occur without dilation or hypertrophy in right-sided heart chambers, and do not require closure [17]. After implantation of the IASD, dual antiplatelet therapy is recommended for 6 months, unless the patient is already receiving an oral anticoagulant (Table 5.1).

The original REDUCE-LAP HF trial was performed to assess safety and device performance [18]. This was a multi-center, nonrandomized, prospective, open-label, single-arm study. A total of 64 patients with NYHA II or greater heart failure symptoms and an ejection fraction greater than 40% were implanted. Hemodynamic criteria for participation included pulmonary capillary wedge pressure either at rest (> 15 mmHg) or with exercise (> 25 mmHg), and a right atrial pressure that was lower than left atrial pressure. Primary performance endpoints included successful device implantation, reduction in wedge pressure after 6 months, and persistent left-to-right shunting. Primary safety endpoints included periprocedural and 6-month major adverse cardiac and cerebrovascular events (death, stroke, myocardial infarction, or a systemic embolic event), or need for cardiac surgical device removal. Secondary outcomes included quality-of-life measures. The mean core laboratory determined ejection fraction of the cohort was 47%, most were NYHA III (72%), and hypertension was prevalent (81%). At 6 months, 42 patients (71%) had reduction in wedge pressure either at rest or during exercise (Fig. 5.3) and

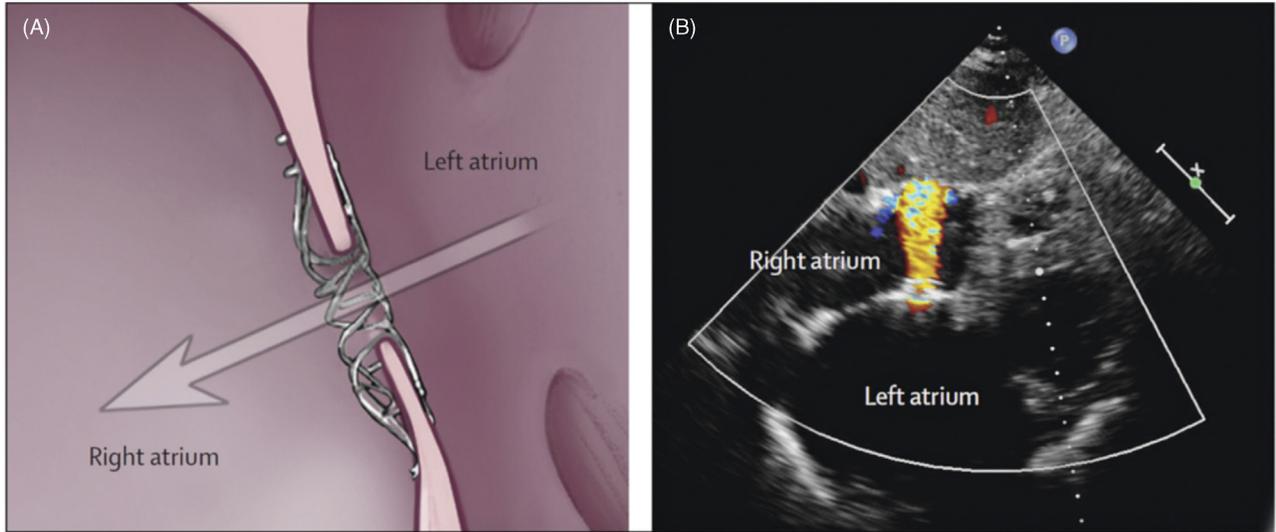


FIGURE 5.2 (A) Schematic of Corvia IASD after implantation. (B) Transthoracic echo with color Doppler demonstrating left to right shunt [18]. Reproduced with permission from Corvia.

Table 5.1 Comparison of interatrial shunt devices.

| Device | Manufacturer | Population | Mechanism | Unique features |
|---------------|---------------------|------------------|----------------------|---|
| IASD | Corvia Medical Inc. | HFpEF and HFmrEF | Bidirectional shunt | First device tested in HF Most robust data at this point |
| V-Wave | V-Wave Ltd | HFpEF, HFfrEF | Unidirectional shunt | Bovine pericardial tri-leaflet valve to prevent paradoxical embolism and shunt reversal |
| AFR | Occlutech | HFpEF, HFfrEF | Bidirectional Shunt | Repositionable, Retrievable Comes in various sizes |

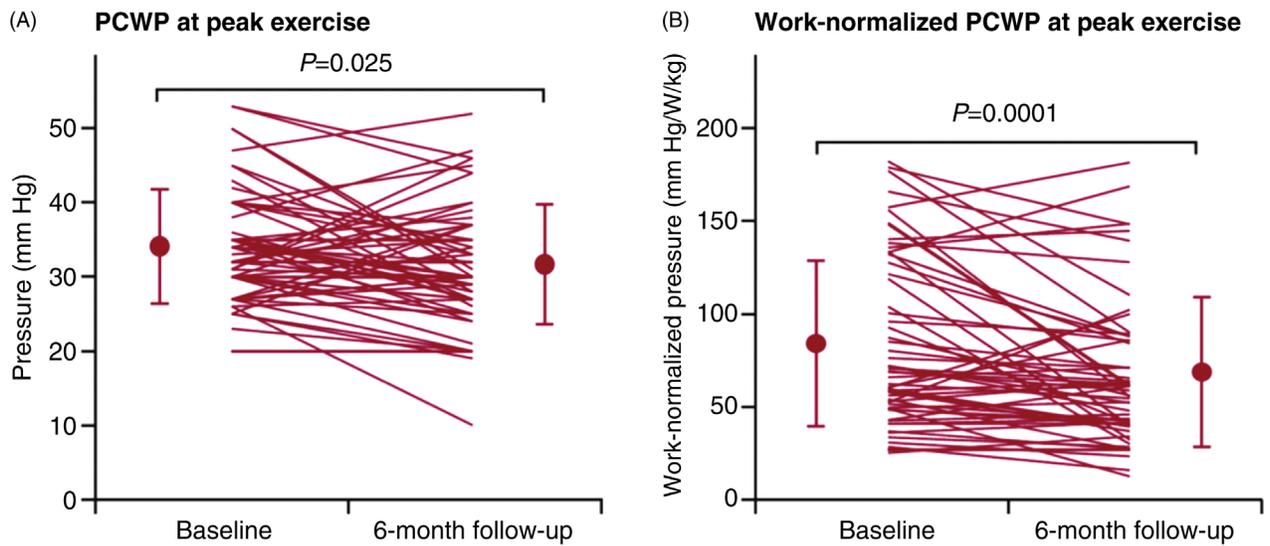


FIGURE 5.3 REDUCE-LAP data demonstrating change in pulmonary capillary wedge pressure (PCWP) and work normalized PCWP at max exercise. Reproduced with permission from Hasenfuss et al. [18].

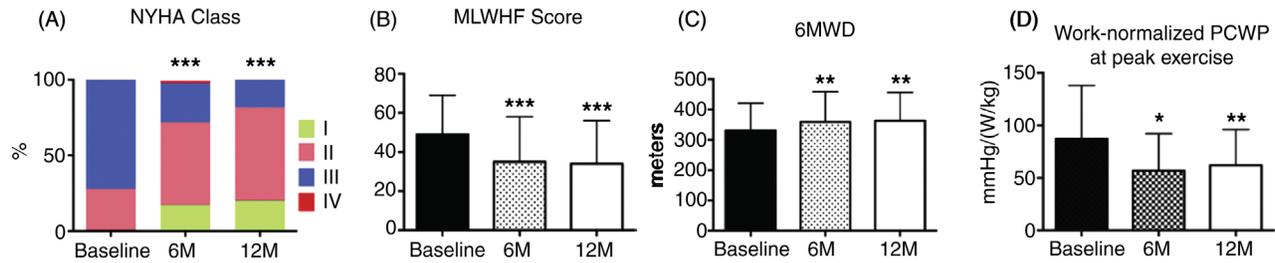


FIGURE 5.4 Twelve-month follow-up of REDUCE-LAP. (A) Changes in New York Heart Association Class. (B) Minnesota Living with Heart Failure Score. (C) Six-minute walk distance. (D) Work-normalized pulmonary capillary wedge pressure at peak exercise. *Reproduced with permission from Kaye et al. [19].*

there were improvements in NYHA functional class, Minnesota Living with Heart Failure Questionnaire, and 6-minute walk test distance [19]. The 1-year follow-up on these patients was reported at the European Society of Cardiology Meeting in 2018 (Fig. 5.4). At this time, all shunts remained patent, exercise associated reductions in pulmonary capillary wedge pressure were again observed, and the improvements in functional status (exercise time, MLWH NYHA class) were maintained. There was a small increase in right ventricular size at 6 months, which did not progress at 12 months; right ventricular function was maintained. At 12 months, death had occurred in three patients, and one patient had suffered a stroke [28].

A randomized double-blinded sham-controlled trial followed shortly thereafter. REDUCE-LAP HF I randomized 44 patients to either the IASD or a sham control procedure [20]. Eligible patients were randomized immediately following exercise right heart catheterization. Inclusion required NYHA \geq III, an exercise pulmonary capillary wedge pressure (PCWP) \geq 25 mmHg, with left atrial pressure at least a 5 mmHg greater than right atrial pressure. At 1 month there was a significant \sim 3–5 mmHg reduction in exercise PCWP compared to control, and there were no periprocedural adverse events. One-year follow-up was recently reported [21]. All shunts were patent, and 81% of patients had not experienced a heart failure hospitalization. This reduction, in this underpowered study, compared to control, was nearly significant ($P = 0.06$) as was improvement in NYHA class ($P = 0.08$).

To date, the aggregate safety profile of the IASD has been encouraging. In a total of 97 publicly reported cases, 1 and 2 year survival has been 96% and 91% and freedom from stroke 99%, respectively. There has been no identified thrombus on the device, they have uniformly remained patent, and none have required closure or surgical explant.

REDUCE-LAP HF II (NCT03088033), a double-blinded sham-controlled pivotal clinical trial with the same hemodynamic entry criteria, has commenced with the goal of randomizing 608 patients to the IASD or control (1:1). Primary outcomes include aggregate cardiovascular mortality or nonfatal stroke; total rate of HF events requiring intravenous diuresis and change in KCCQ (Kansas City Cardiomyopathy Questionnaire) at 12 months.

5.3.2 V-Wave device

The V-Wave® device (V-Wave Ltd, Caesarea, Israel) is an hour-glass shaped nitinol frame, covered with ePTFE in effort to prevent tissue ingrowth (Fig. 5.5). The initial 5 mm central opening generation of this device contained a one-way valve to restrict flow in one direction: left to right. However, early clinical testing identified a high rate of pannus infiltration and shunt stenosis or occlusion at 12 months. The second-generation device with a 5.1 mm central opening has established patency through 6 months in animal models [23]. The device is implanted after femoral venous access (14 Fr), standard trans-septal puncture in the middle of the fossa ovalis. The fully deployed device provides an interatrial connection that is 5 mm in diameter. The recommendation is for 6 months of dual antiplatelet therapy, and aspirin 81 mg thereafter.

Preclinical evaluation utilized an ovine model of microembolization-induced ischemic cardiomyopathy. Twenty-one were evaluated: 14 received V-Wave implants and the remaining 7 were sham controls. Both groups were followed with echocardiography and hemodynamics for 12 weeks. At study termination, the V-Wave group had higher ejection fraction ($46 \pm 11\%$ vs. $18 \pm 3\%$), lower-left atrial pressure (14 ± 3 mmHg vs. 25 ± 5 mmHg), and right atrial pressure (8 ± 4 mmHg vs. 15 ± 4 mmHg; all $P < 0.05$). There was also an apparent survival advantage among those that received the V-Wave device (13/14 vs. 4/7, $P = 0.047$) [24].

In humans, initial proof of principle and safety of the generation 1 device was established in 10 patients with HFrEF and NYHA III or greater symptoms. Implantation was successful in all patients with no periprocedural complications. One patient died before the 3 month follow-up (ventricular tachycardia), and eight of nine remaining in the cohort had an improvement in NYHA class. There was a significant reduction in PCWP at 3 months (mean 6 mmHg; $P = 0.035$) [23].

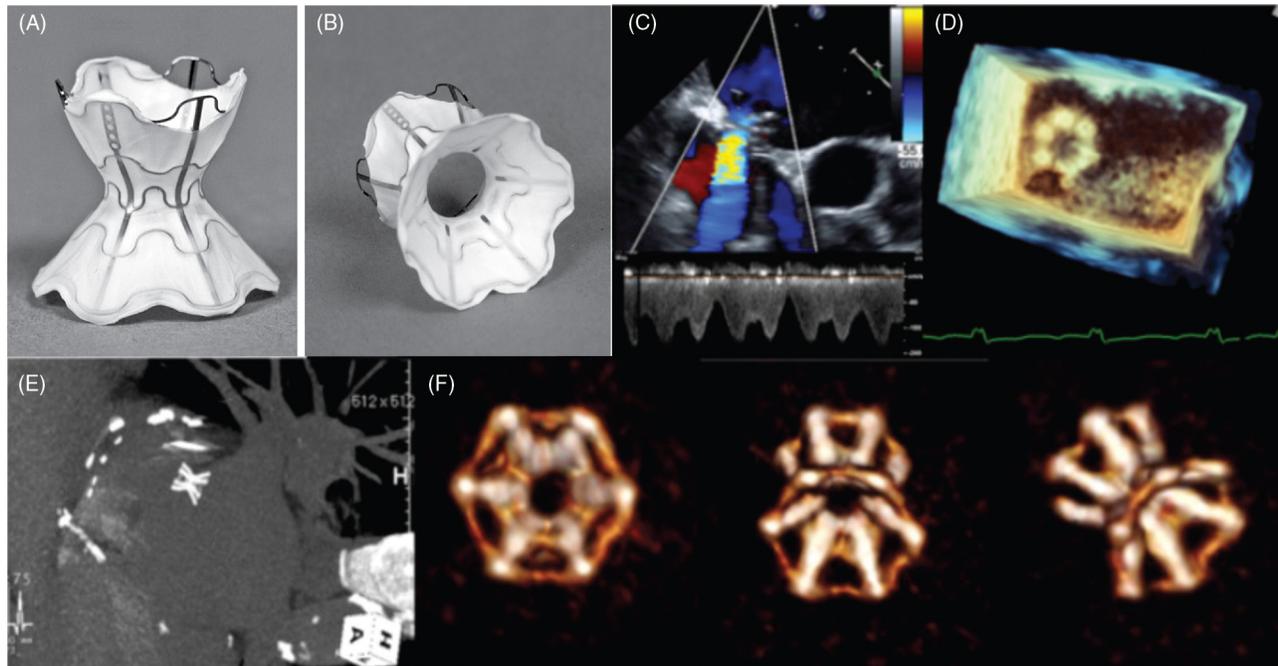


FIGURE 5.5 V-Wave® Device (V-Wave Ltd, Caesarea, Israel). Panel A demonstrates the initial V-Wave device, comprising an ePTFE-coated nitinol frame, with a one-way valve. The valve was removed in subsequent iterations of the device due to decreased shunt patency. Panels B, C, D are transesophageal images of the V-Wave device deployed in the interatrial septum. (E) Color doppler is used to demonstrate shunt patency and direction. (F) Computed tomography imaging and reconstruction of the device post implant. *Reproduced with permission from Amat-Santos et al. [22] and Guimarães et al. [33].*

The combined open label study data from 38 patients (30 HFrEF, 8 HFpEF) ensued. Implant success was 100%. There was one procedural pericardial tamponade that required pericardiocentesis. At 1 year, there were two deaths, non-device-related; no strokes were observed in the cohort. Patency rates however were suboptimal. Half (50%) of the cohort had absent left to right flow (14%) or reduced left to right flow (36%) at 1 year follow-up. Histology implicated pannus infiltration as the source of reduced flow. Interestingly, this was observed less frequently among patients with lower ejection fractions, or higher baseline left atrial pressures. Among the 50% of patients with patent shunts, pulmonary capillary wedge pressure declined ($P = 0.009$) and ejection fraction improved ($P = 0.007$) as did 6-minute walk distance ($P = 0.001$) [29].

“Reducing Lung Congestion Symptoms in Advanced Heart Failure” (RELIEVE-HF; NCT03499236) is a randomized controlled trial with the second-generation V-Wave device. Estimated enrollment, including approximately 120 roll-in patients, is 500 patients with HFpEF or HFrEF and NYHA III or greater heart failure symptoms. Study participants will be randomized to the device or sham procedure control. First enrollments occurred in September 2018.

5.3.3 Atrial flow regulator

The atrial flow regulator (AFR; Occlutech, Istanbul, Turkey) was initially studied in severe pulmonary hypertension, although left-sided failure trials are now ongoing. This device is a nitinol mesh device composed of two flat disks with a 1- to 2-mm connecting neck and central fenestration that enables bidirectional flow (Figs. 5.6 and 5.7). It is available in 6, 8, and 10 mm sized fenestrations. The device self-centers prior to release and conforms to the atrial septum. It is repositionable and retrievable after deployment, and there are a variety of sizes to choose from. Depending on the size elected, it is delivered via a 10–12 Fr sheath in the femoral vein.

The initial experience with this device involved a 54-year-old woman with severe irreversible pulmonary hypertension [26]. Implantation was successful and was associated with right-to-left shunting and a manifest in part by a decrease in arterial saturation (from 95% to 89%). The patient experienced functional improvement at 6 weeks. More recently, a nonrandomized single-center study was performed to assess feasibility, safety, and efficacy in 12 patients with severe pulmonary hypertension, right heart failure, and syncope. All devices were implanted successfully and were patent at last

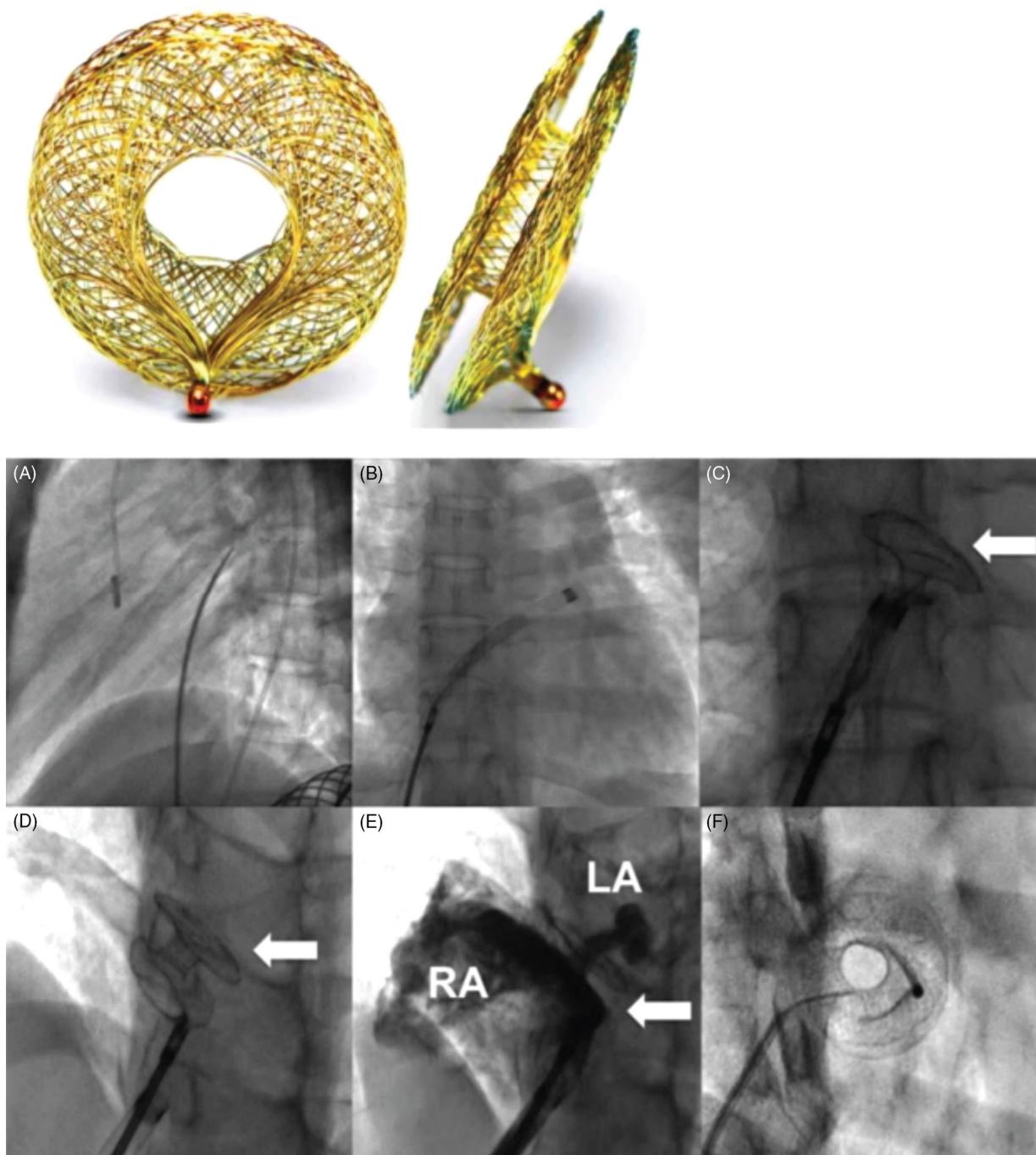


FIGURE 5.6 Atrial flow regulator (AFR; Occlutech, Istanbul, Turkey). Top: the AFR device. Bottom: AFR implantation. After trans-septal puncture (A), the delivery sheath is passed across the septum (B). One at a time disks are deployed straddling the septum (C, D). Confirmation of fenestration patency with contrast injection and direct visualization can then be performed (E, F). *Reproduced with permission from Rajeshkumar et al. [25].*

follow-up (median 189 days, range 10 to 296 days). There was a significant improvement in symptoms as well with relief of syncope, improved 6-minute walk distance (377.3 ± 33.2 to 423 ± 31.32 m), and increased cardiac output (2.36 ± 0.52 to 2.89 ± 0.56 L/min/m²) [25].

An international open-label nonrandomized trial is ongoing for patients with HFpEF and HFrEF with NYHA III or greater and at least 1 heart failure hospitalization in the preceding 12 months. The Pilot Study to Assess Safety and Efficacy of a Novel Atrial Flow Regulator in Heart Failure Patients (PRELIEVE; NCT03030274) has primary outcome measures that encompass device safety, stability, and shunt patency.

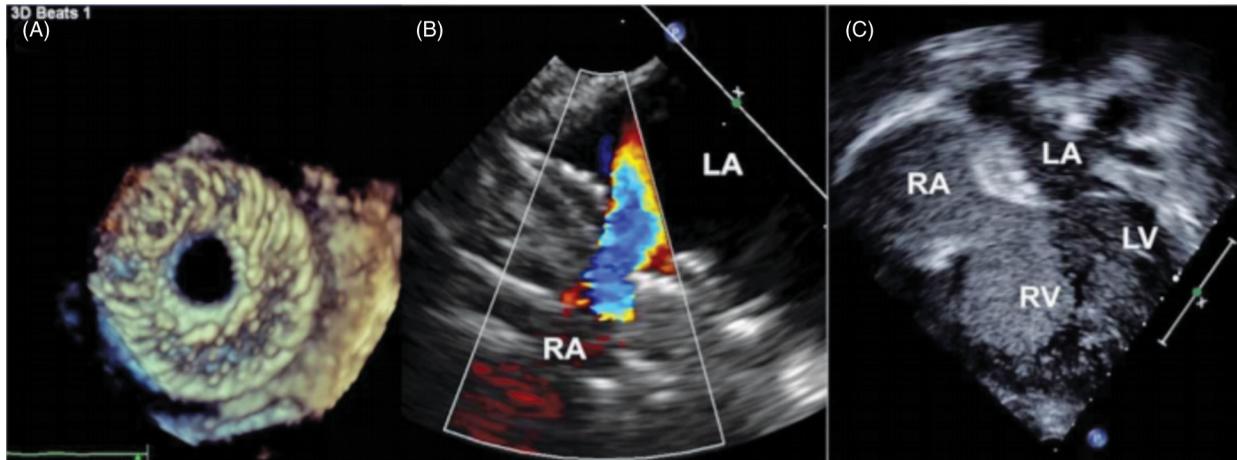


FIGURE 5.7 Echocardiography after atrial flow regulator implantation. (A) Enface view using 3D transesophageal echo. (B) Transesophageal color doppler. (C) Transthoracic agitated saline used to demonstrate shunt. *Reproduced with permission from Rajeshkumar et al. [25].*

5.4 Preclinical technologies

The authors are not aware of additional preclinical technologies that target left atrial decompression.

5.5 Emerging concepts and innovations

There is consensus that left atrial decompression imparts improvements in functional status and can alleviate cardiac dyspnea. Whether these results are durable and have favorable effects on overall outcomes remains the focus of ongoing trials. As the clinical devices described before show promise in heart failure populations, whether they also have utility among patients with moderate or greater mitral or aortic valve disease is of interest, as is a potential role for these devices in advanced pulmonary hypertension. Additionally, future device iterations are likely forthcoming. Among these, reliable mechanisms to prevent paradoxical embolism and enable simple extraction or closure may be incremental developments. Other iterations, such as direct pressure, flow monitoring, and/or rhythm monitoring, might also be clinically useful as the safety and efficacy of additional drug- or device-based therapies are introduced. With the proliferation of devices for heart failure and valve disease, those that are capable of integrating multiple components will have a strategic advantage within the portfolio of cardiovascular therapies.

There are also left atrial devices in early development, designed for heart failure or other indications. The “Left Atrial Appendage Shunt” [31] is a device that intends to create a channel between the left atrial appendage and another cardiovascular target structure (inferior vena cava or pulmonary artery). Although not a device for the heart failure population, it is intended to increase flow in the left atrial appendage and thereby provide some degree of stroke prophylaxis. The authors are aware of no preclinical or clinical trials for this device.

Another left atrial device with a U.S. patent is a form of ventricular assist device, implanted into the left atrium, and connecting to the aorta, with flow driven by an “impellar” [32]. The intent of the device is to unload and reduce wall stress in patients with poorly functioning left ventricles. The authors are aware of no preclinical or clinical trials for this device.

5.6 Conclusions, future challenges and opportunities

While the existing data for interatrial shunt therapies show promise, the long-term consequences remain unknown. For example, the effect of chronic left-to-right shunt on right ventricular size and function will be important to ascertain. Experience from pediatric and adult populations with small atrial septal defects suggests that abnormalities in the atrial septum typically only manifest in right heart symptoms after decades, and the devices described herein (up to ~ 1.3) are perhaps unlikely to result in considerable chronic remodeling. Current guidelines for the care of adults with congenital heart diseases [11] do not recommend therapy for asymptomatic patients without right atrial or ventricular enlargement with Qp:Qs of 1.5:1 or lower. Other concerns include the possibility of paradoxical embolus, or atrial arrhythmias—the latter being often poorly tolerated by patients with HFpEF and observed with other devices implanted in the atrial septum [27]. Longer-term follow-up will be necessary to establish the risks and benefits of these devices.

References

- [1] Iwano H, Little WC. Heart failure: what does ejection fraction have to do with it? *J Cardiol* 2013;62(1):1–3.
- [2] Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016;37(27):2129–200. Epub 2016/05/22. doi: 10.1093/eurheartj/ehw128. PubMed PMID: 27206819.
- [3] Krittanawong C, Kukin ML. Current management and future directions of heart Failure with preserved ejection fraction: a contemporary review. *Curr Treat Options Cardiovasc Med* 2018;20(4):28. doi: 10.1007/s11936-018-0623-1.
- [4] Tsao CW, Lyass A, Enserro D, Larson MG, Ho JE, Kizer JR, et al. Temporal trends in the incidence of and mortality associated with heart failure with preserved and reduced ejection fraction. *JACC Heart Fail* 2018;6(8):678–85. Epub 2018/07/17. doi: 10.1016/j.jchf.2018.03.006. PubMed PMID: 30007560.
- [5] Zakeri R, Cowie MR. Heart failure with preserved ejection fraction: controversies, challenges and future directions. *Heart* 2018;104(5):377.
- [6] Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation* 2017;136(6):e137–61. Epub 2017/04/30. doi: 10.1161/cir.0000000000000509. PubMed PMID: 28455343.
- [7] Borlaug BA, Nishimura RA, Sorajja P, Lam CS, Redfield MM. Exercise hemodynamics enhance diagnosis of early heart failure with preserved ejection fraction. *Circ Heart Fail* 2010;3(5):588–95. Epub 2010/06/15. doi: 10.1161/cirheartfailure.109.930701. PubMed PMID: 20543134; PubMed Central PMCID: PMC3048586.
- [8] Dorfs S, Zeh W, Hochholzer W, Jander N, Kienzle RP, Pieske B, et al. Pulmonary capillary wedge pressure during exercise and long-term mortality in patients with suspected heart failure with preserved ejection fraction. *Eur Heart J* 2014;35(44):3103–12. Epub 2014/08/28. doi: 10.1093/eurheartj/ehu315. PubMed PMID: 25161181.
- [9] Askey JM, Kahler JE. Longevity in extensive organic heart lesions: a case of Lutembacher's syndrome in a man aged 72. *Ann Intern Med* 1950;33(4):1031–6. Epub 1950/10/01. PubMed PMID: 14771769.
- [10] Ewert P, Berger F, Nagdyman N, Kretschmar O, Dittrich S, Abdul-Khalqi H, et al. Masked left ventricular restriction in elderly patients with atrial septal defects: a contraindication for closure? *Catheter Cardiovasc Interv* 2001;52(2):177–80. Epub 2001/02/15. PubMed PMID: 11170324.
- [11] Beyer J. Atrial septal defect: acute left heart failure after surgical closure. *Ann Thorac Surg* 1978;25(1):36–43. doi: https://doi.org/10.1016/S0003-4975(10)63484-4.
- [12] Seib PM, Faulkner SC, Erickson CC, Van Devanter SH, Harrell JE, Fasules JW, et al. Blade and balloon atrial septostomy for left heart decompression in patients with severe ventricular dysfunction on extracorporeal membrane oxygenation. *Catheter Cardiovasc Interv* 1999;46(2):179–86. Epub 1999/05/29. doi: 10.1002/(sici)1522-726x(199902)46:2 < 179::aid-ccd13 > 3.0.co;2-w. PubMed PMID: 10348539.
- [13] Baruteau AE, Barnette T, Morin L, Jalal Z, Boscamp NS, Le Bret E, et al. Percutaneous balloon atrial septostomy on top of venoarterial extracorporeal membrane oxygenation results in safe and effective left heart decompression. *Eur Heart J Acute Cardiovasc Care* 2018;7(1):70–9. Epub 2016/10/16. doi: 10.1177/2048872616675485. PubMed PMID: 27742755.
- [14] Johnston TA, Jaggars J, McGovern JJ, O'Laughlin MP. Bedside transeptal balloon dilation atrial septostomy for decompression of the left heart during extracorporeal membrane oxygenation. *Catheter Cardiovasc Interv* 1999;46(2):197–9. Epub 1999/05/29. doi: 10.1002/(sici)1522-726x(199902)46:2 < 197::aid-ccd17 > 3.0.co;2-g. PubMed PMID: 10348543.
- [15] Aiyagari RM, Rocchini AP, Remenapp RT, Graziano JN. Decompression of the left atrium during extracorporeal membrane oxygenation using a transeptal cannula incorporated into the circuit. *Crit Care Med* 2006;34(10):2603–6. Epub 2006/08/18. doi: 10.1097/01.ccm.0000239113.02836.f1. PubMed PMID: 16915115.
- [16] Kaye D, Shah SJ, Borlaug BA, Gustafsson F, Komtebedde J, Kubo S, et al. Effects of an interatrial shunt on rest and exercise hemodynamics: results of a computer simulation in heart failure. *J Card Fail* 2014;20(3):212–21. Epub 2014/02/04. doi: 10.1016/j.cardfail.2014.01.005. PubMed PMID: 24487087.
- [17] Stout KK, Daniels CJ, Aboulhosn JA, Bozkurt B, Broberg CS, Colman JM, et al. 2018 AHA/ACC guideline for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2019;73(12):e81–e192. Epub 2018/08/16. doi: https://doi.org/10.1016/j.jacc.2018.08.1029.
- [18] Hasenfuss G, Hayward C, Burkhoff D, Silvestry FE, McKenzie S, Gustafsson F, et al. A transcatheter intracardiac shunt device for heart failure with preserved ejection fraction (REDUCE LAP-HF): a multicentre, open-label, single-arm, phase 1 trial. *Lancet* 2016;387(10025):1298–304. Epub 2016/03/31. doi: 10.1016/s0140-6736(16)00704-2. PubMed PMID: 27025436.
- [19] Kaye DM, Hasenfuss G, Neuzil P, Post MC, Doughty R, Trochu JN, et al. One-year outcomes after transcatheter insertion of an interatrial shunt device for the management of heart failure with preserved ejection fraction. *Circ Heart Fail* 2016;9(12):e003662.
- [20] Feldman T, Mauri L, Kahwash R, Litwin S, Ricciardi MJ, van der Harst P, et al. Transcatheter interatrial shunt device for the treatment of heart failure with preserved ejection fraction (REDUCE LAP-HF I [Reduce Elevated Left Atrial Pressure in Patients with Heart Failure]): a phase 2, randomized sham-controlled trial. *Circulation* 2018;137(4):364–75. Epub 2017/11/17. doi: 10.1161/circulationaha.117.032094. PubMed PMID: 29142012.

- [21] Shah SJ, Feldman T, Ricciardi MJ, Kahwash R, Lilly S, Litwin S, et al. One-year safety and clinical outcomes of a transcatheter interatrial shunt device for the treatment of heart failure with preserved ejection fraction in the Reduce Elevated Left Atrial Pressure in Patients with Heart Failure (REDUCE LAP-HF I) trial: a randomized clinical trial. *JAMA Cardiol* 2018;3(10):968–77. Epub 2018/09/01. doi: 10.1001/jamacardio.2018.2936. PubMed PMID: 30167646.
- [22] Amat-Santos IJ, Del Trigo M, Bergeron S, Pibarot P, Altisent O, Campelo-Parada F, et al. Left atrial decompression using unidirectional left-to-right interatrial shunt: initial experience in treating symptomatic heart failure with preserved ejection fraction with the W-Wave device. *JACC Cardiovasc Interv* 2015;8(6):870–2. doi: <https://doi.org/10.1016/j.jcin.2015.02.009>.
- [23] Del Trigo M, Bergeron S, Bernier M, Amat-Santos IJ, Puri R, Campelo-Parada F, et al. Unidirectional left-to-right interatrial shunting for treatment of patients with heart failure with reduced ejection fraction: a safety and proof-of-principle cohort study. *Lancet* 2016;387(10025):1290–7. Epub 2016/03/31. doi: 10.1016/s0140-6736(16)00585-7. PubMed PMID: 27025435.
- [24] Eigler NL, del Rio CL, Verheye S, McConnell PI, Lilly SM, George R, et al. Cardiac unloading with an implantable interatrial shunt in heart failure: serial observations in an ovine model of ischemic cardiomyopathy. *Structural Heart* 2017;1(1–2):40–8. doi: 10.1080/24748706.2017.1326647.
- [25] Rajeshkumar R, Pavithran S, Sivakumar K, Vettukattil JJ. Atrial septostomy with a predefined diameter using a novel Occlutech atrial flow regulator improves symptoms and cardiac index in patients with severe pulmonary arterial hypertension. *Catheter Cardiovasc Interv* 2017;90(7):1145–53. Epub 2017/09/02. doi: 10.1002/ccd.27233. PubMed PMID: 28862384.
- [26] Patel MB, Samuel BP, Girgis RE, Parlmer MA, Vettukattil JJ. Implantable atrial flow regulator for severe, irreversible pulmonary arterial hypertension. *EuroIntervention* 2015;11(6):706–9. Epub 2015/10/20. doi: 10.4244/eijy15m07_08. PubMed PMID: 26477643.
- [27] Elgendy AY, Elgendy IY, Mojadidi MK, Mahmoud AN, Barry JS, Jneid H, et al. New-onset atrial fibrillation following percutaneous patent foramen ovale closure: A systematic review and meta-analysis of randomised trials. *EuroIntervention*. 2018.
- [28] David Kaye. REDUCE LAP HF 2 Year outcomes. Munich, Germany: European Society of Cardiology; 2018.
- [29] Rodes-Cabau J. Interatrial shunting for treating heart failure: early and late results of the first-in-human experience with the V-Wave interatrial shunt system. 67th Annual Scientific Sessions, ACC 2018. Orlando, FL. Oral Presentation.
- [30] Rajeshkumar R, Sivakumar K. Atrial septostomy with a predefined diameter using a novel Occlutech atrial flow regulator improves symptoms and cardiac index in patients with severe pulmonary arterial hypertension. CSI Asia-Pacific 2018. Ho Chi Minh, Vietnam. Abstract.
- [31] Martinez M. Left Atrial Appendage Shunt. US20140228733A1. (2014). <https://patents.google.com/patent/US20140228733>.
- [32] Arnold J. Left ventricular assist device and method for temporary and permanent procedures. US4995857A. (1989). <https://patents.google.com/patent/US4995857A/en?q=Patent+US4995857A+>.
- [33] Guimarães L, Bergeron S, Bernier M, Rodriguez-Gabella T, del Val D, Pibarot P, et al. Interatrial shunt with the second-generation v-wave system for patients with advanced chronic heart failure. *EuroIntervention* 2020;15(16):1426–28. doi: 10.4244/EIJ-D-19-00291.