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Interatrial Shunting for Heart Failure

Early and Late Results From the First-in-Human Experience With the V-Wave System

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ABSTRACT

OBJECTIVES This was a first-in-human study to assess the feasibility, safety, and exploratory efficacy of interatrial shunting for treating high-risk heart failure (HF) in patients with reduced and preserved ejection fraction.

METHODS A single-arm open-label study of patients with New York Heart Association functional class III or IV HF on optimal therapy was performed at 6 centers. The V-Wave shunt, an hourglass-shaped implant containing a 1-way bioprosthetic valve, was implanted by transseptal catheterization. Clinical, functional, echocardiographic, and hemodynamic evaluations were performed at baseline, 3 and 12 months, and annually (clinical follow-up) thereafter (median follow-up 28 months; interquartile range: 21 to 31 months).

RESULTS A total of 38 patients were enrolled (30 with HF with reduced ejection fraction and 8 with HF with preserved ejection fraction; mean age 66 ± 9 years; 97% and 3% in classes III and IV, respectively), and the shunt device was successfully implanted in all cases without periprocedural mortality. The rate of major device- or procedure-related complications during the first 12 months was 2.6% (periprocedural cardiac tamponade in 1 patient). At 3- and 12-month follow-up, there were improvements in New York Heart Association functional class (classes I and II in 78% and 60% of patients, respectively), quality of life (improvements ≥5 points in 74% and 73% of patients, respectively), and 6-min walk distance (mean increases of 41 ± 63 and 28 ± 83 m, respectively) ($p < 0.02$ for all, data available for 36 patients), without changes in objective measures of left- or right-sided function. All shunts were patent at 3 months, but 5 of 36 (14%) had occluded, and another 13 of 36 (36%) were stenotic at the valve by 12 months. Patients with widely patent shunts had lower long-term rates of death, left ventricular assist device placement or heart transplantation ($p = 0.001$), and HF hospitalization ($p = 0.008$), along with a reduction of pulmonary capillary wedge pressure (from 23.3 ± 5.4 mm Hg at baseline to 18.0 ± 4.0 mm Hg at 12 months, $p = 0.011$).

CONCLUSIONS Interatrial shunting with the V-Wave system was feasible and safe in patients with HF with reduced and preserved ejection fraction. Improvements in clinical and functional status were observed early and at 12 months despite attenuation of shunt patency in one-half of the patients. Patients with preserved shunt patency tended to maintain clinical benefit during longer term follow-up. Device modification that improves the durability of patency is likely worthwhile before confirmation of these findings in a randomized trial. (J Am Coll Cardiol Intv 2018;■:■–■) © 2018 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

HF = heart failure

HFpEF = heart failure with preserved ejection fraction

HFrEF = heart failure with reduced ejection fraction

IQR = interquartile range

LVEF = left ventricular ejection fraction

MACNE = major adverse cardiovascular and neurological event(s)

NYHA = New York Heart Association

PCWP = pulmonary capillary wedge pressure

TEE = transesophageal echocardiography

TTE = transthoracic echocardiography

Heart failure (HF), whether with reduced or preserved ejection fraction, continues to be a major public health care burden, with persistent high morbidity and mortality rates notwithstanding decades of advances in medical and device management (1). Increased left atrial pressure leading to pulmonary congestion is the common mechanism precipitating worsening symptoms and acute decompensation. Studies with implantable hemodynamic pressure monitoring have shown improved outcomes and a decrease in HF hospitalization by titration of medications to control left atrial pressure (2,3).

Creating an interatrial shunt for left atrial decompression has been successfully applied with blade and balloon septostomy for patients with myocarditis or end-stage cardiomyopathy and intractable pulmonary edema (4,5). More recently, percutaneously implantable permanent interatrial shunt devices have been developed for treating patients with chronic HF and have shown promising early clinical and hemodynamic results (6–9). Most reports have focused on patients with HF with preserved ejection fraction (HFpEF), and data on HF with reduced ejection fraction (HFrEF) have been limited to very small numbers of patients with short-term follow-up. The objective of this first-in-human study was to determine the feasibility, early and late safety, and exploratory efficacy of the V-Wave Interatrial Shunt (V-Wave, Caesarea, Israel) for treating patients with advanced chronic HFrEF and HFpEF who remained severely symptomatic despite standard medical treatment.

METHODS

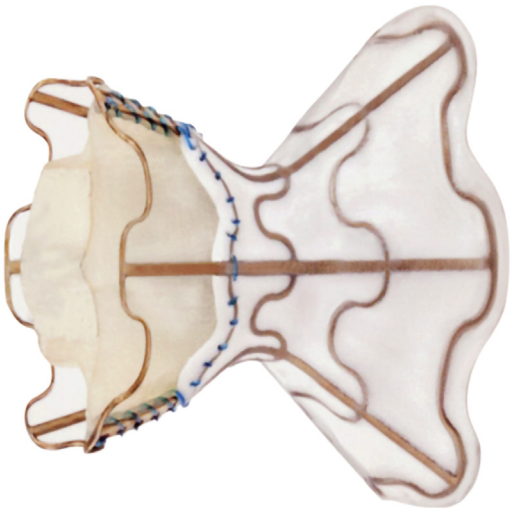
STUDY DESIGN AND PATIENTS. This was a first-in-human, prospective, multicenter, open-label feasibility experience in patients with chronic HF. Eligible patients (≥18 years of age) required a history of chronic (>6 months) ischemic or nonischemic cardiomyopathy regardless of left ventricular systolic function (HFrEF or HFpEF) with New York Heart Association (NYHA) functional class III or ambulatory class IV symptoms despite optimal medical and device therapy as defined by American College of Cardiology/American Heart Association guidelines (guideline-directed medical therapy). Patients had at least 1 hospitalization in the prior 12 months for worsening HF treated with intravenous or invasive therapy or body mass index–adjusted N-terminal pro-brain natriuretic peptide level ≥1,500 pg/ml. Patients with left ventricular ejection fractions (LVEF) >40% included HF with mildly reduced ejection fraction and HFpEF according to European Society of Cardiology guidelines (10). The main exclusion criteria were LVEF <15%, severe right ventricular dysfunction (tricuspid annular plane systolic excursion <11 mm) or severe pulmonary hypertension (pulmonary artery systolic pressure >70 mm Hg), stroke or thromboembolic event in the past 6 months, severe renal dysfunction (estimated glomerular filtration rate $<25\ \text{ml} \cdot \text{min}^{-1} \cdot 1.73\ \text{m}^{-2}$), coagulation disorders or contraindications to anticoagulation therapy, and presence of intracardiac thrombus.

Patients were enrolled in 2 similar cohort studies that were combined into a single experience (shunt study). A single-center study was performed at a Canadian site under a special-access program. After assessment for eligibility criteria, patients were approved for device implantation by Health Canada on a case-by-case basis. All patients provided informed consent for the procedures and the recording and scientific use of baseline, procedural, and follow-up data. Ethics committee approval was obtained for data collection and analysis. The second cohort consisted of a prospective first-in-human study carried out at 5 centers in Spain and Israel (NCT01965015). The study protocol was approved by local ethics committees, and all patients provided informed consent to participating in the trial. The 3-month results of the first 10 patients included in this series have been previously reported (9).

PROCEDURES. Baseline assessments included medical history and examination, evaluation of NYHA functional class, quality of life (Kansas City Cardiomyopathy Questionnaire or Minnesota Living With Heart Failure Questionnaire), 6-min walk distance, neurohormone levels, right heart catheterization, and transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE).

Details of the shunt device and its implantation procedure have been previously reported (9). Briefly, the first-generation V-Wave Interatrial Shunt is an hourglass-shaped, self-expanding, percutaneously implanted device designed to span the fossa ovalis and shunt blood from the left to the right atrium as a function of the instantaneous interatrial pressure gradient (**Figure 1**). It is constructed on a nitinol frame and encapsulated with an expanded polytetrafluoroethylene skirt on the left atrial end extending through the neck and one-third on to its right atrial side. The internal diameter at the neck is 5.1 mm, and the total length of the device is 12 mm. A glutaraldehyde-fixed porcine pericardial trileaflet valve sutured to the right

FIGURE 1 The V-Wave Interatrial Shunt



atrial side of the shunt frame is designed to close when the pressure gradient becomes right to left. Implantation procedures were performed under general anesthesia guided by TEE and fluoroscopy. Standard transseptal catheterization was followed by device implantation using a dedicated shunt delivery system through a 14-F introducer sheath.

Post-implantation medical management consisted of anticoagulation with warfarin for 3 months and aspirin (81 to 100 mg/day) indefinitely. Patients already managed with anticoagulant agents (warfarin or direct oral anticoagulant agents) before the procedure were left on their prior regimens. All other HF therapies were managed by clinical assessment per guideline-directed medical therapy, and all medication changes were recorded. Patients were followed in the clinic at 1, 3, 6, 9, and 12 months and yearly thereafter or more frequently as required by clinical events for up to 5 years. TTE was performed at 1 and 6 months and TTE or TEE at 1 to 3 and 12 months. Right heart catheterization was performed at 3- and 12-month follow-up. Extended annual follow-up for 5 years included TTE at 24 months with TEE if shunt flow was not seen.

OUTCOMES. The primary outcomes were: 1) device- or procedure-related major adverse cardiovascular and neurological events (MACNE), defined as death, stroke, device embolization, pericardial effusion requiring intervention, reintervention, or surgery at 3- and 12-month follow-up (safety outcome); and 2) procedural success, defined as successful device implantation with no periprocedural death. Additional safety outcomes included all-cause MACNE, all serious adverse events, and serious adverse device effects.

The definition of HF hospitalization required a nonelective in-hospital stay with worsening HF that was present at the time of admission and considered the primary cause of admission and that included at least 1 calendar date change and the use of intravenous or mechanical HF therapies. All adverse events were adjudicated by a combined independent clinical events and safety monitoring committee.

Secondary exploratory efficacy outcomes included the changes in NYHA functional class, quality of life, and 6-min walk distance. Two quality-of-life

TABLE 1 Baseline Characteristics of the Study Population (n = 38)

Demographics	
Age, yrs	66 ± 9
Male	35 (92)
Body mass index, kg/m^2	30 ± 6
Medical history	
NYHA functional class	III (97), IV (3)
Ischemic cardiomyopathy	30 (79)
Myocardial infarction	26 (68)
Atrial fibrillation	20 (53)
Hypertension	32 (84)
Diabetes	26 (68)
Chronic kidney disease	23 (61)
Stroke	4 (11)
Treatment history	
ACE inhibitor/ARB; mg enalapril equivalent	27 (71); 20 (7.5-30)
Beta-blocker; mg carvedilol equivalent	38 (100); 25 (12.5-37.5)
MRA; mg spironolactone equivalent	26 (68); 12.5 (12.5-25)
Loop diuretic agent; mg furosemide equivalent	33 (87); 60 (40-140)
CRT-D or ICD	28 (74)
CRT	15 (39)
Laboratory	
eGFR, ml · min^{-1} · 1.73 m^{-2}	54 ± 20
NT-proBNP, pg/ml	1,871 (1,066-3,341)
ln NT-proBNP, pg/ml	7.5 ± 0.9
LVEF ≥40%	8 (21)
LVEF, % (HFrEF)	26 ± 7
LVEF, % (HFmrEF/HFpEF)	50 ± 9
6-min walk distance, m	289 ± 112
Hemodynamics	
Systolic BP, mm Hg	116 ± 19
Diastolic BP, mm Hg	66 ± 9
Heart rate, beats/min	69 ± 9
Pulmonary wedge pressure, mm Hg	21 ± 5
Right atrial pressure, mm Hg	8 ± 4
Pulmonary artery systolic pressure, mm Hg	44 ± 11
Pulmonary artery mean pressure, mm Hg	30 ± 7

Values are mean ± SD, n (%), or median (interquartile range).

ACE = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BP = blood pressure; CRT = cardiac resynchronization therapy; CRT-D = cardiac resynchronization therapy with defibrillation; eGFR = estimated glomerular filtration rate; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association.

TABLE 2 Procedural and 12-Month Follow-Up Outcomes Measures (n = 38)

Procedural/in-hospital	
Successful device implantation	38 (100)
Shunt patency on procedural TEE	38 (100)
Device embolization/dislocation	0
Need for a second device	0
Procedural time, min	72 ± 24
Hospitalization length (days)	1 (1–2)
Device- or procedure-related MACNE	1 (2.6)
Cardiac tamponade	1 (2.6)
Safety outcomes (12-month follow-up)	
Cumulative device- or procedure-related MACNE	
Death	0
Stroke	0
Cardiac tamponade	1 (2.6)
Device embolization	0
Device infection	0
Reintervention or surgery	0
Overall device- or procedure-related MACNE	1 (2.6)
Cumulative all-cause MACNE	
Death	2 (5.2)
Stroke	0
Systemic embolism	0
Cardiac tamponade	1 (2.6)
Myocardial infarction	0

Values are n (%), mean ± SD, or median (interquartile range).
MACNE = major adverse cardiovascular and neurologic event(s); TEE = transesophageal echocardiography.

TABLE 3 Functional, Echocardiographic, and Hemodynamic Parameters at Baseline and 3- and 12-Month Follow-Up

	Baseline (n = 38)	3 Months (n = 36)	12 Months (n = 36)	p Value*
Functional status/quality of life				
NYHA functional class III or IV	38 (100)	8 (22)	14 (39)	<0.001
NYHA functional class I or II	0 (0)	28 (78)	22 (61)	
KCCQ/MLHFQ (improvement ≥5 points)	-	27 (74)	26 (73)	<0.001
6-min walk distance (m)	290 ± 112	340 ± 94	324 ± 105	0.012
Laboratory parameters				
ln NT-pro BNP (pg/ml)	7.5 ± 0.9	7.4 ± 1.0	7.5 ± 0.9	0.83
eGFR (ml · min^{-1} · 1.73 m^{-2})	54 ± 20	55 ± 23	53 ± 22	0.92
Echocardiographic variables				
LVEF, % (HFrEF)	26 ± 7	27 ± 9	28 ± 8	0.54
LVEF, % (HFmrEF, HFpEF)	50 ± 9	52 ± 10	54 ± 9	0.74
MR grade†	3.9 ± 1.5	3.5 ± 1.2	3.5 ± 1.3	0.51
LAVI (ml/m^2)	42 ± 13	42 ± 13	41 ± 15	0.84
TAPSE (mm)	16 ± 4	17 ± 4	16 ± 4	0.94
Cardiac output (l/min)	1.9 ± 1.0	1.9 ± 0.5	1.9 ± 0.4	0.92
Q_P/Q_S	0.99 ± 0.11	1.17 ± 0.12	1.10 ± 0.13	0.005
Hemodynamic status				
PCWP, mm Hg	21 ± 5	20 ± 7	19 ± 7	0.49
RAP, mm Hg	8 ± 4	9 ± 5	9 ± 4	0.51
Mean PAP, mm Hg	30 ± 7	29 ± 8	30 ± 10	0.97

Values are n (%) or mean ± SD. *Kruskal-Wallis test and one-way analysis of variance for ordinal and interval data, respectively. †MR grade: 1 = none to 7 = severe.
KCCQ = Kansas City Cardiomyopathy Questionnaire; LAVI = left atrial volume index; MLHFQ = Minnesota Living With Heart Failure Questionnaire; MR = mitral regurgitation; PAP = pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; RAP = right atrial pressure; TAPSE = tricuspid annular plane systolic excursion; other abbreviations as in Table 1.

questionnaires were used in the study (the Kansas City Cardiomyopathy Questionnaire in Canada and the Minnesota Living With Heart Failure Questionnaire at European centers). As these instruments show worsening or improvement on oppositely directed scales, it was decided to reconcile the results as a 3-tiered ordinal scale as follows: a ≥5-point improvement in either instrument was labeled as "improved," a ≥5-point worsening was labeled as "worsened," and a <5-point change was called "no change."

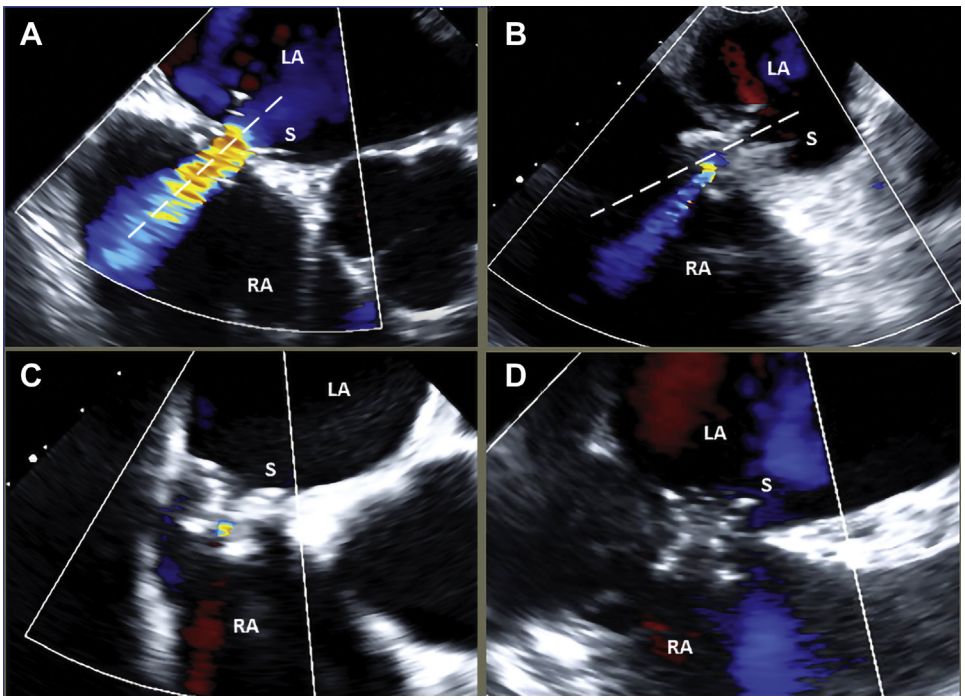
Echocardiograms were evaluated at the central echocardiography core laboratory of the Quebec Heart & Lung Institute. Shunt patency was determined by TEE color Doppler echocardiography. Shunt occlusion was defined as the absence of flow through the device. If flow was present, shunt stenosis was defined as a >50% diameter narrowing of the vena contracta compared with the shunt neck.

STATISTICAL ANALYSIS. The sample size of 38 patients was set so that the upper boundary of the 95% confidence interval for the primary outcome measure would be 20% if 4 device- or procedure-related MACNE were observed. All numeric variables were evaluated for normality, and data are presented as mean ± SD or as median (interquartile range) according to variable distribution. Changes in interval variables from baseline to follow-up were compared using paired or unpaired Student *t* tests, or analysis of variance as appropriate, or their nonparametric equivalents as for ordinal scaled or skewed data. Other reported p values were obtained using the chi-square test for proportions or rate comparisons. Mortality and recurrent HF event rates were assessed by the cumulative hazard function using the Nelson-Aalen estimator and compared using Mann-Whitney *U* tests. Statistical significance was set at a 2-tailed probability level of 0.05.

RESULTS

Between October 2013 to March 2016, 38 consecutive patients were enrolled in the shunt study (22 and 16 patients in the special-access program and first-in-human cohorts, respectively). Extended follow-up was through October 15, 2017, with a median length of follow-up of 28 months (interquartile range [IQR]: 21 to 31 months; range 18 to 48 months). One patient withdrew at 18 months, and no other patients were lost to follow-up. Table 1 summarizes the baseline characteristics of the shunt study patients. Patients were elderly, predominantly male, and moderately obese. Except for 1 NYHA functional class IV patient

FIGURE 2 Examples of Transesophageal Echocardiographic Color Doppler Shunt Patency Analysis at 12-Month Follow-Up



(A) Widely patent (nonstenotic) shunt with vena contracta of 4.8 mm. **(B)** Stenotic shunt. The vena contracta is 2 mm and skewed off axis **(dashed line)** by 26°. **(C)** Stenotic shunt with subtotal occlusion. **(D)** Occluded shunt. LA = left atrium; RA = right atrium; S = shunt.

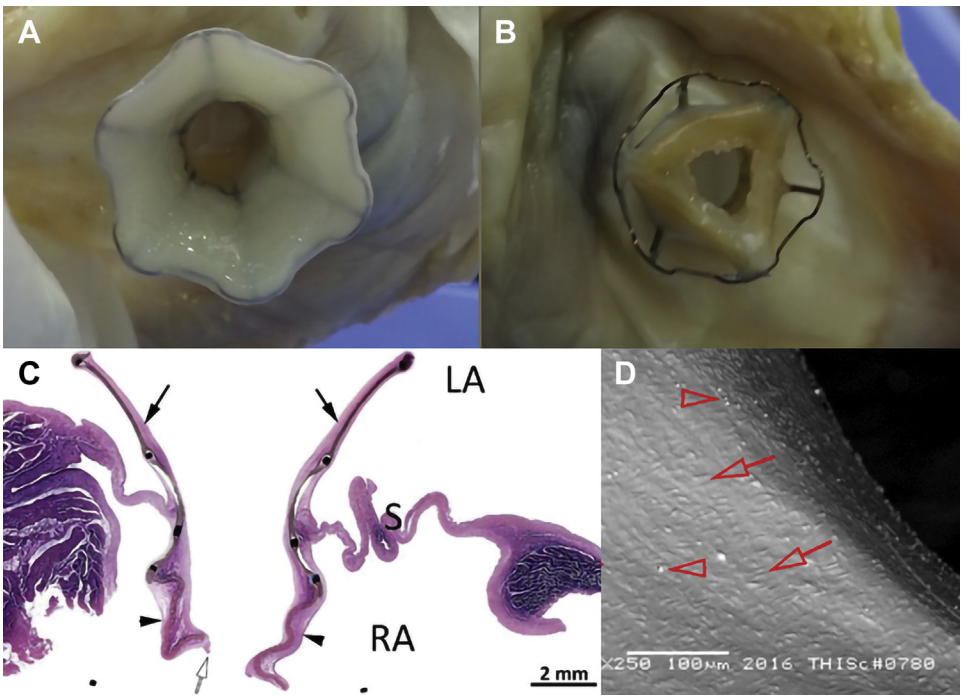
treated with outpatient milrinone infusions, 37 patients (97%) were in class III. A substantial majority (79%) had HF of ischemic etiology. The use of renin antagonists, beta-blockers, mineralocorticoid receptor antagonists, implanted cardioverter-defibrillators, and cardiac resynchronization therapy was consistent with guideline-directed medical therapy. Natriuretic peptide levels were markedly elevated at 1,871 pg/ml (IQR: 1,066 to 3,341 pg/ml), as were resting pulmonary capillary wedge pressure (PCWP) and pulmonary artery pressure, whereas exercise capacity and cardiac output and index were reduced. At baseline, 26 of 38 patients (68%) were taking anticoagulant agents (20 warfarin and 6 direct oral anticoagulant agents). Eight of 38 patients (21%) had LVEFs >40%.

PROCEDURAL AND SAFETY OUTCOMES. Table 2 summarizes the main procedural outcomes and cumulative MACNE to 12 months. The shunt was successfully implanted in all patients with confirmation by TEE of correct positioning across the fossa ovalis and the presence of unidirectional left-to-right flow through the device. The average procedure time was 72 ± 24 min, which included TEE, right heart and transseptal catheterization, shunt implantation, post-implantation right heart catheterization, and hemostasis. One patient (2.6%) had a cardiac tamponade within the hours following the procedure that was successfully treated with pericardiocentesis. This was the only periprocedural MACNE. There were no stroke or mortality events, and all but 2 patients were discharged 24 h after the procedure. The reasons for a late hospital discharge were cardiac tamponade post-procedure (n = 1) and a vascular access complication (n = 1).

The rate of the primary safety endpoint (device- or procedure-related MACNE at 3 and 12 months) was 2.6%. After hospital discharge, there were no further device-related or implantation procedure-related serious adverse events. At 12 months, there were 2 deaths of cardiac causes, not related to the device or study procedures, and there were no strokes or systemic thromboembolic events. All serious adverse events requiring hospitalization during the first year after shunt implantation are listed in Online Table 1.

FUNCTIONAL, ECHOCARDIOGRAPHIC, AND HEMODYNAMIC CHANGES. Table 3 displays changes in patient symptoms, exercise capacity, and main echocardiographic and hemodynamic parameters at 3 and 12 months

FIGURE 3 Explanted Stenotic Shunt Specimen



Pathological examination of a stenotic shunt explanted from a transplant patient at 27-month follow-up. **(A)** Left atrial view; orifice is patent. **(B)** Right atrial view shows stenotic bioprosthetic leaflets are thickened with fused commissures. **(C)** Axial section (hematoxylin and eosin). **Arrows** denote complete coverage of the inflow by thin fibrocellular pannus (neoendocardium); **arrowheads** denote coverage of the leaflets by mature fibrocellular neoendocardium; **clear arrow** denotes minute fibrin deposit at the tip of a cusp in the right atrium. **(D)** Scanning electron microscope view of left atrial inflow lumen. **Arrow** denotes convex endothelial cell nuclear profiles streaming in the direction of the arrows. There is complete coverage of the neoendocardium by confluent and well-differentiated $CD31^+$ staining endothelial cells. LA = left atrium; RA = right atrium; S = septum.

after shunting compared with baseline. Data at 3- and 12-month follow-up were available in all but 2 patients, who died <3 months following the procedure. At 3 months, 78% of patients improved from NYHA functional class III or IV at enrollment to class I or II, and at 12 months, 60% continued to be improved ($p < 0.001$). For quality-of-life instruments, 74% and 73% of patients improved by ≥5 points at 3 and 12 months, respectively ($p < 0.001$). The 6-min walk distance increased by 41 m at 3 months ($p = 0.004$) and by 28 m at 12 months ($p = 0.048$).

The only hemodynamic parameter exhibiting a significant change over time was the shunt ratio Q_p/Q_s (as determined by Doppler echocardiography), which increased from unity to 1.17 at 3 months ($p = 0.005$). The shunt ratio was overall small and appeared to decrease on average to 1.10 by 12 months. Shunting was not associated with consistent or progressive worsening of left- or right-sided echocardiographic, hemodynamic, or renal function over the first year.

SHUNT PATENCY. Left-to-right flow through the shunt was confirmed in all patients at 3 months. At 12-month follow-up, there were 5 of 36 cases (14%) with total occlusions. In the remaining patients with flow across their shunts, TEE showed that by 12 months, an additional 13 of 36 patients (36%) had developed in-shunt stenosis, consistent with the location of the bioprosthetic leaflets. Stenosis severity was assessed as subtotal in 7 cases, and the jets were measured to be skewed (range 9° to 26°) from the long axis of the shunt in 5 of 6 remaining cases (Figure 2). Stenotic shunt cases were objectively differentiated from patients with widely patent shunts by measured vena contracta diameters (stenotic: 0.0 mm (IQR: 0 to 2.5 mm) vs. patent: 3.1 mm (IQR: 3.0 to 3.8 mm); $p < 0.001$) and Q_p/Q_s (stenotic: 1.05 ± 0.12 vs. patent: 1.17 ± 0.12; $p = 0.023$). There was no thrombus seen in or near the shunts, no migration of shunts from the site of deployment, and no erosion into adjacent cardiac structures. Shunt stenosis or occlusion was not associated with

precipitation of acute adverse clinical events, including thromboembolic events. The root cause of stenosis or occlusion was suggested from a stenotic shunt that was explanted during cardiac transplantation at 27-month follow-up (**Figure 3**). The bioprosthetic leaflets were thickened and stenotic with neoendocardial hyperplasia (pannus).

Compared with patients who developed shunt stenosis or occlusion, those who maintained patent shunts had baseline features with trends generally consistent with a poorer prognosis, including older age, more severe underlying heart disease and comorbidities, reduced exercise capacity, poorer systolic function, and worse hemodynamic status (Online Table 2).

Figure 4 shows baseline and 12-month hemodynamic status according to shunt patency status at 12 months (n = 18 stenotic or occluded and n = 18 patent). Notwithstanding starting with generally poorer baseline hemodynamic status, by 1 year, patients with patent shunts exhibited improvements in PCWP (from 23.3 ± 5.4 mm Hg at baseline to 18.0 ± 4.0 mm H g at 12 months, p = 0.011), without worsening of right atrial or pulmonary artery pressures. These improvements were also significant relative to a lack of change in the stenotic or occluded subgroup. Patent shunt patients with reduced systolic function (n = 14) exhibited a rise in LVEF from 23 ± 7% to 26 ± 8% (p = 0.007) compared with a nonsignificant increase in LVEF (from 29 ± 6% at baseline to 32 ± 8% at 12 months, p = 0.066) among those patients with HFrEF and occluded or stenotic shunts (n = 16).

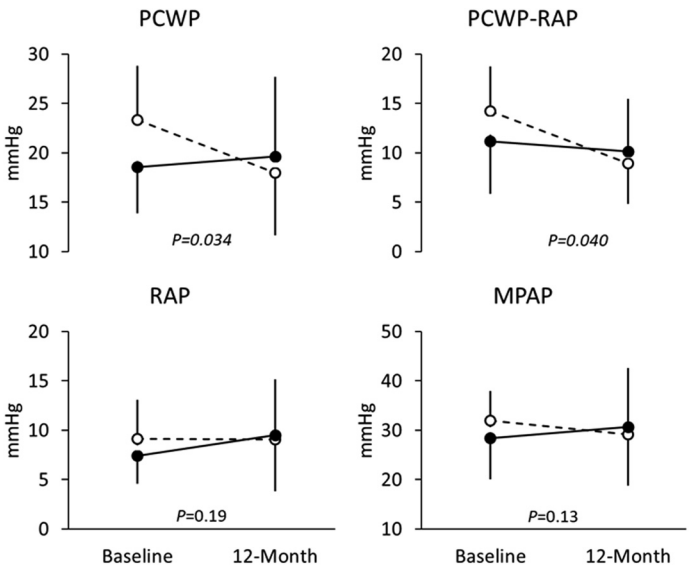
Online Table 3 summarizes echocardiographic parameters of right ventricular structure and function according to shunt patency. Patients had moderate baseline right ventricular dilation, with systolic and diastolic dysfunction, mild to moderate tricuspid regurgitation, and pulmonary hypertension. Both patency subgroups maintained stable right ventricular function at 1 year.

LATE CLINICAL OUTCOMES. Throughout the total follow-up duration, there were 10 deaths (8 cardiovascular and 2 of noncardiovascular causes). One patient received a left ventricular assist device as destination therapy at 15 months, and another underwent heart transplantation at 27 months. There were 30 HF hospitalization events in 11 patients (29%), and 45 non-HF hospitalizations in 19 patients (50%). Of the non-HF hospitalizations, 14 (31%) had coexisting worsening of HF.

Beyond the 12-month follow-up data, 10 patients with patent shunts surviving to their 24-month anniversary underwent TTE. One patient was found to have no flow, which was confirmed to be occluded on TEE. For the purposes of associating shunt patency with long-term clinical events, there were 17 and 19 patent and stenotic or occluded shunts, respectively.

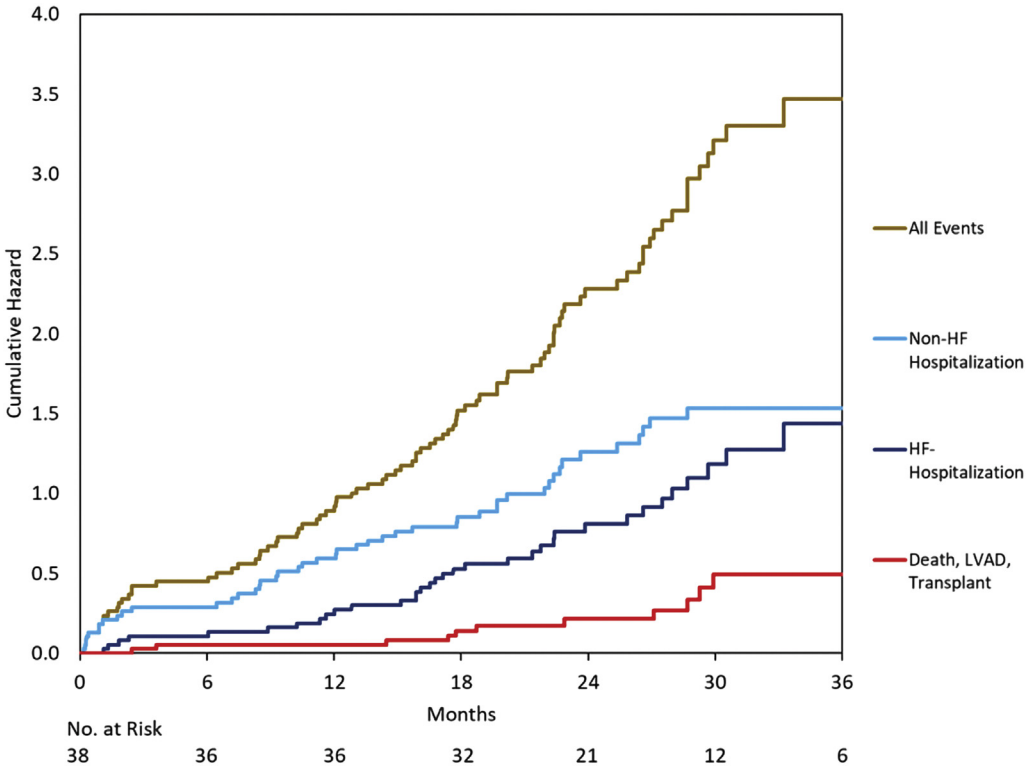
Figure 5 shows the cumulative hazard functions of event types for all patients, and **Figure 6** compares cumulative events according to shunt patency subgroup. Patients with patent shunts had a significantly lower risk for the combination of death, transplantation, or left ventricular assist device placement (p = 0.001), of HF hospitalization (p = 0.008), of non-HF hospitalization (p = 0.002), and of all combined events (p = 0.002), compared with those with stenotic or occluded shunts. Patients who would lose shunt patency tended to have low event rates during the first year, but then event rates increased corresponding to the period after documented shunt stenosis or occlusion. For example, the rate of HF hospitalization was 0.21 per patient-year during the first 12 months, increasing to 0.65 per patient-year thereafter (p = 0.035). The increased rate of non-HF hospitalization seen in stenotic or occluded patients was in part associated with a larger number of cases with coexisting worsening HF during the hospital

FIGURE 4 Changes in Hemodynamic Parameter Values According to Patency Subgroup at Baseline and 12 Months



Patent shunt patients **(open circles)** and stenotic or occluded shunt patients **(solid circles)**. P values are for comparisons between subgroups of the differences between baseline and 12 months. MPAP = mean pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; RAP = right atrial pressure.

FIGURE 5 Cumulative Hazard Functions for Clinical Events (All Patients)



HF = heart failure; LVAD = left ventricular assist device.

admission (10 of 27 events vs. 4 of 17 events in stenotic or occluded and patent patients, respectively).

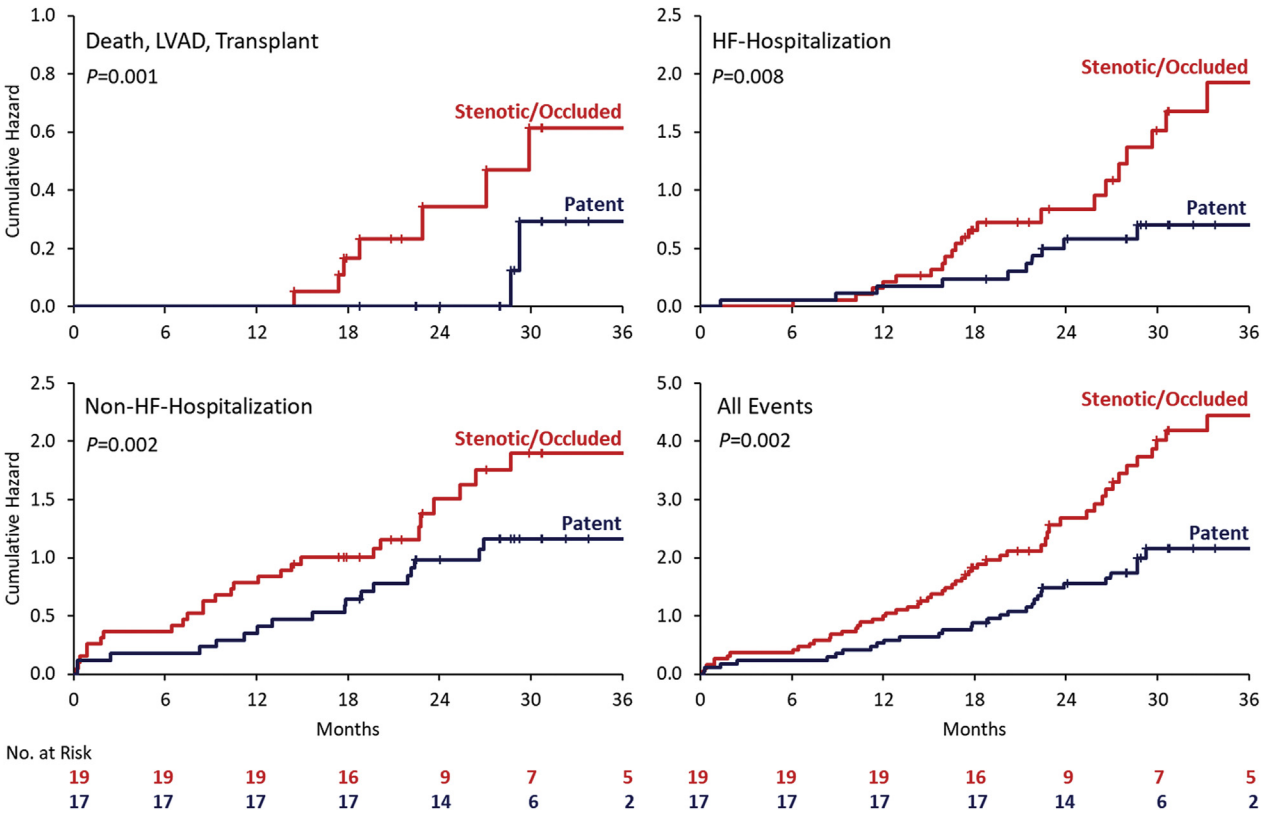
DISCUSSION

FEASIBILITY AND SAFETY OF INTERATRIAL SHUNT THERAPY. Shunts were implanted with high procedural success and low morbidity rates by multiple operators. The device was successfully implanted across the fossa ovalis in all patients, with no cases of device malposition, embolization, shunt repositioning, or need for a second device. The implantation procedure was relatively similar to the placement of atrial septal defect closure devices and fairly straightforward compared with other contemporary transcatheter interventions for treating structural heart disease.

There were few early adverse events related to the transseptal implantation procedure. The only procedure-related MACNE was an episode of cardiac tamponade. There were no unanticipated events and no late events related to device function or bioincompatibility.

SERIAL SUBJECTIVE AND OBJECTIVE OBSERVATIONS. Interatrial left-to-right shunting resulted in early and sustained improvements in symptoms, quality of life, and exercise capacity, with hemodynamic and echocardiographic evidence of preserved right- and left-sided cardiac function. The shunt created a small left-to-right interatrial shunt with a Q_p/Q_s ratio averaging approximately 1.2 at 3 months, becoming 1.1 by 1 year. There was no deterioration of right heart function due to additional chronic volume overloading from the shunt. Specifically, there were no changes in right atrial pressure or pulmonary artery pressure or a panel of echocardiographic parameters assessing right-sided geometry, systolic, diastolic, and global right ventricular function. This is consistent with decades of observations showing the lack of right heart sequelae in adults with small congenital atrial septal defects (11). Measurements of PCWP, cardiac output, LVEF, and left atrial volume did not show clinically consistent or statistically significant directional changes. There was evidence of potential clinical benefit in the form of significant reductions in symptoms, improvements in quality of life, and increased exercise capacity. These changes appeared by 3 months and were maintained at 1 year, and their magnitude was clinically meaningful and similar to that reported in studies with

FIGURE 6 Cumulative Hazard Functions for Clinical Events by Patency Subgroup



Numbers at risk apply to **upper** and **lower panels**. Abbreviations as in Figure 5.

well-established HF therapies (12,13). Similar findings have been reported at 1-year follow-up with another interatrial shunt (IASD System II implant [Corvia Medical, Tewksbury, Massachusetts]) used in a population of patients with HFpEF (7).

DEVICE DURABILITY. Not infrequently, the outcome of first-generation device human feasibility testing is the detection of a previously underappreciated negative effect requiring design iteration before more widespread human application is attempted. Shunt stenosis or occlusion occurred in one-half of the patients by 1 year, as evaluated by TEE. The likely mechanism was found to be pannus infiltration of the bioprosthetic leaflets resulting in early valve degeneration. In a prior juvenile ovine model of ischemic cardiomyopathy with high baseline interatrial left-to-right pressure gradients, the same shunt was found to be hemodynamically effective and to heal well with only minor, nonobstructive pannus formation (14). In patients with HF, it was found that shunt patency was associated with the presence of more severe baseline clinical disease, including higher PCWP, and with having initial higher shunt flow. In contradistinction, patients with baseline features consistent with better outcomes were more likely to develop shunt stenosis or occlusion. A series of additional preclinical studies were performed with valved and "valveless" shunts in sheep with normal physiology (unpublished data). The results reproduced the human pathological findings of severe pannus infiltration of the bioprosthetic leaflets within 3 months in 11 of 12 implanted animals (Online Figure 1). Valveless shunts remained patent with no loss in luminal diameter out to 6 months in 18 of 18 sheep. Kaye et al. (7) reported shunt patency data at 1-year follow-up as evaluated by TTE in 64 patients with HFpEF following the implantation of the IASD System. Transthoracic echocardiographic images were considered not appropriate for determining shunt patency in 16 patients (25%). The shunt was patent in all patients with appropriate transthoracic echocardiographic images (48 of 48).

EXPLORATORY OUTCOMES. The most important limitation of small single-arm human feasibility studies is they have little ability to assess exploratory

clinical outcome measures, because they lack control group comparisons. Although the patency subgroup analysis we performed was post hoc, with its own set of limitations, its strength is that event observers were not likely to be aware of the degree of shunt patency loss. They can be thought of as losing shunt function over a known period between serial echocardiographic examinations and then reverting to the natural history and progressive course of HF with increasing morbidity and mortality. Patients who maintained long-term shunt patency had reductions in all HF events and concomitant improvements in hemodynamic status and LVEF. These benefits occurred despite the patent shunt subgroup's having baseline features usually predictive of worse outcomes, including older age, more severe underlying heart disease and comorbidities, especially reduced renal function, lower exercise capacity, worse resting hemodynamic status, and lower LVEF in patients with HFrEF. However, these findings should be interpreted as "hypothesis generating" because of the observational, nonrandomized nature of the study and the multiplicity of potential confounders that may have influenced the results.

STUDY LIMITATIONS. The small study size, lack of a randomized design, and potential observer bias from lack of blinding limit the ability to reach definitive conclusions about the clinical effectiveness of this HF management strategy. These deficiencies can best be overcome in subsequent adequately powered randomized controlled trials once modifications are made that result in durable device patency.

CONCLUSIONS

Interatrial shunting with the V-Wave system for treating patients with advanced HFrEF and HFpEF refractory to current standard therapy was feasible, safe, and associated with promising efficacy data in terms of functional improvement and reduction of cardiovascular events. A high frequency of shunt stenosis or occlusion at 1 year likely secondary to pannus infiltration of the bioprosthetic leaflets was associated with poorer hemodynamic and longer term clinical outcomes. Having a patent shunt was associated with sustained low morbidity and mortality. Implementing modifications that likely improve device patency duration while maintaining hemodynamic and functional benefits are worthwhile before launching a randomized trial to confirm these findings in a larger population.

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PERSPECTIVES

WHAT IS KNOWN? Increased left atrial pressure leading to pulmonary congestion is the common mechanism precipitating worsening symptoms and acute decompensation in patients with HF.

WHAT IS NEW? In patients with HF with reduced and preserved LVEF, interatrial shunting with the V-Wave system was feasible and safe and associated with improvements in clinical and functional status at mid-term follow-up.

WHAT IS NEXT? A large randomized trial should determine the efficacy of interatrial shunting for alleviating symptoms and reducing major clinical events in patients with HF.

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KEY WORDS hemodynamic, HFpEF, HFrEF, left atrial pressure, patency, pulmonary congestion

APPENDIX For supplemental tables and a figure, please see the online version of this paper.