

## Percutaneous Pericardial Resection A Novel Potential Treatment for Heart Failure With Preserved Ejection Fraction

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**Background**—People with heart failure and preserved ejection fraction develop increases in left ventricular (LV) end-diastolic pressures during exercise that contribute to dyspnea. In normal open-chest animal preparations, the pericardium restrains LV filling when central blood volume increases. We hypothesized that resection of the pericardium using a minimally invasive epicardial approach would mitigate the increase in LV end-diastolic pressure that develops during volume loading in normal and diseased hearts with the chest intact.

**Methods and Results**—Invasive hemodynamic assessment was performed at baseline and after saline load before and after pericardial resection in normal canines with open (n=3) and closed chest (n=5) and in a pig model with features of human heart failure and preserved ejection fraction with sternum intact (n=4). In closed-chest animals, pericardiectomy was performed using a novel subxiphoid procedure. In both experimental preparations of normal dogs, pericardiectomy blunted the increase in LV end-diastolic pressure with saline infusion, while enhancing the saline-mediated increase in LV end-diastolic volume. With chest intact in the pig model, percutaneous pericardial resection again blunted the increase in LV end-diastolic pressure secondary to volume expansion (+4±3 versus +13±5 mm Hg;  $P=0.014$ ), while enhancing the saline-mediated increase in LV end-diastolic volume (+17±1 versus +10±2 mL;  $P=0.016$ ).

**Conclusions**—This proof of concept study demonstrates that pericardial resection through a minimally invasive percutaneous approach mitigates the elevation in LV filling pressures with volume loading in both normal animals and a pig model with diastolic dysfunction. Further study is warranted to determine whether this method is safe and produces similar acute and chronic hemodynamic benefits in people with heart failure and preserved ejection fraction. (*Circ Heart Fail.* 2017;10:e003612. DOI: 10.1161/CIRCHEARTFAILURE.116.003612.)

**Key Words:** blood volume ■ heart failure ■ hemodynamics ■ humans ■ pericardium

Half of patients with heart failure (HF) have preserved ejection fraction (HFpEF), and few effective treatments are available.<sup>1–3</sup> HFpEF is mechanistically characterized by elevation in left ventricular (LV) filling pressures that contribute to symptoms of dyspnea and exercise intolerance.<sup>4–7</sup> Filling pressures are elevated at rest in patients with more advanced HFpEF, and they become elevated when venous return to the heart increases during exercise in patients with earlier stage HFpEF.<sup>4,8</sup> Acute removal of the pericardium in animal models improves effective LV diastolic compliance even as myocardial properties remain unchanged because the external constricting effect of the pericardium is eliminated.<sup>9–15</sup> Indeed, studies in normal animals have demonstrated improvements in filling pressures, cardiac output reserve, and exercise capacity after pericardiectomy.<sup>16,17</sup>

with HFpEF. However, typical patients with HFpEF are elderly and frail, making them poor candidates for conventional surgical pericardiectomy. Accordingly, we sought to develop and test a novel, minimally invasive pericardial resection procedure that could be performed in the catheterization laboratory to remove the restraining effects of the pericardium without the need for open sternotomy. We hypothesized that removing this restraining effect of the pericardium using minimally invasive methods would attenuate the increase in LV filling pressures accompanying states of increased venous return, while leaving muscle properties intact. To test this hypothesis, we assessed the hemodynamic effects of pericardial resection using our newly developed subxiphoid technique in normal dogs and then in a hypertensive pig model with features of human HFpEF.

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On the basis of these observations, we reasoned that pericardial resection might constitute a novel treatment for people

### Methods

The goal of this study was to develop and test the hemodynamic effects of a new prototype device and technique designed to enable percutaneous resection of the anterior parietal pericardium. To test this new device and procedure, we evaluated the hemodynamic effects at baseline and

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with acute saline loading in (1) open-chest normal dogs, and then in (2) a second group of closed-chest normal dogs, and (3) a closed-chest pig model with features of HFpEF. Experiments for (1) were performed with chest open, whereas (2) and (3) were performed using a novel minimally invasive, subxiphoid approach that we have developed.

Five bench tests were conducted in ex vivo porcine hearts using preliminary prototypes, which were further refined and reprototyped for subsequent surgeries around the beating heart. These devices were designed to be deployed into a subxiphoid sheath enabling access to epicardial space for in vivo testing in large animals (Figure 1). After prototype development, mongrel dogs weighing 30 to 40 kg underwent open-chest (n=3) experiments. After these experiments, another 5 normal dogs then underwent minimally invasive, percutaneous closed-chest procedures using the prototyped tools and technique.

To test the effects of pericardial resection in diseased hearts, we used a recently developed hypertensive, hypercholesterolemic pig model displaying typical features of HFpEF.<sup>18–20</sup> In this model, domestic pigs are fed a high-fat diet (2% cholesterol and 15% lard by weight) for 6 weeks followed by surgical induction of renovascular hypertension by unilateral renal artery coiling. Animals then continue with high-fat diet for an additional 10 weeks. This model has been shown to display increased LV mass, diastolic dysfunction, impaired coronary microvascular function, a proinflammatory milieu, and increased myocardial oxidative stress despite preserved EF,<sup>18–20</sup> mirroring changes seen in human HFpEF.<sup>1–3</sup>

For all experiments, an intramuscular sedative was administered in fasted animals before obtaining vascular access. Animals were instrumented under general anesthesia using 1% to 3% isoflurane after appropriate induction with 10 mg/kg ketamine and 0.5 mg/kg diazepam. Body temperature was monitored and maintained with a dorsal water flow heating pad and solutions warmed to 41°. These studies were approved by the Mayo Clinic Institutional Animal Care and Use Committee.

### Open-Chest Surgical Experiments

In the first stage of experiments, sternotomy was conducted, after which a puncture was made into the pericardium to gain epicardial access. The prototype cutting device was deployed in the epicardial space to allow slitting of the pericardium, taking care to avoid the phrenic nerves. Once slit, control of the slit margins was obtained at 2

sites, and the anterior pericardium was reflected away from the initial slit and then resected and removed.

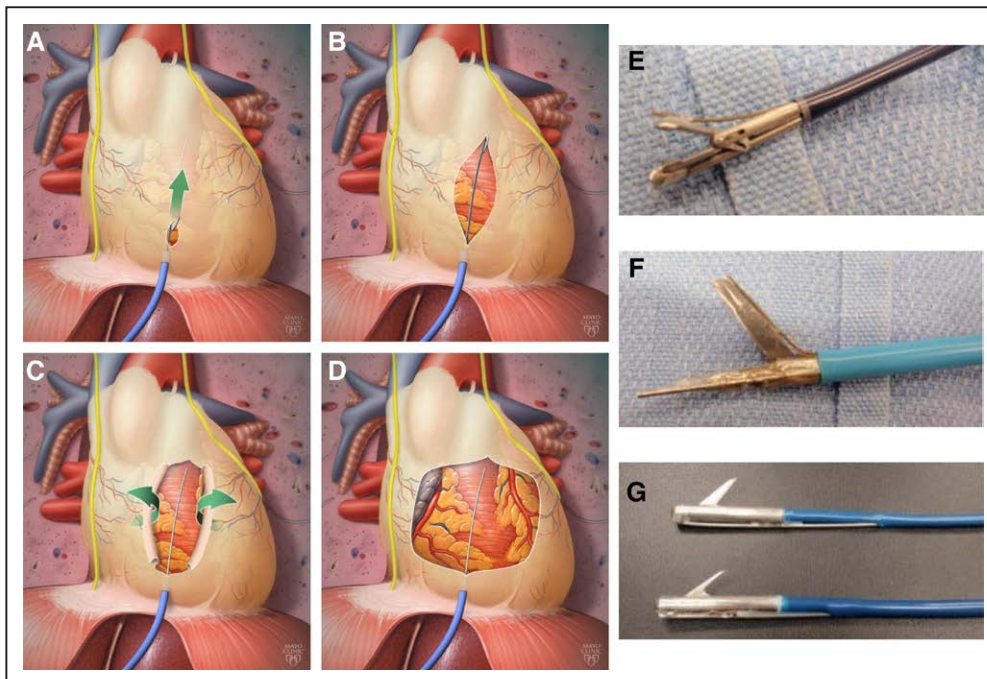
### Closed-Chest Percutaneous Surgery

Minimally invasive pericardial resection was then performed with chest intact in normal dogs and subsequently in model pigs (Figure 1). Percutaneous epicardial access was obtained using a method similar to that described by Sosa et al.<sup>21–23</sup> The devices were deployed in the epicardial space under fluoroscopic guidance and used to slit the pericardium in a scissor-like fashion, similar to the procedure performed in the open experiments. Damage to the phrenic nerve is avoided by use of a pacing electrode that stimulates diaphragmatic contraction when the cutting tool approaches the phrenic nerve. After pericardial resection and after completion of all hemodynamic assessments, the sternum was opened to allow direct visualization of the heart, lungs, and resected pericardium, followed by animal euthanization.

### Hemodynamic Assessment

Intracardiac pressures were measured using fluid-filled catheters placed under fluoroscopic guidance in the LV, right atrium, and pulmonary artery. LV end-diastolic pressure (LVEDP) was measured by visual inspection just before the rapid upstroke of LV pressure. Left ventriculography was performed in the right anterior oblique position to measure LV end-diastolic volume (LVEDV), end-systolic volume, and left ventricular ejection fraction using a 6F pigtail catheter. Angiographic data were recorded in digital format at 30 frames per second. LV volume was measured using the area-length method, where calculated volume (V<sub>calc</sub>) is determined from the silhouette area (A) and long-axis length (L) by the following equation:  $V_{calc} = 8A^2/3\pi L$ . Magnification correction was determined based on a distance of 18 cm from table to LV cavity. Actual LV volume was then calculated using a regression formula ( $V = 0.81 V_{calc} + 1.9$  mL) as validated by Kennedy et al.<sup>24</sup> LV stroke volume (SV) was calculated as the difference between LVEDV and LV end-systolic volume. Cardiac output was determined by the product of SV and heart rate.

To examine diastolic LV reserve after pericardial modification, hemodynamics were then reassessed immediately after rapid infusion of prewarmed normal saline (500 mL over 3 minutes) to simulate



**Figure 1.** A–D, Illustration depicting release of pericardial restraint using the percutaneous subxiphoid approach. Used with permission of Mayo Foundation for Medical Education and Research, all rights reserved. Prototypes built to date that can track over a guidewire and grasp the pericardium (E), deliver electric energy to stimulate the phrenic nerve and cut the pericardium in a forward scissors-like motion (F), and cut the pericardium with an actuating reverse-cutting blade (G).

the increase in central blood volume that accompanies physiological stressors such as exercise. Saline infusion was performed before and after pericardial modification in all experiments. Because fluids redistribute after saline load, the same timing and order of assessment was used after bolus completion at both time points. Specifically, intracardiac and pulmonary pressures were assessed first, immediately after completion of the saline bolus, followed immediately by left ventriculography within 10 to 20 s of pressure records.

### Statistical Analysis

Data are reported as mean±SD when providing a description of the sample data. Hemodynamics for the preliminary open-chest experiment were compared using paired *t* tests given their limited sample size (*n*=3). Hemodynamics for the closed-chest experiments (dogs and HFpEF model pigs) were compared between states (baseline and saline) and before and after pericardial modification using a linear mixed model. A separate model was fit for each outcome, stratified by animal type. The fitted regression model consisted of a random intercept (blocking factor for each animal) and a fixed effect term for the experimental period. Further evaluation of the appropriateness of the model was conducted by visual inspection of the distribution of values by experimental condition. To test planned hypotheses, statistical contrasts of estimated means were used. Reported *P* values are 2-sided and have not been adjusted for multiple comparisons. *P* values <0.05 were considered statistically significant. Analyses were performed using JMP 10.0.0 and SAS 9.4 (SAS Institute, Cary, NC).

## Results

### Effects of Complete Pericardiectomy With Open Chest

With the chest closed and pericardium intact in the first 3 animals, saline infusion increased LVEDP from 15±2 to 32±5

mmHg (*P*=0.026). Similar changes were observed with saline infusion with the chest open and pericardium intact, with LVEDP increasing from 15±2 to 33±4 mmHg (*P*=0.007). Open pericardiectomy had no effect on baseline LVEDP. However, the saline-mediated increase in LVEDP after full pericardiectomy with open chest was >50% lower when compared with pericardium intact (+7±6 versus +18±3 mmHg; *P*=0.07).

### Effects of Anterior Pericardial Resection With Chest Intact in Normal Dogs

Given the salutary benefits of full pericardiectomy noted in preliminary open-chest experiments, the effects of anterior pericardial resection via minimally invasive, subxiphoid pericardiectomy were then assessed with the chest intact in a different set of 5 acute canine studies using the prototyped tools developed in the bench and preliminary open-chest experiments. Before pericardial modification with chest intact, rapid saline infusion increased biventricular filling pressures, pulmonary artery pressure, cardiac output, SV, and LVEDV dramatically, with an increase in LVEDP from 11 to 30 mmHg (*P*<0.001; Table 1). After volume expansion, LVEDP returned to baseline values (*P*=0.92).

Pericardial resection was then performed via percutaneous subxiphoid approach (Figure 1). As in the open-chest experiments, hemodynamics were not statistically different after pericardial resection at baseline in these closed-chest experiments (Table 1). However, the increase in LV filling pressures in response to saline infusion with the chest closed

**Table 1. Effects of Pericardial Resection in the Dog**

|                              | Pericardium Intact |     |        |     |          |            |                |      | Pericardium Incised |      |        |     |             |                | Incised vs Intact |             |                |
|------------------------------|--------------------|-----|--------|-----|----------|------------|----------------|------|---------------------|------|--------|-----|-------------|----------------|-------------------|-------------|----------------|
|                              | Baseline           |     | Saline |     | Delta 1* |            |                |      | Baseline            |      | Saline |     | Delta 2*    |                | Delta 3†          |             |                |
|                              | Mean               | SD  | Mean   | SD  | Est      | 95% CI     | <i>P</i> Value | Mean | SD                  | Mean | SD     | Est | 95% CI      | <i>P</i> Value | Est               | 95% CI      | <i>P</i> Value |
| Primary outcome measure      |                    |     |        |     |          |            |                |      |                     |      |        |     |             |                |                   |             |                |
| LVEDP, mm Hg                 | 11                 | 2   | 30     | 6   | 19       | (14, 23)   | <0.001         | 11   | 4                   | 18‡  | 5      | 7   | (3, 12)     | 0.002          | -11               | (-17, 5)    | 0.001          |
| Secondary outcome measures   |                    |     |        |     |          |            |                |      |                     |      |        |     |             |                |                   |             |                |
| LVEDV, mL                    | 43                 | 8   | 56     | 13  | 13       | (5, 20)    | 0.005          | 44   | 5                   | 66§  | 9      | 22  | (14, 30)    | <0.001         | 10                | (-1, 20)    | 0.077          |
| RA pressure, mm Hg           | 11                 | 3   | 16     | 3   | 6        | (3, 8)     | <0.001         | 10   | 3                   | 12§  | 3      | 2   | (-0, 5)     | 0.062          | -3                | (-7, 0)     | 0.062          |
| PA systolic pressure, mm Hg  | 25                 | 5   | 36     | 4   | 10       | (7, 14)    | <0.001         | 27   | 6                   | 32   | 8      | 5   | (2, 9)      | 0.003          | -5                | (-9, -1)    | 0.029          |
| PA diastolic pressure, mm Hg | 11                 | 1   | 20     | 6   | 9        | (4, 14)    | 0.001          | 12   | 3                   | 17   | 4      | 5   | (-0, 9)     | 0.055          | -4                | (-11, 2)    | 0.18           |
| Cardiac output, L/min        | 2.0                | 0.5 | 2.9    | 0.7 | 0.9      | (0.2, 1.8) | 0.047          | 2.5  | 0.5                 | 3.2  | 0.8    | 0.6 | (-0.3, 1.5) | 0.145          | -0.3              | (-1.6, 1.0) | 0.63           |
| Stroke volume, mL            | 19                 | 4   | 28     | 8   | 9        | (3, 14)    | 0.008          | 24   | 6                   | 34   | 9      | 10  | (4, 15)     | 0.004          | 1                 | (-7, 9)     | 0.77           |
| LVEF (%)                     | 51                 | 15  | 57     | 17  | 6        | (-2, 14)   | 0.127          | 59¶  | 12                  | 55   | 11     | -4  | (-12, 4)    | 0.30           | -10               | (-21, 1)    | 0.077          |
| Heart rate, beats per minute | 105                | 8   | 107    | 10  | 3        | (-12, 17)  | 0.70           | 106  | 19                  | 96   | 12     | -10 | (-25, 5)    | 0.158          | -13               | (-33, 8)    | 0.20           |

Est indicates estimates; LVEDP, left ventricular end-diastolic pressure; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; PA, pulmonary artery; and RA, right atrium.

\*Delta 1 and Delta 2 are the model-based estimates of the change observed with the introduction of saline in the intact and incised pericardium conditions, respectively.

†Delta 3 is the difference in deltas between pericardium intact and pericardium incised.

‡*P* values of <0.001 for comparison of the 2 saline conditions.

§*P* values of (0.001, 0.01) for comparison of the 2 saline conditions.

||*P* values of (0.01, 0.05) for comparison of the 2 saline conditions.

¶*P* values in the range of (0.01, 0.05) for comparison of the 2 baseline conditions.

was significantly attenuated by minimally invasive pericardial modification, whereas the increase in LVEDV was enhanced (Table 1; Figures 2 and 3).

### Effects of Anterior Pericardial Resection With Chest Intact in Pig Model

Next the effects of pericardial resection were tested in the swine model with features of HFpEF ( $n=4$ ). These animals displayed high LVEDP ( $18\pm 5$  mmHg) and normal ejection fraction at baseline, consistent with human HFpEF (Table 2). Like the normal dogs, saline infusion led to marked increases in filling pressures, with increases in cardiac output and SV in pigs according to the Frank–Starling mechanism. After saline infusion with pericardium intact, hemodynamics returned to baseline values.

Percutaneous anterior pericardial resection did not alter biventricular filling pressures at baseline in the pig model, but it did increase LVEDV and SV (Table 2). Similar to the normal dogs, the saline-mediated increase in LVEDP was markedly attenuated after anterior pericardial resection, with greater increase in LVEDV from volume loading with chest intact (Table 2; Figures 2 and 3).

### Gross Pathology and Safety

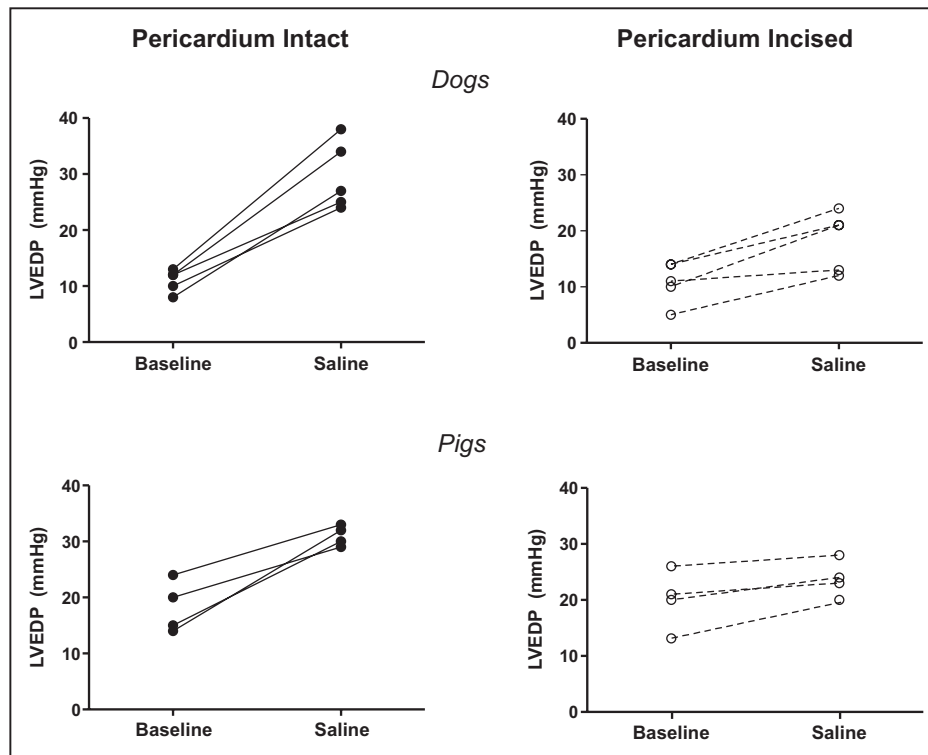
There were no acute cardiac complications from the open or minimally invasive pericardial resections, with no tamponade developing and no damage to the phrenic nerves. One animal developed a laceration of the left lung caused by the pericardial cutting tool noted at the time of euthanization. The hemodynamic improvements after subxiphoid pericardial modification were coupled with wide resection of the

pericardium noted on gross pathology, with little to no residual coverage of the anterior surface of the heart observed in all animals. Figure 4 displays typical gross results after conclusion of the experiments and opening of the chest.

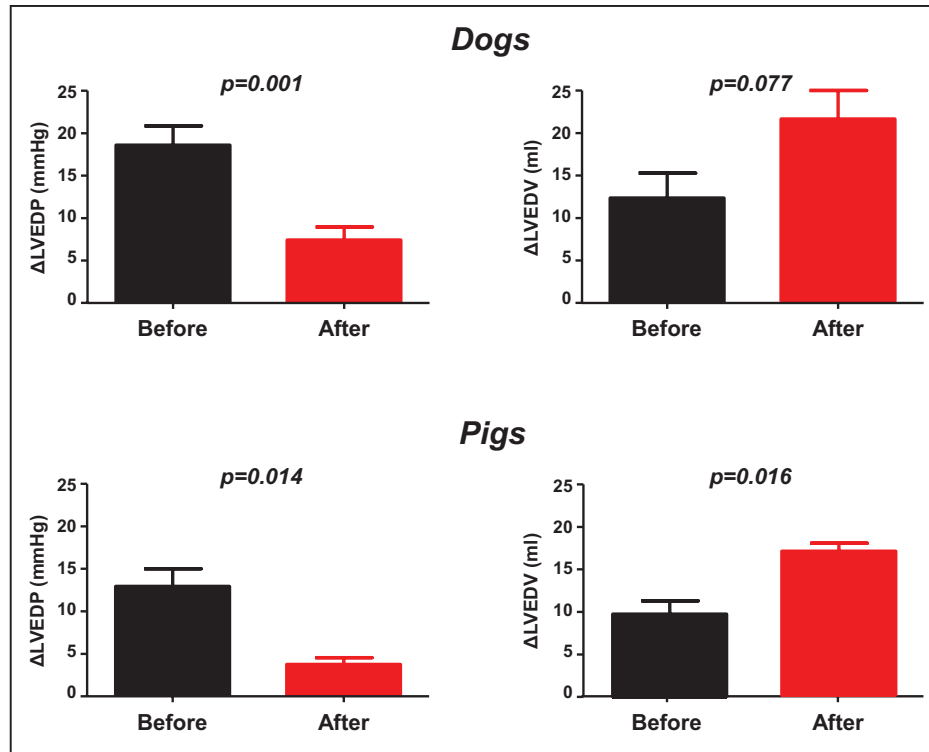
### Discussion

The normal pericardium restrains ventricular filling, contributing to the elevation in intracardiac pressures that develop during conditions of increased venous return such as exercise. Patients with HFpEF characteristically develop marked increases in filling pressures with exercise or volume loading owing to diastolic dysfunction.<sup>4–7</sup> We show here for the first time in normal canines and pigs with hemodynamic features of HFpEF that pericardial resection using a novel, minimally invasive approach substantially mitigates the increase in filling pressures associated with volume loading. Importantly, the procedure and its hemodynamic benefits are seen with the chest intact and with limited anterior pericardial resection, suggesting that full pericardiectomy is not required to observe salutary effects on filling pressures. Although saline infusion does not fully recapitulate the hemodynamic loading seen with exercise,<sup>7</sup> the current results suggest that anterior pericardial resection, which can be performed using this new procedure without the need for open sternotomy in the catheterization laboratory, might be an effective treatment for human HFpEF.

Trials in patients with HFpEF have failed to identify an effective medical treatment, possibly because of heterogeneity in the underlying causes.<sup>1–3</sup> Despite this heterogeneity, pathological elevation in cardiac filling pressures during exercise is common to all patients<sup>4–7</sup> and represents a viable therapeutic target that may improve clinical status, regardless of the underlying cause.



**Figure 2.** Left ventricular end-diastolic pressures (LVEDPs) at rest and after saline load for all individual animals in chest intact experiments before (left, solid lines) and after pericardial resection (right, dotted lines).



**Figure 3.** Hemodynamic effects of volume loading before and after pericardial resection. With chest intact, minimally invasive percutaneous pericardial resection significantly attenuated the increase in left ventricular end-diastolic pressure (LVEDP) during rapid saline loading and enhanced the increase in left ventricular end-diastolic volume (LVEDV), both in normal dogs (**top**) and in a pig model with features of human heart failure and preserved ejection fraction (**bottom**). Error bars reflect the standard error of the mean.

Traditional approaches to reduce filling pressures have relied on drugs.<sup>1–3</sup> However, a substantial proportion of the pressure within the LV during diastole is attributable to external restraining effects exerted by the pericardium and right heart.<sup>9,25</sup> Acute removal of the pericardium in open-chest normal animal preparations results in a downward/rightward shift in the diastolic pressure–volume relationship.<sup>9–15</sup> This effect becomes greater when venous return is augmented. Indeed, above an LVEDP of 9 mmHg, 65% of any further increase in LV diastolic pressure is caused by pericardial restraint rather than muscle properties alone.<sup>13</sup> In human HFpEF patients, the LV diastolic pressure–volume relationship shifts upward during exercise in HFpEF, consistent with an increase in pericardial restraint as venous return increases.<sup>5</sup> These observations support the idea that removal of pericardial restraint may improve exercise hemodynamics in HFpEF.

Previous animal studies tested pericardiectomy with the chest open and in normal hearts only.<sup>9–15</sup> The current data show for the first time that even with the chest intact and in animals with features of human HFpEF, the pericardium restrains filling because acute disruption of pericardial restraint substantially abrogated the increase in LVEDP during volume loading (Figures 2 and 3). Also in contrast to previous studies, we show that these salutary hemodynamic effects can be achieved with limited anterior pericardial resection, without the need for complete open pericardiectomy.

Importantly, the lowering of filling pressures with saline infusion observed in the porcine model in this study suggests that pericardial resection may be an effective treatment even

when the dominant cause of congestion is because of changes in viscoelastic properties of the LV. This model has been shown to display several features of human HFpEF, including elevation in LVEDP, hypertension, oxidative stress, and coronary microvascular dysfunction.<sup>18–20,26–29</sup> However, we did not perform experiments to demonstrate that these animals had diastolic dysfunction or true clinical heart failure, and further study is warranted in this regard.

The improvement in filling pressures in patients with myocardial disease may be subtle, and we do not expect that this approach would normalize elevated LVEDP that is principally caused by diastolic dysfunction. However, even modest benefits could be clinically meaningful and may enable greater benefit from other therapies such as exercise training. The fact that pericardial resection can be performed in a single procedure, without the need for daily pharmacotherapy, is also a potential benefit.

In addition to acute experiments, 2 chronic studies performed in different species (dogs and swine) have demonstrated improvements in the exercise-induced augmentation in SV, cardiac output, and maximal exercise capacity after pericardiectomy in normal animals.<sup>16,17</sup> This benefit was related to a greater ability to use the Frank–Starling mechanism to enhance cardiac output.<sup>17</sup> Pericardial resection in animals and humans is associated with mild, balanced increases in LV dimension and mass.<sup>17,30</sup> This modest increase in chamber size, if confirmed in chronic animal studies and in humans, would be expected to improve forward SV and cardiac output, which limit exercise capacity in many patients with HFpEF.<sup>6</sup>

**Table 2. Effects of Pericardial Resection in the Pig**

|                              | Pericardium Intact |     |        |     |          |            |         |      | Pericardial Incised |      |        |     |            |         |     |             | Incised vs Intact |  |  |
|------------------------------|--------------------|-----|--------|-----|----------|------------|---------|------|---------------------|------|--------|-----|------------|---------|-----|-------------|-------------------|--|--|
|                              | Baseline           |     | Saline |     | Delta 1* |            |         |      | Baseline            |      | Saline |     | Delta 2*   |         |     |             | Delta 3†          |  |  |
|                              | Mean               | SD  | Mean   | SD  | Est      | 95% CI     | P Value | Mean | SD                  | Mean | SD     | Est | 95% CI     | P Value | Est | 95% CI      | P Value           |  |  |
| Primary outcome measure      |                    |     |        |     |          |            |         |      |                     |      |        |     |            |         |     |             |                   |  |  |
| LVEDP, mm Hg                 | 18                 | 5   | 31     | 2   | 13       | (8, 17)    | <0.001  | 20   | 6                   | 24‡  | 3      | 4   | (-0, 9)    | 0.058   | -9  | (-15, -2)   | 0.014             |  |  |
| Secondary outcome measures   |                    |     |        |     |          |            |         |      |                     |      |        |     |            |         |     |             |                   |  |  |
| LVEDV, mL                    | 35                 | 8   | 46     | 5   | 10       | (7, 14)    | <0.001  | 41§  | 9                   | 57¶  | 8      | 17  | (13, 20)   | <0.001  | 6   | (2, 11)     | 0.016             |  |  |
| RA pressure, mm Hg           | 12                 | 3   | 17     | 2   | 5        | (3, 6)     | <0.001  | 12   | 3                   | 14‡  | 1      | 2   | (0, 3)     | 0.032   | -3  | (-5, -1)    | 0.020             |  |  |
| PA systolic pressure, mm Hg  | 31                 | 5   | 38     | 4   | 8        | (3, 12)    | 0.006   | 30   | 7                   | 34   | 5      | 5   | (-0, 9)    | 0.062   | -3  | (-10, 4)    | 0.34              |  |  |
| PA diastolic pressure, mm Hg | 18                 | 4   | 26     | 3   | 8        | (4, 12)    | 0.002   | 18   | 4                   | 20   | 1      | 2   | (-2, 6)    | 0.29    | -6  | (-11, 0)    | 0.056             |  |  |
| Cardiac output, L/min        | 1.9                | 0.5 | 2.7    | 0.5 | 0.9      | (0.5, 1.2) | <0.001  | 2.3§ | 0.7                 | 3.3‡ | 0.4    | 1.0 | (0.6, 1.4) | <0.001  | 0.1 | (-0.4, 0.6) | 0.66              |  |  |
| Stroke volume, mL            | 21                 | 5   | 31     | 4   | 9        | (3, 16)    | 0.011   | 27   | 8                   | 39¶  | 6      | 12  | (6, 19)    | 0.002   | 3   | (-6, 12)    | 0.48              |  |  |
| LVEF (%)                     | 61                 | 9   | 67     | 2   | 7        | (-8, 21)   | 0.34    | 66   | 16                  | 68   | 8      | 3   | (-12, 17)  | 0.71    | -4  | (-25, 17)   | 0.67              |  |  |
| Heart rate, beats per minute | 87                 | 7   | 89     | 5   | 2        | (-9, 13)   | 0.68    | 89   | 8                   | 86   | 9      | -3  | (-13, 8)   | 0.61    | -5  | (-20, 11)   | 0.52              |  |  |

Est indicates estimates; LVEDP, left ventricular end-diastolic pressure; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; PA, pulmonary artery; and RA, right atrium.

\*Delta 1 and Delta 2 are the model-based estimates of the change observed with the introduction of saline in the intact and incised pericardium conditions, respectively.

†Delta 3 is the difference in deltas between pericardium intact and pericardium incised.

‡P values of (0.001, 0.01) for comparison of the 2 saline conditions.

§P values in the range of (0.01, 0.05) for comparison of the 2 baseline conditions.

||P values of <0.001 for comparison of the 2 saline conditions.

¶P values of (0.01, 0.05) for comparison of the 2 saline conditions.

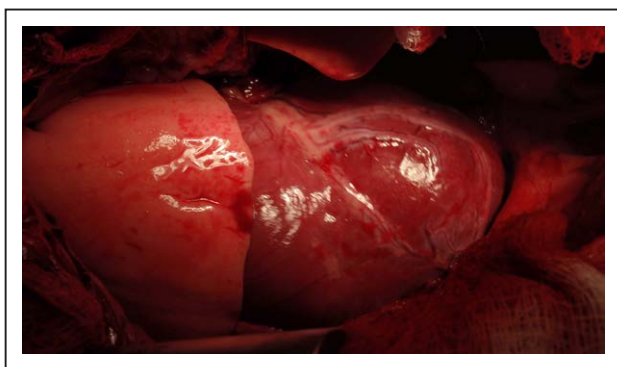
However, implementation of conventional surgical approaches would be problematic for people with HFpEF, most of whom are elderly and frail, making open heart surgery a less palatable option. The novel part of this study was not the demonstration of lowered filling pressures with pericardial resection seen in previous open-chest studies evaluating normal animals, but rather the observations that these salutary effects can be seen after resection of the anterior pericardium alone, without full pericardiectomy, with the chest intact, using a new device prototype and procedure that may eventually enable application to patients a minimally invasive,

epicardial approach. With appropriate further development and human studies, this could potentially be performed in the clinical catheterization laboratory without the risk and long recovery time associated with conventional cardiac surgery.

Further study is clearly required to determine whether the salutary effects of percutaneous pericardial modification observed in this study will be sustained over time, and whether the procedure is safe and translates to similar hemodynamic benefits in people with HFpEF. If there is residual pericardial restraint over 1 side of the heart but not the other, this could alter the coupling between left and right heart pressures and volume. The restraining effect of the pericardium may prevent RV dilation and maintenance of RV function in the setting of pulmonary hypertension, and resection may not be advised in these patients. Finally, the potential effects of pericardial resection remains unclear in HFpEF patients with increased heart volume.<sup>31</sup> If the pericardium dilates more than the heart in these circumstances, there could be less potential to derive benefit from resection. Alternatively, if heart size increases more than the pericardium dilates, this could increase ventricular interaction and make patients more likely to derive benefit.

### Limitations

Experiments were performed in a small number of healthy dogs and in a porcine model with features of HFpEF. Although we visually observed that the anterior pericardium was removed after the experiments in all animals, we cannot ascertain how much of the observed reduction in LVEDP with saline load was because of removal of pericardial restraint



**Figure 4.** Photograph from a representative animal taken after closed-chest experiments were completed and after the sternum was opened before euthanization, showing that the epicardial surface of the heart is unrestrained and the lack of pericardial coverage after minimally invasive percutaneous pericardial resection in a normal canine.

over the LV, decrease in RV restraint mediated across the septum (ventricular interaction), or both. However, either or both mechanisms would be expected to decrease pulmonary capillary hydrostatic pressures and reduce dyspnea and long-term risk for developing pulmonary hypertension and right heart failure. Hemodynamics decayed toward baseline fairly quickly after saline load, but intracardiac pressure assessments, ventriculography, and CO measurements were performed rapidly and in the exact same time sequence after saline infusion before and after pericardiectomy. Each animal served as its own control, as the effects of the saline load were transient and hemodynamics returned to baseline levels before recording the postpericardiectomy basal parameters. Central venous pressures were somewhat elevated at rest in the animals, and this could influence the hemodynamic response to volume manipulation leading to greater effect of saline loading because of the nonlinear pressure–volume relationship in both ventricles. Although one could envision a progressively hypervolemic state from serial volume infusions before and after pericardiectomy, this would only be expected to bias our results toward the null, as progressive saline infusions would lead to greater hypervolemia and distention of the heart to the steeper portions of its 4-chamber pressure–volume relationship. This study examined acute effects only, and it remains unknown whether these benefits will be sustained over time, or whether untoward effects of pericardial resection such as excessive dilatation, fibrosis with constriction, or herniation might occur. Although the data were consistent in normal animals and a porcine model with features of human HFpEF, it remains unclear whether similar beneficial effects on hemodynamics would extend to human HFpEF, and this will require further study in early-phase trials. Saline loading does not recapitulate all of the physiological changes of exercise, so we cannot conclude from these data that pericardial resection would also improve exercise LVEDP.<sup>7</sup> HFpEF represents a complex and heterogenous disorder, and although elevation filling pressures represent an important therapeutic target, reducing these pressures may not lead to symptomatic benefit in all patients, particularly in those whose symptoms are related to abnormalities in the periphery.<sup>32</sup>

## Conclusions

Pericardial resection performed with the chest intact using a minimally invasive, subxiphoid approach improves LV diastolic reserve during saline loading in both normal dogs and in a porcine model with features of HFpEF. Further study is required to determine whether these beneficial acute effects are sustained chronically in animals, and whether similar acute and chronic benefits may be translatable to human HFpEF.

## Disclosures

Drs Borlaug, Asirvatham, and Melenovsky have a provisional patent (No. 61/798,382) for the tools and approach for the minimally invasive pericardial modification procedure.

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### CLINICAL PERSPECTIVE

People with heart failure and preserved ejection fraction develop marked elevation in cardiac filling pressures that contribute to symptoms of dyspnea, particularly during stresses associated with increased venous return to the heart, such as exercise. The pericardium contributes to this increase in cardiac filling pressures that occurs with high venous return, as it restrains further ventricular filling. Here, we demonstrate that percutaneous resection of the anterior pericardium, performed in a minimally invasive subxiphoid procedure, attenuates the rise in left ventricular filling pressures during volume loading in normal dogs and in a hypertensive pig model with features of human heart failure and preserved ejection fraction. In addition to reducing filling pressures, improvements in left ventricular volume with saline loading were also observed, suggesting improvement in Frank–Starling reserve. This proof of concept study shows for the first time that resection of the anterior pericardium, which can be accomplished through a minimally invasive approach, without the need for sternotomy, may be a viable option to improve hemodynamic reserve in heart failure and preserved ejection fraction. Further study is required testing this concept in chronic animal studies and in humans.



### **Percutaneous Pericardial Resection: A Novel Potential Treatment for Heart Failure With Preserved Ejection Fraction**

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