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ORIGINAL RESEARCH

# Cardiac Unloading with an Implantable Interatrial Shunt in Heart Failure: Serial Observations in an Ovine Model of Ischemic Cardiomyopathy

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## ABSTRACT

**Background:** Patients with dilated cardiomyopathy often have progressive heart failure with systolic dysfunction, ventricular remodeling and clinical decompensation heralded by elevations of filling pressures. Our hypothesis is that an interatrial shunt device can regulate left atrial pressure and stabilize left ventricular function without overloading the right heart.

**Methods:** Sheep ($N = 21$) were subjected to repeat coronary microembolization until left ventricular dysfunction with reduced LVEF was documented. After study group assignment, animals were chronically instrumented during thoracotomy. Shunts were implanted in $n = 14$ and $n = 7$ were sham controls. Hemodynamic and echocardiographic responses were serially evaluated for 12 weeks.

**Results:** Comparisons at study termination showed improved outcomes with interatrial shunting (LVEF 46 ± 11% vs. 18 ± 3%; fractional shortening 19 ± 6% vs. 6 ± 1%; ventricular septal thickness 1.2 ± 0.2 cm vs. 1.0 ± 0.3 cm; left atrial pressure 14 ± 3 mmHg vs. 25 ± 5 mmHg; mean pulmonary artery pressure 24 ± 4 mmHg vs. 37 ± 8 mmHg; right atrial pressure 8 ± 4 mmHg vs. 15 ± 4 mmHg; LV $dP/dt_{max}$ 1515 ± 391 mmHg·s$^{-1}$ vs. 879 ± 333 mmHg–s$^{-1}$; LV $dP/dt_{min}$ −2116 ± 569 mmHg·s$^{-1}$ vs. −1138 ± 545 mmHg·s$^{-1}$; $p \leq 0.03$ for all comparisons). These findings were supported by gross pathological observations and there was a survival advantage with shunting (13/14 vs. 4/7 at 12 weeks, $p = 0.047$). Shunts were small with Qp:Qs 1.2 ± 0.1 and all devices were patent at necropsy.

**Conclusion:** In an animal model of ischemic cardiomyopathy, interatrial shunting selectively unloaded the left-heart leading to sustained reductions in left-atrial pressure, improved left ventricular performance, preserved inotropic and lusitropic function with blunted remodeling. Secondary pulmonary hypertension was absent and right-sided cardiac pressures and function were preserved.

**ARTICLE HISTORY** Received 14 April 2017; Accepted 1 May 2017

**KEYWORDS** Animal model; atrial septum; cardiomyopathy; heart failure; hemodynamics; shunt prosthesis

## Introduction

Small human feasibility trials of percutaneously implanted devices that create interatrial left-to-right shunts for treating patients that have heart failure with reduced and preserved ejection fraction (HFrEF and HFpEF) have reported early safety and general improvement in symptoms, quality of life metrics, and exercise capacity, without deterioration in right-sided cardiac function.[1–3] The rationale for developing shunting devices was based on observations of: (1) reduced pulmonary congestion in patients with mitral disease and atrial septal defects or anomalous pulmonary venous return to the right atrium;[4,5] (2) reports of pulmonary edema after closing congenital atrial septal defects in patients with preexisting left ventricular abnormalities;[6–8] and (3) the left atrial decompressive effects of atrial septostomy in patients with intractable pulmonary edema.[9] Computer modeling studies of simulated small diameter (restrictive) atrial septal defects predict a reduced left atrial pressure response to exercise in patients with HFpEF, without creating severe RV volume overload or pulmonary hypertension.[10] As yet, the physiological mechanisms and adaptive cardiac responses to interatrial shunting devices have not been demonstrated in controlled studies, whether in large animal models or in human heart failure.

We postulated that in the setting of a rapidly failing and remodeling left ventricle, the placement of a shunt that permits left to right atrial flow, but restricts the resting pulmonary to systemic flow ratio (Qp:Qs) to less than 1.5, would moderate high left-sided filing pressures and mitigate stretch-induced progressive worsening of ventricular function. Moreover, the shunt would be small enough to not precipitate right heart volume overload, and consequent dilation and pulmonary hypertension. We tested this hypothesis in the previously validated sheep model of severe untreated heart failure that closely resembles human ischemic cardiomyopathy.[11] These studies were performed in advance of human studies with the V-Wave Interatrial Shunt device.

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The specific aims included assessment of device-induced changes in hemodynamic and echocardiographic indices over a 12-week follow-up period with necropsy confirmation.

## Materials and methods

### Shunt design

The V-Wave Shunt is constructed on an hourglass-shaped, self-expanding Nitinol frame (Figure 1). It is encapsulated with expanded polytetrafluoroethylene (ePTFE) on the left atrial end of the device, extending through the neck and 1/3 on to its right atrial side. The internal diameter at the neck is 5.1 mm and total length of the device is 12 mm. A glutaraldehyde-fixed porcine pericardial valve attached to the nitinol frame and ePTFE using polypropylene suture is disposed at the right atrial side of shunt. The valve closes when the pressure gradient becomes right to left. The shunt is implanted in the fossa ovalis, and extends several millimeters into the left and right atria. Two types of shunts were used, an earlier prototype with a bi-leaflet valve ($n$ = 6) and a tri-leaflet design ($n$ = 8) that would be used for human implants. These design differences were to evaluate closing characteristics of these valves and had no material effect on left to right flow. For the purposes of this report, both shunt designs are analyzed as a single group. The delivery system was modified to perform direct right atrial implants.

### Study design

Two chronic survival studies were conducted at QTest Labs, Columbus, Ohio. This report pools the data from two protocols using the same animal model, procedures and methods of data collection with the described shunt modifications used, each including concurrent sham controls. Protocols were approved by the Institutional Animal Care and Use Committee (IACUC) for compliance with regulations and accepted practices.

Figure 2 shows the experimental interventions and diagnostic studies performed. Mixed-breed sheep from the Ohio State University Sheep Center underwent heart failure induction using a previously validated coronary microembolization model that mimics ischemic dilated cardiomyopathy and results in depressed left ventricular systolic function and elevated filling pressures.[12] Briefly, subselective catheterization of the left circumflex coronary artery was performed under general anesthesia. Polystyrene latex microspheres (90 µm, up to 60,000) were injected and the animals recovered.

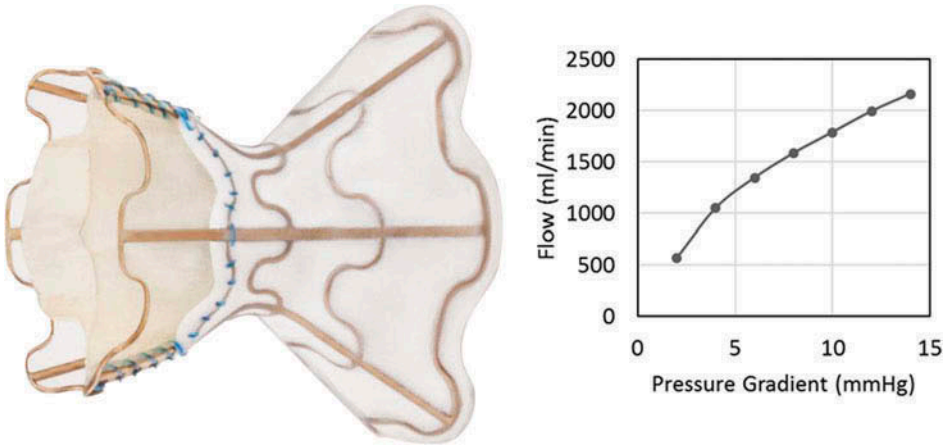


Figure 1. Left: The V-Wave shunt device version with tri-leaflet porcine valve, sutured to expanded polytetrafluoroethylene encapsulation and nitinol frame. Right: Plot of left to right flow through the shunt (saline, constant pressure, 37°C).

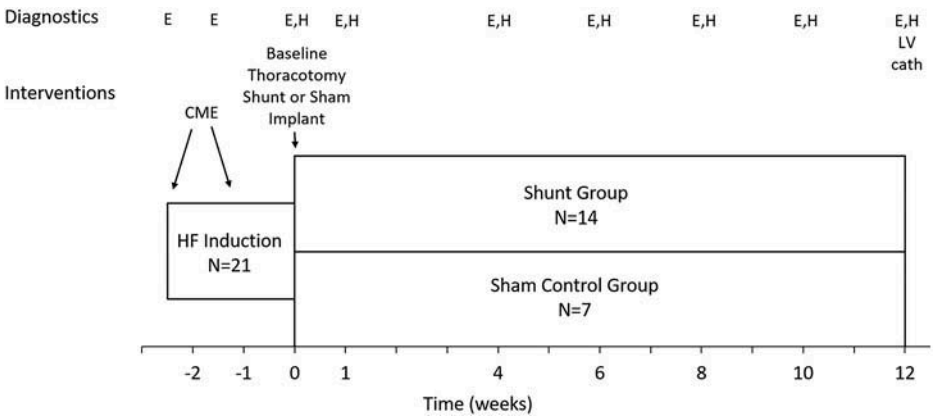


Figure 2. Schematic of experimental interventions and diagnostic procedures. HF, heart failure; CME, coronary microembolization; E, echocardiography; H, hemodynamic measurements; LV cath, left ventricular catheterization.

Microembolization procedures were repeated weekly (7.2 ± 0.7 days apart) until the left ventricular ejection fraction (LVEF) enrollment target between 25% and 40% was achieved (2.0 ± 0.2 microembolization procedures per animal).

Study enrollment (baseline, time = 0) occurred when sheep were instrumented for acute and chronic cardiac evaluations. Under general anesthesia and aseptic technique, Swan-Ganz catheterization from a jugular vein was performed. In a beating heart procedure, a right thoracotomy was performed and fluid filled catheters were inserted, secured in place and tunneled externally, providing chronic access for oximetry sampling and pressure recording from the left atrium, pulmonary artery, right atrium, and superior vena cava.

Following catheter placement, animals were assigned to two study arms. In the Shunt group ($n$ = 14), direct right atrial puncture was performed through the right atrial appendage using the Seldinger technique and the appendage was manipulated to allow the needle and guidewire to cross the fossa ovalis under fluoroscopic and ultrasound guidance. The V-Wave shunt was then placed using its modified delivery system. In the Control group ($n$ = 7), no septostomy was created or shunt placed (sham). Both groups received the same antithrombotic and antiplatelet therapy after enrollment. Warfarin 10–20 mg daily for up to 8 weeks with enoxaparin 40 mg SQ twice daily for 4 days post operatively; aspirin 325 mg, and clopidogrel 75 mg after a 300-mg loading dose were both given daily. The use of heart failure medications, specifically renin-angiotensin antagonists, beta blockers, vasodilators, diuretics, or inotropes was not permitted. The health of the animals was monitored daily by the veterinary staff.

Following recovery from surgery, serial left atrial pressure (LAP), mean pulmonary artery pressure (MPAP), and right atrial pressure (RAP), oximetry, echocardiographic and blood sampling measurements were obtained and recorded in conscious or lightly sedated animals for 12 weeks. For Qp:Qs calculation, blood samples from the left atrium were used for pulmonary venous and arterial oxygen saturation and the SVC was used as the mixed venous saturation. Serial 2D, M-mode, and Doppler echocardiographic recordings were made using 3.5 to 5.0 MHz transducers. Measurements were obtained for LVEF, left ventricular fractional shortening (LVFS), left ventricular internal dimension during diastole (LVIDd), and inter-ventricular septum wall-thickness during systole (IVSs). At the end of the study, the animals were terminally anesthetized, and high fidelity LV pressure measurements were recorded (Konigsberg Instruments, Pasadena, CA, USA) followed by euthanasia under anesthesia. Gross inspection of the heart for device placement and patency and full post mortem examinations were performed in the subset of animals from the second protocol (Control $n$ = 3, Shunt $n$ = 6) by a board-certified veterinary pathologist with expertise in cardiovascular pathology. Detailed results of shunt healing will be reported elsewhere.

### Statistical analysis

All pressure waveform data are reported as mean pressures. Interval scaled data are presented as mean ± standard deviation and ranges. Comparison between time points within animals was by Wilcoxon signed rank test and comparisons between groups was by Mann-Whitney U test as normally distributed data could not be assumed due to small group sizes. Survival proportions were compared by Fisher Exact test.

## Results

### Model characteristics

Heart failure induction was successfully completed in 21 sheep averaging 0.6 ± 0.2 years old and weighing 45 ± 5 kg. Two left-circumflex coronary artery embolizations were performed in 20 sheep, while one animal required a single embolization procedure. The time to enrollment was 11 ± 7 days after the last embolization.

Table 1 summarizes the echocardiographic and hemodynamic characteristics of all animals before induction and after establishing baseline heart failure, regardless of study arm assignment. Moderate left ventricular dysfunction was manifest by significant reductions in systolic function with LVEF falling to 35.8 ± 5.9%. The left ventricle enlarged with LVIDd increasing by 42%, and the myocardium remote from the site of microembolic infarction, IVSs, thinned by 13%, consistent with ventricular remodeling. There was a moderate rise in LAP to 15.9 ± 3.6 mmHg with mildly elevated pulmonary artery pressure and normal right atrial pressure. Cardiac index (CI) was normal in 20 of 21 sheep. Table 2 compares baseline heart failure echocardiographic and hemodynamic indices and shows that there were no differences between Shunt and Control groups with the exception that before implantation, Shunt group animals started with mildly but significantly poorer systolic function with lower left ventricular ejection fraction and fractional shortening than Controls.

Figure 3 plots intracardiac pressures and echocardiographic variables for the Control and Shunt group animals from the baseline through 12-week follow-up. After 4 weeks, Control sheep had significant elevations of LAP, MPAP, RAP, and falling LVEF and fractional shortening compared to baseline. Three of the seven Control group animals died (43%) presenting evidence of pulmonary edema at 4, 6, and 10 weeks after enrollment. The final pre-morbid hemodynamics in these sheep (animals

**Table 1.** Echocardiographic and hemodynamic model characteristics before induction and after baseline heart failure was established in all sheep ($N$ = 21).

| | Before induction | Baseline | $p$ |
|---|---|---|---|
| LVEF, % | 64.7 ± 6.2 (55–83) | 35.8 ± 5.9 (24–48) | < 0.001 |
| LVFS, % | 29.7 ± 4.5 (24–44) | 13.9 ± 2.7 (9–20) | < 0.001 |
| IVSs, cm | 1.3 ± 0.2 (0.9–1.6) | 1.1 ± 0.2 (0.7–1.5) | < 0.001 |
| LVIDd, cm | 3.5 ± 0.6 (2.4–4.8) | 4.9 ± 0.7 (3.3–6.1) | < 0.001 |
| LAP, mmHg | – | 15.9 ± 3.6 (10–25) | – |
| MPAP, mmHg | – | 22.6 ± 2.4 (20–28) | – |
| RAP, mmHg | – | 5.6 ± 2.1 (1–9) | – |
| CI, $L{\cdot}min^{-1}{\cdot}m^{-2}$ | – | 2.9 ± 0.4 (2.3–3.2) | – |

*Note*. Data are summarized as mean ± standard deviation (range).
LVEF, left ventricular ejection fraction; LVFS, left ventricular fractional shortening; IVSs, inter-ventricular septum wall-thickness during systole; LVIDd, left-ventricular internal dimension during diastole; LAP, mean left-atrial pressure; MPAP, mean pulmonary artery pressure; RAP, mean right-atrial pressure; CI, cardiac index by thermodilution.

**Table 2.** Control and shunt group echocardiographic and hemodynamic indices at baseline establishment of heart failure.

| | Control group ($n$ = 7) | Shunt group ($n$ = 14) | $P$ |
|---|---|---|---|
| LVEF, % | 38.7 ± 3.8 (33–46) | 34.3 ± 6.3 (25–48) | 0.046 |
| LVFS, % | 15.2 ± 1.8 (13–18) | 13.2 ± 2.9 (9–20) | 0.046 |
| IVSs, cm | 1.2 ± 0.2 (0.7–1.5) | 1.1 ± 0.2 (0.8–1.5) | 0.68 |
| LVIDd, cm | 4.6 ± 0.9 (3.3–6.0) | 5.0 ± 0.5 (4.4–6.1) | 0.32 |
| LAP, mmHg | 14.2 ± 2.6 (11–18) | 16.6 ± 3.8 (10–25) | 0.24 |
| MPAP, mmHg | 22.1 ± 1.6 (20–25) | 22.2 ± 4.3 (14–29) | 0.66 |
| RAP, mmHg | 5.2 ± 2.2 (3–9) | 5.8 ± 2.1 (1–9) | 0.28 |
| CI, $L{\cdot}min^{-1}{\cdot}m^{-2}$ | 2.8 ± 0.5 (2.3–3.1) | 3.0 ± 0.3 (2.5–3.2) | 0.55 |
| HR, $min^{-1}$ | 101 ± 31 (74–147) | 100 ± 21 (72–133) | 0.97 |
| MAP, mmHg | 76 ± 18 (65–97) | 81 ± 18 (64–106) | 0.45 |
| Qp:Qs | 0.9 ± 0.2 (0.6–1.0) | 0.8 ± 0.2 (0.6–1.0) | 0.83 |

*Note.* Data are summarized as mean ± standard deviation (range).
LVEF, left ventricular ejection fraction; LVFS, left ventricular fractional shortening; IVSs, inter-ventricular septum wall-thickness during systole; LVIDd, left-ventricular internal dimension during diastole; LAP, mean left-atrial pressure; MPAP, mean pulmonary artery pressure; RAP, mean right-atrial pressure; CI, cardiac index by thermodilution; HR, heart rate; MAP, mean aortic pressure; Qp:Qs, ratio of pulmonary to systemic cardiac output.

euthanized after readings) showed they had decompensated heart failure with a resting sinus tachycardia of 169 ± 31 bpm. They had severe left ventricular dysfunction with LAP and LVEF averaging 23.5 ± 2.6 mmHg and 19.1 ± 2.7%, respectively. They also had developed marked pulmonary hypertension with MPAP 41.6 ± 6.3 mmHg and right ventricular dysfunction/volume overload with RAP elevated to 11.5 ± 1.3 mmHg. Compared with surviving Controls at the same time points, these three animals were more ill, characterized by each having the highest resting heart rate (HR), the lowest ejection fraction, and amongst the highest pulmonary pressures. Surviving Control group animals ($n$ = 4) also had worsening heart failure with progressively elevated left- and right-sided filling pressures, pulmonary hypertension, systolic dysfunction, and evidence of further remodeling with a statistical trend for late thinning of the interventricular septum in surviving animals (IVSs 0.95 ± 0.17 cm at 12 weeks vs. 1.23 ± 0.20 cm at baseline, $p$ = 0.068).

### Responses to interatrial shunting

Devices were successfully implanted in all sheep assigned to the Shunt group. In these animals, LAP acutely decreased from 16.6 ± 3.8 mmHg to 14.0 ± 3.9 mmHg ($p$ < 0.001) during the implantation procedure and then averaged 13.6 ± 2.2 mmHg ($p$ = 0.005) for the duration of the study (Figure 3). Similarly, the interatrial pressure gradient (LAP minus RAP) fell from 10.7 ± 3.1 mmHg to 8.3 ± 3.6 mmHg intraoperatively ($p$ < 0.001), and then averaged 6.0 ± 1.6 mmHg for the rest of the study ($p$ < 0.001). RAP, which was 5.8 ± 2.1 mmHg at baseline remained unchanged acutely at 5.7 ± 2.4 mmHg ($p$ = 0.68) then plateaued averaging 7.6 ± 2.7 mmHg ($p$ = 0.19) thereafter. MPAP remained mildly elevated at 24.4 ± 3.6 mmHg but was unchanged from baseline ($p$ = 0.31) with 3/14 animals having mild pulmonary hypertension. Left ventricular systolic function was significantly

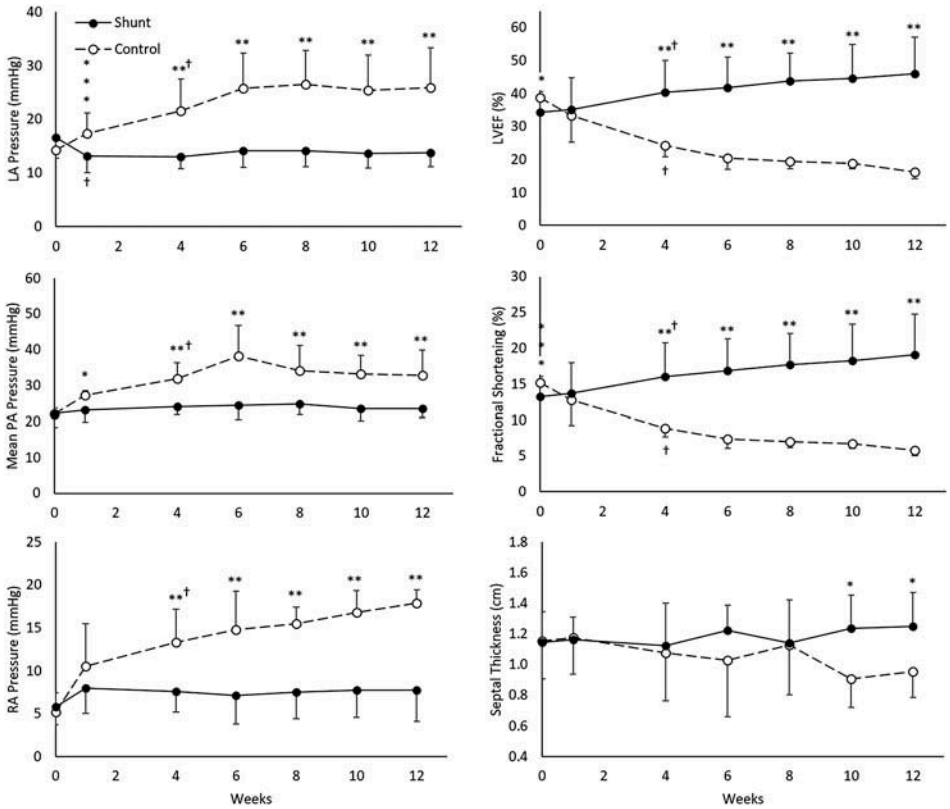


**Figure 3.** Plots showing time course of hemodynamic and echocardiographic parameters starting at baseline (time 0) after induction of heart failure for shunt group (●) and control group (○) sheep. LA, left atrial; PA, pulmonary arterial; RA, right atrial; LVEF, left ventricular ejection fraction. *$p$ < 0.05 shunt versus control; **$p$ < 0.01 Shunt versus Control; †$p$ < 0.05 versus baseline. Error bars = standard deviations.

improved by 4 weeks and continued to progressively improve thereafter with LVEF increasing a relative 36% compared to baseline to an absolute value of 46.1 ± 10.6% and LVFS improved to 19.1 ± 5.5% at the end of follow-up ($p < 0.001$ for both). Interventricular septal thickness remained unchanged from baseline at 1.2 ± 0.2 cm ($p = 0.37$). Oximetry confirmed that shunts were small but patent at 1 week; Qp:Qs was 1.1 ± 0.2 in the Shunt group compared with 0.7 ± 0.1 in the Control group ($p = 0.002$). Shunt patency was maintained with an aggregate Qp:Qs of 1.2 ± 0.1 vs. 0.8 ± 0.1 in Controls for the study duration ($p < 0.001$). Note that Qp:Qs<1 was likely due to the SVC overestimating mixed venous oxygen saturation.

In comparison to Controls, the Shunt group had lower observed mortality (7%, $p = 0.047$) with 13 of 14 animals surviving to study completion. The single fatality occurred at 10 weeks. Pre-morbid data showed that the animal was improving from its baseline status with LAP decreasing from 20 mmHg to 14 mmHg and LVEF increasing from 33% to 46%. The cause of death was unknown. As summarized in Table 3, at the last available time point (12-week or pre-morbid), Shunt group sheep had significantly lower LAP, MPAP, and RAP compared with Control group animals. Similarly, the Shunt group had better left-ventricular ejection fraction, fractional shortening and less septal thinning. There were no intergroup differences in serial measurements of heart rate, temperature, body weight, or blood sampling including hematocrit, white blood cell count, total protein or fibrinogen.

Table 4 shows left-ventricular hemodynamics and derived mechanical indices under anesthesia at the end of the study. Shunted animals had normal left ventricular end diastolic pressure and $dP/dt_{max}$. By contrast, LVEDP was elevated by 110% to 23.0 ± 8.3 mmHg in Controls and $dP/dt_{max}$ was reduced 42% while having comparable heart rates and left ventricular end-systolic pressures. Device-treated animals also had lower left ventricular $dP/dt_{min}$ values and tended to have shorter time-constants of relaxation (tau), consistent with improved diastolic function. Shunt group animals had a significantly higher thermodilution cardiac index 2.8 ± 0.2 $L{\cdot}min^{-1}{\cdot}m^{-2}$, compared to Controls at 2.2 ± 0.2 $L{\cdot}min^{-1}{\cdot}m^{-2}$ ($p = 0.014$), which is consistent in part with their patent shunts contributing to right-sided cardiac output.

Figure 4 shows an echocardiographic example of a patent shunt at 12-weeks and Figure 5 are photographs of a gross pathological specimen of a shunt at the time of study completion. All implants were securely deployed in the interatrial septum with 12 of 14 placed within the fossa ovalis. All shunts were patent without leaflet perforation and there was no visual evidence of inflammation, vegetations, or thrombi involving the device or surrounding tissue. In the subgroup of three Controls and six Shunt-treated sheep comprising the 2nd experimental group of animals, post-mortem examinations were performed and the gross pathological observations are listed in Table 5. Although not reaching statistical significance, the proportion of Shunt group sheep with moderate or severe left atrial or left ventricular enlargement or pulmonary or splenic congestion was less than in controls. Shunt group sheep were significantly less likely to have moderate or severe right ventricular dilation.

**Table 3.** Control and shunt group echocardiographic and hemodynamic indices at 12-weeks or last pre-morbid measurement.

| | Control group ($n = 7$[a]) | Shunt group ($n = 14$[b]) | $p$ |
|---|---|---|---|
| LVEF, % | 17.5 ± 2.6 (14–21) | 46.1 ± 10.6 (32–66) | <0.001 |
| LVFS, % | 6.2 ± 1.0 (5–8) | 19.1 ± 5.5 (12–30) | <0.001 |
| IVSs, cm | 1.0 ± 0.3 (0.5–1.5) | 1.2 ± 0.2 (0.9–1.6) | 0.031 |
| LVIDd, cm | 5.2 ± 0.7 (3.8–5.7) | 5.4 ± 0.8 (4.0–6.7) | 0.91 |
| LAP, mmHg | 24.7 ± 5.2 (21–35) | 13.7 ± 2.5 (9–17) | <0.001 |
| MPAP, mmHg | 37.2 ± 7.7 (29–48) | 24.4 ± 3.6 (19-33) | <0.001 |
| RAP, mmHg | 14.7 ± 3.7 (10-20) | 7.6 ± 3.5 (2–13) | 0.002 |
| HR, $min^{-1}$ | 136 ± 38 (90–201) | 109 ± 17 (77–142) | 0.094 |
| Qp:Qs | 0.8 ± 0.1 (0.7–0.9) | 1.2 ± 0.2 (0.9–1.6) | <0.001 |

*Note*. [a]Includes four control group sheep at 12-weeks and last pre-morbid measurements from three control group sheep that died during follow-up at 4, 6, and 10 weeks. [b]Includes 13 shunt group sheep at 12 weeks and one shunt group sheep that died after 10-week follow-up.

LVEF, left ventricular ejection fraction; LVFS, left ventricular fractional shortening; IVSs, inter-ventricular septum wall-thickness during systole; LVIDd, left-ventricular internal dimension during diastole; LAP, mean left-atrial pressure; MPAP, mean pulmonary artery pressure; RAP, mean right-atrial pressure; HR, heart rate; Qp:Qs, ratio of pulmonary to systemic cardiac output. Data are summarized as mean ± standard deviation (range).

**Table 4.** Control and shunt group left ventricular hemodynamics indices at study termination (12 weeks).

| | Control group ($n = 4$) | Shunt group ($n = 13$) | $p$ |
|---|---|---|---|
| LVEDP, mmHg | 23.0 ± 8.3 (14–32) | 11.0 ± 2.3 (7–14) | 0.003 |
| LVESP, mmHg | 70.2 ± 7.0 (62–79) | 80.2 ± 9.3 (67–97) | 0.10 |
| $dP/dt_{max}$, $mmHg{\cdot}s^{-1}$ | 879 ± 333 (598–1354) | 1515 ± 391 (1123–2386) | 0.023 |
| $dP/dt_{min}$, $mmHg{\cdot}s^{-1}$ | −1138 ± 545 (−1830– −562) | −2116 ± 569 (−3172– −1297) | 0.010 |
| vmax, $s^{-1}$ | 33.2 ± 12.3 (22–51) | 49.1 ± 16.7 (29–81) | 0.013 |
| Tau, msec | 33 ± 8 (23–42) | 27±8 (14–41) | 0.34 |
| HR, $min^{-1}$ | 97 ± 22 (70–119) | 96 ± 16 (74–119) | 0.96 |

*Note*. Data are summarized as mean ± standard deviation (range).

LVEDP, indicates left ventricular end-diastolic pressure; LVESP, left ventricular end-systolic pressure; $dP/dt_{max}$ and $dP/dt_{min}$, first derivatives of LV pressure rise and decay; vmax, contractile element shortening velocity at zero load; Tau, time constant of LV pressure decay; HR, heart rate.

**Table 5.** Gross pathological observations in the subgroups of control and shunt group sheep.

| | Control ($n$ = 3) | Shunt group ($n$ = 6) | $p$ |
|---|---|---|---|
| LA dilation (moderate/severe) | ●●○ | ●○○○○○ | 0.12 |
| LV dilation (moderate/severe) | ●●○ | ●●○○○○ | 0.29 |
| RV dilation (moderate/severe) | ●●● | ○○○○○○ | 0.006 |
| Lung/splenic congestion (moderate/severe) | ●●○ | ●○○○○○ | 0.12 |

*Note.* LA, left atrium; LV, left ventricle; RV, right ventricle; ●, present; ○, absent.

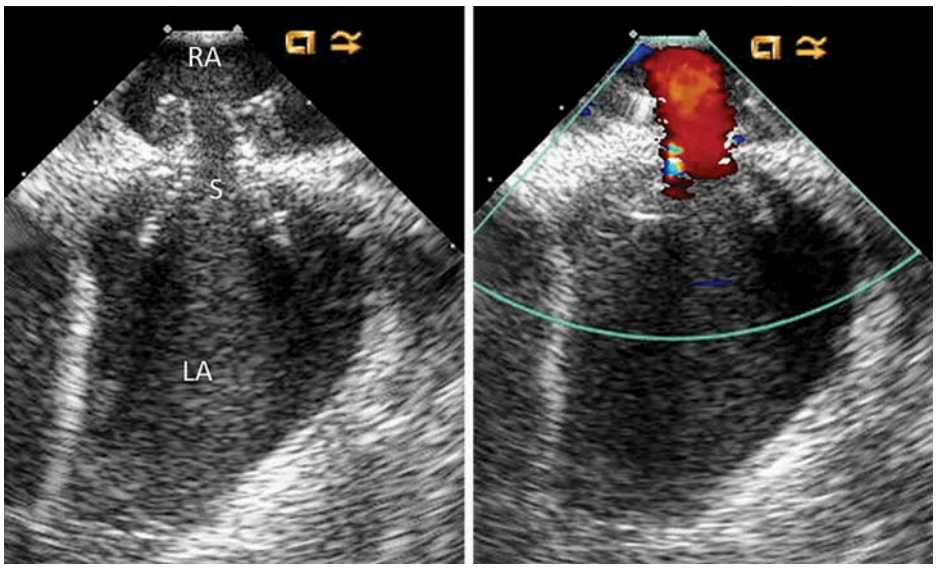


**Figure 4.** Intracardiac echocardiographic images of tri-leaflet valve shunt at 12-weeks. Left: 2-dimensional scan showing LA, left atrium; RA, right atrium; and S, Shunt device positioned across fossa ovalis. Right: Similar view with color Doppler showing left-to-right flow jet extending into the right atrium demonstrating shunt patency.

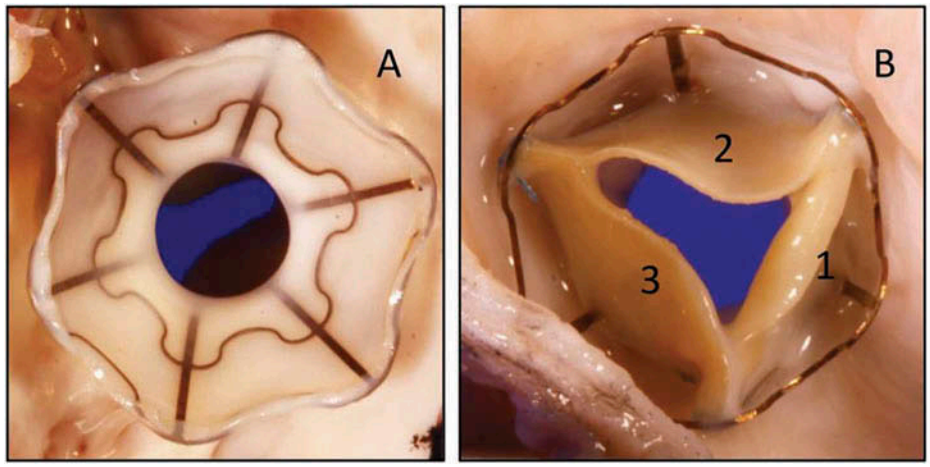


**Figure 5.** Photographs showing formalin fixed shunt device *in situ* in fossa ovalis at 12 weeks after implantation. Shunt is widely patent. (A) Left atrial side has thin pannus at free edge. (B) Right atrial side (1, anterior; 2, posterior; 3, inferior). There is pannus at base of leaflets with thickening of leaflet 1 on its septal side.

## Discussion

We evaluated the implantable V-Wave Interatrial Shunt in an ovine model of ischemic heart failure. Our study shows that a hemodynamically small left-to-right shunt, with a resting pulmonary to systemic flow ratio of 1.2, has the potential to stabilize, prevent, and in some instances partially reverse a variety of manifestations of rapidly progressing cardiac failure.

The sheep coronary microembolization model closely resembles human ischemic cardiomyopathy with regional myocardial necrosis accompanied by progressive left ventricular dilation and systolic dysfunction, hemodynamic decompensation, neurohormone activation that ultimately results in interstitial fibrosis, ventricular remodeling, and clinical heart failure.[11–13] The model has been used to study the cellular and molecular mechanisms of apoptotic cardiomyocyte death,

myocyte regenerative capacity and testing of pharmacological, surgical, and device-based interventions.[14–16]

In this study, heart failure induction resulted in the rapid development of left ventricular dysfunction with LVEF falling to 36% within 2 weeks. The thickness of the interventricular septum was used as an index of myocardial remodeling and declined from 1.3 to 1.1 cm. Concurrently left atrial pressure rose to 16 mmHg while mean pulmonary artery and right atrial pressures were either slightly elevated or remained normal. The impact of these initial ischemic events likely resulted in the exhaustion of myocardial reserve, such that surviving Control group animals continued to progressively deteriorate so that by the end of the study, LVEF was markedly reduced to 18%, the septum thinned to 1.0 cm and LAP monotonically elevated to 25 mmHg. Control animals developed severe secondary pulmonary hypertension (MPAP 37 mmHg), and worsening right atrial pressure averaging 15 mmHg, consistent with right ventricular volume overload. Control animals had a 43% mortality, which was associated with rapidly worsening hemodynamics, particularly pulmonary hypertension and tachycardia. Huang and colleagues reported that 15 of 38 (39%) of similarly microembolized sheep died during the first several months after reaching LVEF baseline targets.[13]

Despite comparable or even slightly worse left ventricular function at baseline in the Shunt group, there were marked contrasts in the evolution of objective heart failure indices between the control and shunted animals consistent with a device treatment effect. Shunting abolished the course of rapidly deteriorating left and right ventricular function and induced stability that was associated with global improvement of left ventricular systolic function. Specifically, after shunt placement, instead of LAP rising to levels resulting in pulmonary congestion, left atrial pressure fell significantly, approaching normal and remained steady for the study duration. Instead of developing severe pulmonary hypertension and RV volume overload, pulmonary artery and right atrial pressure remained minimally elevated. Instead of progressive worsening of LVEF to 18%, shunting improved systolic function with the ejection fraction increasing to 46% and was still trending upward at study conclusion. The interventricular septum ceased to thin, consistent with interruption of the ventricular remodeling seen in controls. At study termination, high fidelity measurements of left ventricular pressure showed that Control group sheep had diminished indices of contractility and reduced diastolic function, while in shunted animals these indices were near normality. Although these measurements are load-dependent, the magnitude and breadth of these data suggest that shunting prevented deterioration of left ventricular inotropic and lusitropic states. Finally, shunting was also associated with a statistically significant survival benefit. Reduced LVEF,[17] the extent of remodeling,[18] secondary pulmonary hypertension and elevated left-sided filling pressure[19–21] are known to correlate with morbidity and mortality in humans with dilated heart failure. It seems reasonable to conjecture that interatrial shunting, through its mechanisms of stabilizing and improving these parameters had a direct influence on survival.

The observed device shunt ratio Qp:Qs, was small, averaging 1.2. This would equate to a shunt flow of approximately 700 ml/min. From bench studies using saline at constant pressure, the flow through the shunt at the observed 6 mmHg interatrial gradient is 1300 ml/min. The differences are explained by the viscous losses associated with accelerating/decelerating blood across the shunt with pulsatile flow. All shunts were found to be patent without thrombosis on gross inspection.

There is limited prior information on the experimental effects of left to right interatrial shunting. Roven and coworkers[22] created acute elevations in left atrial pressure in dogs by reducing left coronary blood flow or increasing afterload with a balloon in the aorta. They shunted blood between the atria via a conduit and controlled the flow with a pump. They showed that left atrial pressure could be reduced in relation to shunt flow and pressure gradient with minimal reduction in systemic flow or elevation of right atrial pressure over a large range of shunt sizes. They believed that a shunt made the right ventricle a less efficient generator of left atrial pressure, which would control the pressure delivered to the left ventricle and that the excess volume returned to the right side would be distributed in the highly compliant great veins and liver. These experiments, however, lasted only minutes and were generally at much higher shunt flows.

We think it likely that the mechanism(s) of action in heart failure are probably even more dependent on the left ventricular compliance relationship. In dilated cardiomyopathy, a variety of precipitants, often relatively minor, results in sympathetic activation causing rapid central volume redistribution and slower renal retention of sodium and water. Excess effective volume returning to the left ventricle, when operating on the steeper portion of its diastolic compliance curve, causing its filling pressure to exceed 25 mmHg for a period of days to weeks, results in pulmonary congestion.[22–24] An interatrial shunt diverts a small amount of this volume instead to the right atrium as a function of the interatrial pressure gradient. Thus, although shunting results in a modest reduction in LV end-diastolic volume, it produces an obligate substantial and instantaneous fall in end-diastolic pressure with a commensurate fall in upstream filling pressures including left atrial, pulmonary venous, and pulmonary artery pressure. The anticipated clinical result will be prevention of pulmonary congestive symptoms. When left-sided filling pressures are lower, shunt flow is smaller and the effect on LV diastolic volume/pressure becomes negligible. Interatrial shunting as a therapeutic strategy for heart failure may thus be conceptualized as a continuous regulator of LV filling volume and pressure, load-dependently increasing the effective/perceived end-diastolic ventricular compliance. As demonstrated in this study, decreased ventricular loading also has a beneficial effect on active remodeling and less stretching of the interventricular septum may benefit the right ventricle as well. In the absence of severe right ventricular dysfunction, the right heart can tolerate small left-to-right atrial shunts (Qp:Qs <1.5) because the additional blood volume causes only a minimal rise in filling pressure due to the intrinsically high compliance of the right heart.[25] By preferentially decompressing the left atrium and preventing pulmonary venous hypertension, the benefits of reducing afterload may outweigh a small increase in volume handled by the right ventricle.

These animal model data have several limitations that should be considered before making inferences about clinical applications. Interatrial shunting is intended for treating patients with established heart failure who have already been treated with maximally tolerated, guideline-directed medical and device therapies and remain symptomatic and at high risk for heart failure morbidity and mortality. For example, Del Trigo and co-authors described 3-month results in the first 10 chronic NYHA class III heart failure patients with reduced ejection fraction, treated with the same interatrial shunt.[3] These patients were on optimal medical therapy with renin-angiotensin antagonists, beta blockers, mineralocorticoid antagonists and 50% had prior cardiac resynchronization therapy. A significant decrease in pulmonary capillary wedge pressure from 23 to 17 mmHg was recorded with no increase in right atrial or pulmonary artery pressure or pulmonary resistance. LVEF and LV volume changes were small and inconsistent. This one study is too small and the duration of follow-up too limited to know if the results of shunting in humans will be similar to the findings seen in the experimental model presented here. There are several reasons why they may differ. The sheep in this study had recently induced heart failure, were still actively remodeling, and had not received prior treatment with neurohormonally active medications or resynchronization device therapy. It is also not yet known if the single 5-mm shunt size used in the sheep will be sufficient in humans or if additional sizes are needed. The long-term durability of the shunt or the clinical utility of having a valve to prevent reverse shunting or paradoxical emboli, have not been demonstrated. The investigators performing these studies were not blinded to study arm assignments, so selection or other bias is possible. These limitations notwithstanding, the totality of the data, echocardiographic, hemodynamic, survival, and post mortem, which is consistent, coherent and highly statistically significant, make the presence of a true device effect reasonable and highly likely.

## Conclusion

In a controlled study, it was demonstrated in a large animal model of rapidly developing heart failure that resembles ischemic cardiomyopathy that a small interatrial shunt device can selectively unload the heart, resulting in sustained reductions of left-atrial pressure and improved left ventricular function while right-sided cardiac pressures and function were preserved. Shunt-induced reductions in wall stress due to decreased loading and attenuated remodeling may be important mechanisms behind these salutatory effects. These data help to establish a preclinical proof-of-principle for interatrial shunting as a possible therapeutic approach for patients with heart failure with reduced systolic function.

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## Disclosure Statement

Dr Eigler is a corporate officer, employee, and has an equity interest in V-Wave Ltd. Dr Shkurovich is also an employee with an equity interest. Drs Keren, Verheye, and Abraham disclose consultancies and equity interests in V-Wave Ltd. The remaining authors report no conflicts.

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