Interatrial shunt devices for heart failure with normal ejection fraction: a technology update

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Abstract: Heart failure with normal ejection fraction (HeFNEF) accounts for ~50% of heart failure admissions. Its pathophysiology and diagnostic criteria are yet to be defined clearly which may hinder the search for effective treatments. The clinical hallmark of HeFNEF is exertional breathlessness, often due to an abnormal increase in left atrial pressure during exercise. Creation of an interatrial communication to offload the left atrium is a possible therapeutic approach. There are two percutaneously delivered devices currently under investigation which are discussed in this review.

Keywords: IASD, V-Wave, device therapy, HeFNEF, review, preserved EF, HeFPEF, HFpEF

Introduction
Heart failure with normal ejection fraction (HeFNEF) accounts for ~50% of heart failure diagnoses,1,2 yet the underlying pathophysiology and diagnostic criteria are poorly defined.3–5 Partly as a consequence, no medical treatment has yet shown convincing outcome benefit for patients with HeFNEF.6–8 There is a clear unmet need for effective treatments for patients with HeFNEF. Implantable devices, such as cardiac resynchronisation therapy (CRT), improve symptoms and life expectancy in a subset of patients with heart failure and reduced ejection fraction (HeFREF).9 Some others allow early adjustment of medical therapy to avoid hospitalizations by monitoring cardiac haemodynamics.10 However, trials exploring the role of implantable devices such as CRT and rate-adaptive pacing in patients with HeFNEF have stalled, mainly due to recruitment failure,11–13 perhaps reflecting a reluctance of older patients with several comorbidities to participate.

The clinical hallmark of HeFNEF is exertional breathlessness, at least in part due to an abnormal increase in left atrial pressure (LAP) during exercise.14,15 In patients with severe pulmonary artery hypertension (PAH), creation of a right to left atrial shunt reduces right atrial and ventricular pressures and improves symptoms,16–19 possibly due to increased systemic oxygen delivery due to increased cardiac output despite increasing cyanosis.20 Decompressing the left atrium might similarly provide symptomatic and haemodynamic improvement in patients with HeFNEF.

Reducing LAP with a percutaneously delivered atrial septal device is a novel potential therapeutic strategy. This review summarizes the potential clinical implications of reducing LAP with an interatrial shunt device in patients with HeFNEF and discusses the preliminary results of the clinical trials conducted so far.
Consequences of changing LAP

There are many potential mechanisms leading to reduced exercise tolerance in patients with HeFNEF. In normal physiology, increased stroke volume during exercise is accomplished in part by the positive lusitropic consequence of sympathetic activation: left ventricular (LV) relaxation is enhanced with lower LV pressure in early diastole. Impaired LV relaxation and increased LV stiffness in patients with HeFNEF prevents an increase in end diastolic LV volume during exercise, thus increasing pressure in the left atrium. The excessive increase in LAP, measured by pulmonary capillary wedge pressure (PCWP), during exercise is a common finding in patients with HeFNEF and identifies those with a worse prognosis.

Although patients with HeFNEF reach a lower peak workload (watts per kilogram of body weight) during incremental exercise tests compared with normal controls, both reach similar peak exercise PCWP. Increased workload-indexed peak exercise PCWP may be diagnostic of early-stage HeFNEF. A higher ratio of peak exercise PCWP to workload is associated with increased risk of 10-year mortality in patients with HeFNEF.

Surgical and medical interventions that alter LAP might have a significant impact on symptoms and mortality in various cardiac pathologies. One example is that a device making invasive measurement of LAP as a guide for medical therapy in patients with HeFREF (n=40) was associated with reduced LAP, improved symptoms, and reduced rates of worsening symptoms requiring intravenous diuretic therapy.

In an observational study of 5 patients with high LAP and lower right atrial pressure (RAP) as a result of congenital obstructive left heart defects, the creation of an interatrial communication alleviated left atrial hypertension and improved symptoms. Conversely, pulmonary edema can develop in some patients secondary to dramatic increases in LAP following closure of an atrial septal defect (ASD).

Two devices, the V-Wave® (V-Wave Ltd, Or Akiva, Israel) and IASD® (DC Devices Inc., Tewksbury, MA, USA) have been tested in patients with heart failure (Table 1).

V-Wave device

The V-Wave device is a tri-leaflet porcine tissue valve on an hourglass-shaped nickel-titanium frame (Figure 1). The device is implanted via a femoral venous approach under general anesthetic with fluoroscopic and trans-esophageal echocardiography (TOE) guidance. Following radiofrequency trans-septal puncture, the center of the hourglass (5 mm diameter) is placed across the fossa ovalis with the ends of the hourglass sitting in left and right atria securing the device in place. The left atrial orifice is lined with expanded polytetrafluoroethylene (ePTFE) designed to improve blood flow and restrict new tissue growth over the device. Blood flows from the left to right via the porcine valve which is designed to close when RAP exceeds 2 mmHg, thus preventing right to left shunting. After device implantation, patients require anticoagulation with warfarin or direct-acting oral anticoagulant (DOAC) for 3 months and with low-dose aspirin indefinitely.

A proof-of-principle study was conducted in a single center in Canada, in patients with heart failure and reduced ejection fraction. They had raised PCWP (≥15 mmHg) without substantial right ventricular dysfunction (n=10; average age 62 years; average left ventricular ejection fraction (LVEF) 25%; average PCWP 23 mmHg; and average NTproBNP 2712 pg/mL). After 3 months, insertion of the device was associated with a reduction in New York Heart Association (NYHA) class, increased 6-minute walk test distance, and improved quality of life (QoL) and physical function assessed by Kansas City cardiology questionnaire and Duke activity status index. Device implantation was associated with a modest decrease in LV volumes and PCWP (23 mmHg pre-procedure to 17 mmHg at 3 months; p=0.035); However, natriuretic peptides (NPs), RAP (9 vs 8 mmHg at 3 months; p=0.18), and mean pulmonary artery pressure (29 vs 26 mmHg at 3 months, p=0.37) were unchanged.

A preliminary case report demonstrated the feasibility and safety of the V-Wave device in a patient severely symptomatic with HeFNEF and a history of ischemic heart disease and atrial fibrillation (AF) (PCWP 22 mmHg, LVEF 50%, taking 240 mg of furosemide per day). Device insertion was associated with improved symptoms (NYHA III at baseline vs II at 6 months), functional capacity (6-minute walk test distance 281 m at baseline vs 617 m at 6 months), and a substantial drop in NTproBNP (2983 pg/mL at baseline vs 1334 pg/mL at 6 months).

A further prospective, nonrandomized, open label, multicenter study of the device is planned in patients with both HeFREF and HeFNEF (NCT02511912) (Table 2).

IASD device

The interatrial shunt device (IASD) differs from the V-Wave device in three ways: first, the device does not incorporate valve tissue; second, the inter-atrial communication is larger (8 mm diameter compared with 5 mm with the V-Wave device); third, the device is a bare metal and not coated with ePTFE. Instead, the left atrial side of the device is flush with the atrial tissue to reduce the risk of thrombus formation (Figure 2).
Table 1 Summary of trials of interatrial shunt devices

<table>
<thead>
<tr>
<th>Trial</th>
<th>Device</th>
<th>Study design</th>
<th>n</th>
<th>Inclusion/exclusion criteria</th>
<th>Patient characteristics</th>
<th>Results</th>
</tr>
</thead>
</table>
| Del Trigo et al36   | V-Wave® | Prospective  | 10 | • ≥18 years of age  
• ≥6 month history of HF  
• NYHA III or IV  
• On optimal medical and device therapy  
• LVEF ≤40%  
• Severe RVSD  
• PCWP ≥15 mmHg  
• Cerebrovascular or thromboembolic event in the last 6 months  
• Coagulation disorders or contraindications for oral anticoagulation  
• Left atrial or ventricular thrombus  
• PASP >70 mmHg  | Average age: 62 years  
Average LVEF: 25%  
Average PCWP: 23 mmHg  
Average NTproBNP: 2712 pg/mL  | • No serious adverse device events after 3 months  
• Reduction in NYHA class, increased 6MWT distance, improved QoL and physical functional status after 3 months  
• Reduction in mean PCWP (23–17 mmHg) after 3 months (p=0.035)  
• NTproBNP unchanged from baseline to 3 months |
| Samara et al34      | IASD®   | Prospective. | 11 | • ≥1 HF hospitalisation in the last year or persistent NYHA class III or IV symptoms for 3 months  
• ≥40 years of age  
• LVEF ≥45%  
• Dilated LA indexed for body size without more than mild mitral valve disease  
• PCWP ≥15 mmHg at rest or ≥25 mmHg during exercise.  
• HR ≤90 bpm if in AF  
• On stable medical therapy: on diuretics for ≥2 months and no changes to cardiovascular medications in ≤2 weeks prior to enrolment.  | Average age: 71 years  
Average LVEF: 57%  
Average PCWP: 19 mmHg  
Median NTproBNP: 148 pg/mL  | • No serious adverse device events after 30 days  
• One hospitalization with worsening HF after 30 days  
• 28% reduction in mean PCWP after 30 days (p=0.005)  
• NYHA, 6MWT, and QoL assessment improvements after 30 days follow-up  
• Improvement in NYHA class sustained after 1 year but improvements in 6MWT and QoL assessment were no longer statistically significant  
• No change in NTproBNP at any time point |

(Continued)
The first in man experience of IASD was a nonrandomized, unblinded, feasibility study in patients with HeFNEF and baseline PCWP ≥15 mmHg at rest or ≥25 mmHg during exercise (n=11, average age 71 years; average LVEF 57%; median NTproBNP 148 pg/mL; average PCWP 19 mmHg). Device implantation was associated with reduction in mean PCWP (by 28%, from 19+5 to 14+3 mmHg, p=0.005) after 30 days alongside symptomatic, functional, and QoL improvements. NTproBNP plasma levels did not significantly change. Devices were successfully implanted in all but one patient in whom device malposition was corrected by the insertion of a new device. There were no reports of device-related complications such as migration or loss of patency (although in one patient the direction of flow could not be detected) after 30 days follow up. During the same period, one patient was admitted with acute heart failure. At 1 year, all patients survived and symptomatic improvement (measured by NYHA class) was sustained, although some patients required an increase in their daily dose of loop diuretics.

**REDUCE LAP-HF trial**

The REDUCE LAP-HF trial was an open-label, nonrandomized phase 1 study of the IASD in patients with HeFNEF and raised PCWP (≥15 mm at rest or ≥25 mmHg during exercise). A total of 68 patients were enrolled in 21 centers, with an average age of 69 years. Average LVEF was 47% and mean PCWP at rest was 17 mmHg; median NT-pro-BNP.

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**Table 1 (Contd)**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Device</th>
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<th>n</th>
<th>Inclusion/exclusion criteria</th>
<th>Patient characteristics</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>REDUCE LAP-HF</td>
<td>IASD</td>
<td>Prospective. Single-arm. Multi-centre. Open-label. Nonrandomised. Un-blinded.</td>
<td>68</td>
<td>Inclusion&lt;br&gt;- ≥40 years of age&lt;br&gt;- NYHA III or IV and/or 1HF hospitalisation and/or treatment with guideline directed therapies within 12 months of enrolment&lt;br&gt;- LVEF ≥40%&lt;br&gt;- Mean PCWP ≥15 mmHg at rest or ≥25 mmHg during exercise. Exclusion&lt;br&gt;- ACS within 3 months of enrolment&lt;br&gt;- CRT within 6 months of enrolment&lt;br&gt;- Severe HF&lt;br&gt;- Cerebrovascular or thromboembolic event within 6 months of enrolment&lt;br&gt;- Significant valvular disease&lt;br&gt;- RVSD&lt;br&gt;- AF with resting HR &gt;100 bpm&lt;br&gt;- Intracardiac vegetation, mass or thrombus&lt;br&gt;- eGFR &lt;25 mL/min&lt;br&gt;- Systolic BP &gt;170 mm Hg</td>
<td>Average age: 69 years&lt;br&gt;Average LVEF: 47%&lt;br&gt;Average PCWP: 17 mmHg&lt;br&gt;Median NTproBNP: 377 pg/mL</td>
<td>• 94% success rate of index procedure&lt;br&gt;• No incidence of serious adverse events after 6 months&lt;br&gt;• Reduced rest or exercise PCWP in 71% of patients after 6 months&lt;br&gt;• Reduced workload-indexed PCWP after 6 and 12 months in subgroup analysis (n=18); however, no change in average rest or exercise PCWP after 6 or 12 months in the same group&lt;br&gt;• Improvement in NYHA class, 6MWT distance, and QoL assessment after 6 and 12 months&lt;br&gt;• Device patency with left–right shunt after 12 months confirmed in all patients with adequate images (n=48)&lt;br&gt;• No change in NTproBNP after 6 or 12 months</td>
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Table 2 Summary of future trials of interatrial shunt devices

<table>
<thead>
<tr>
<th>Trial</th>
<th>Device</th>
<th>Study design</th>
<th>Estimated enrollment</th>
<th>Inclusion/exclusion criteria</th>
<th>Outcome measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>RELIEVE-HF42</td>
<td>V-Wave®</td>
<td>Prospective Single-arm Multicenter Nonrandomized Unblinded</td>
<td>60</td>
<td>Inclusion: • NYHA III or IV taking optimal medical therapy • LVEF ≥15% Exclusion: • RVSD • RAP &gt; LAP • Congenital heart disease • Severe pulmonary hypertension • Severe restrictive or obstructive lung disease</td>
<td>• Device-related MACCE within 6 months of device implantation • Changes in 6MWT after 6 months • Overall MACCE after 12 months</td>
</tr>
<tr>
<td>REDUCE LAP-HFREF68</td>
<td>IASD®</td>
<td>Prospective Single-arm Nonrandomized Un-blinded</td>
<td>10</td>
<td>Inclusion: • NYHA III or IV and signs of pulmonary congestion (rales, chest X-ray findings) and ≥1 HF hospitalization in last 12 months • Stable optimal medical, device, and surgical therapy for 6 months • ≥18 years of age • LVEF 20%–40% on echocardiography • Resting PCWP ≥18 mmHg and PCWP greater than RAP by ≥5 mmHg Exclusion: • NTproBNP &lt;100 pmol/L in SR or &lt;300 pmol/L in AF • MI, PCI, or CABG in previous 3 months • ICD or CRT in previous 3 months • Severe HF • 6MWT &gt;600 m • Cerebrovascular or thromboembolic disease &lt;6 months • Significant valve disease • Contraindication to dual antiplatelet or anticoagulant therapy • AF with HR &gt;100 bpm • Resting RAP &gt;14 mmHg • RVSD • Systolic BP &gt;170 mmHg</td>
<td>• Peri-procedural and 6-month MACCE and systemic embolic events • Percentage of patients who have successful device implantation during index procedure • Percentage of patients with left–right flow through the device</td>
</tr>
</tbody>
</table>

Abbreviations: NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; RVSD, right ventricular systolic dysfunction; RAP, right atrial pressure; LAP, left atrial pressure; MACCE, major adverse cardiac and cerebrovascular events; 6MWT, 6-minute walk test; HF, heart failure; PCWP, pulmonary capillary wedge pressure; NTproBNP, N-terminal B-type natriuretic peptide; SR, sinus rhythm; AF, atrial fibrillation; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; ICD, implantable cardio-defibrilator; CRT, cardiac resynchronization therapy; HR, heart rate; BP, blood pressure.

was 377 pg/mL (interquartile range 222–925 pg/mL).40 The co-primary endpoints were the proportion of patients with successful device implantation, reduction in PCWP at rest and during exercise after 6 months, and evidence of a left–right shunt on echocardiography at the same time point.40

Procedure and short-term safety outcomes

Procedural complication rate was 5 in 66 initial procedures: 3 patients required removal of the initial device (misplacement n=2; suspected right atrial thrombus n=1). All the 3 patients subsequently underwent uncomplicated insertion of a second device. Two procedures had to be abandoned and were not repeated (one due to complications following trans-septal puncture and another due to unsuitable atrial anatomy). Overall, the device was successfully implanted in 64 patients (94%).40

All the patients received dual antiplatelet therapy with aspirin and clopidogrel post procedure. In the first 6 months, there were no major adverse events, such as stroke, myocardial infarction, pulmonary or systemic embolism, or surgical intervention for device-related complications.40 Left to right blood flow through patent devices was confirmed at 6 months in all patients who had adequate images (n=50).40
Hemodynamic outcomes

After 6 months, IASD implantation was associated with reduced 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). The device was associated with reduced rest or exercise PCWP in 71% of patients (n=42) and reduced rest and exercise PCWP in 39% of patients (n=23). However, hemodynamic testing in a subset of patients at 12 months (n=18) showed no difference in average rest or exercise PCWP or RAP between baseline, 6 months, and 12 months. Despite this, IASD insertion was associated with reduction in workload-indexed PCWP at peak exercise from baseline to 6 months (p≤0.05) which was associated with reduction in workload-indexed 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). The device was associated with reduced rest or exercise PCWP in 71% of patients (n=42) and reduced rest and exercise PCWP in 39% of patients (n=23).

QoL and symptom outcomes

Insertion of the IASD was associated with significant improvements in symptoms, QoL, and functional status at 6 months which were sustained at 12 month follow-up: NYHA class (p≤0.001 at 6 and 12 months compared to baseline), QoL score (p≤0.001), and 6-minute walk distance (p≤0.01) all improved (Figure 4).41

Long-term safety of IASD

Of the 64 patients who had the device implanted, 3 patients (5%) died between 6- and 12-month follow-up; 1 death was due to stroke, 1 due to pneumonia, and 1 the cause was undetermined.41 There were 17 HF hospitalizations among 13 patients in the year post implantation, 10 of which occurred in 10 patients in the first 6 months.41 Left–right shunt through a patent device was confirmed on echocardiography at 12 months in all patients with good-quality images (n=48).

Introduction of a left–right atrial shunt with the IASD was associated with an increase in the right ventricular volume and ejection fraction, but not RAP compared to baseline.41 There was no effect on LVEF and left atrial volume, although LV diastolic volume decreased.

Pulmonary artery oxygenation increased from 69% to 75% at 6 month follow-up (p≤0.0001) confirming the presence of a left–right shunt, but was not reported at 12 months.40,41 Although oximetry was used to measure LV output (which remained unchanged at 6 and 12 months), measures of systemic oxygenation were not reported at 6 or 12 months.

Limitations of REDUCE LAP-HF

Creation of a left–right atrial shunt with the IASD seems feasible and safe in the mid-term and may cause symptomatic improvement in some carefully selected patients with heart failure and raised LAP. However, caution is required when interpreting the available data.

- Around one third of the patients had AF,40 in which case PWCP might vary beat to beat. It is not clear whether one-off readings can be considered accurate or whether an average reading from a specific number of cardiac cycles was used instead.
- The change in PCWP (a designated primary outcome) was not significant unless indexed for a subjective, patient-dependent variable such as exercise workload.
- The investigators reported a decrease in the difference between LAPs and RAPs (reduced PCWP-RAP gradient) which, in fact, would have meant an increased RAP/PWCP ratio.40,41 Increased RAP/PWCP ratio is associated with poorer long-term outcome in hospitalized patients with advanced HeFREF (LVEF ≤30%),43 but the clinical importance of this in HeFNEF is not yet known.
Many of the other measured outcomes were obtained through subjective tests in nonrandomized and unblinded participants and investigators. Outcomes such as QoL score, exercise time, and workload are subject to bias. Inevitably, there must be at least some placebo effect from undergoing a novel procedure involving general anesthesia. Improvement in NYHA class was mirrored by an increase in average 6-minute walk distance (331 m at baseline vs 363 m after 12 months, \( p = 0.001 \)). However, inter- and intra-observer NYHA class ascriptions are variable with low validity and reproducibility. Therefore, an improvement in exercise distance of an average 32 m may not be compatible with an improvement in NYHA class and may be due, instead, to a learning effect intrinsic to the test.

HeFNEF was defined as the presence of symptoms and signs compatible with the diagnosis, a LVEF >40%, and PCWP >15 mmHg at rest or >25 mmHg during supine bicycle exercise on right heart catheterization. Although there are no universally accepted criteria to diagnose HeFNEF, some evidence suggests that there is no difference in resting and peak exercise PCWP between healthy controls, patients with hypertension, and patients with HeFNEF. There were no data on the average or median systolic blood pressure of the participants in REDUCE LAP-HF or, indeed, any trial of V-Wave or IASD. A reduction in LAP can be achieved with commonly used heart failure medications, such as angiotensin-converting enzyme inhibitors (ACEi) or beta-blockers. The use of diuretics, alone or in combination with an ACEi or angiotensin receptor blocker, improves symptoms and QoL in patients with HeFNEF. It cannot be known from the published data whether patients in whom the V-Wave or IASD was implanted were eligible for up-titration of their antihypertensive medications as an alternative means to reduce LAP, although 70%–90% were hypertensive. Indeed, 11 patients in REDUCE LAP-HF (17%) required an increased dose of diuretics during 6-month follow-up. The signs and symptoms of heart failure are notoriously nonspecific, and under-diagnosis and misdiagnosis of HeFNEF may be common. Serum NPs are the most powerful prognostic marker in HeFNEF, and raised levels are a diagnostic requirement. However, raised serum NPs were not an inclusion criteria for REDUCE LAP-HF. Patients with HeFNEF and low NP levels probably have a good prognosis and thus are unlikely to benefit from invasive intervention. Of those with higher...
NTproBNP plasma levels, the proportion who had echocardiographic evidence to support the diagnosis of HeFNEF (raised E/E’ ratio or augmented LV mass or left atrial volume), is 26 not reported. Importantly, NP levels were not affected by device implantation.40,41

Future perspective

The long-term effects of the IASD are unknown. A chronic left–right shunt increases pulmonary blood flow and may be well tolerated at younger ages: patients with ASD are at increased risk of PAH and atrial arrhythmias, but clinical problems do not usually emerge until the fourth or fifth decade. However, in elderly individuals (the average age of patients in REDUCE LAP-HF was 69 years) with HeFNEF and altered ventricular compliance, left–right atrial shunts may cause increased pulmonary arterial pressure and subsequent right ventricular dysfunction. Such hemodynamic changes might affect other organs already compromised in HeFNEF, such as the kidneys, with a subsequent negative impact on long-term outcome.

Another factor that may influence long-term outcome is the use of anticoagulation: IASD implantation required 1-year dual antiplatelet therapy, whereas V-Wave implantation required warfarin or DOAC for 3 months following implantation.22 Both the devices require indefinite, low-dose aspirin. A large proportion of patients with HeFNEF have AF and require anticoagulation anyway, which, in combination with aspirin, might increase bleeding risk. It is unclear whether, in patients with sinus rhythm, the anticoagulation required for either device is sufficient thrombo-prophylaxis or increases the risk of adverse events such as GI bleeding: one patient had a stroke during 12-month follow-up post IASD implantation, and one patient had a nonfatal gastrointestinal bleed during 3-month follow-up post V-Wave implantation. Vigilance and caution will be required with future trials.

Finally, changing patient behavior due to study involvement, known as the “Hawthorne effect,” may have influenced the results; possibly by increasing medication compliance during follow-up. In the absence of a control group with a sham procedure or blind readers, trials of V-Wave and IASD may be subject to the same bias that has been observed in trials of other invasive treatments, such as renal nerve denervation.

Conclusion

HeFNEF remains an ill-defined clinical entity, which has lead, in part, to the failure to find effective treatment for the condition. Devices that can directly reduce LAP seem to be safe in the short- and mid-term, but there are no data on their long-term safety and efficacy.

Sham-controlled randomized trials would blind a patient to treatment, reducing the risk of bias which necessarily affects measures with a large subjective influence such as 6-minute walk distance or exercise workload. However, the practicalities may be difficult: the presence of a device would be easily spotted by an investigator during right heart catheterization or echocardiography. Careful selection of relevant endpoints (such as changes in symptoms) in patients blind to treatment (with a sham procedure) should be assessed by physicians also blinded to treatment.

Such a trial is essential to confirm that the benefits reported from unblinded studies are real. It is also unclear whether similar reductions in LAP sufficient to improve symptoms may be achievable with pharmacotherapy in patients with HeFNEF. Care must be taken with future trials (Table 2) to ensure that there is no bias leading to misinterpretation of efficacy.

Disclosure

The authors report no conflicts of interest in this work.

References


