Partial mechanical circulatory support in an ovine model of post-infarction remodeling

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KEYWORDS: chronic heart failure; partial support; ventricular assist devices (VADs); sheep model; reverse remodeling; myocardial infarction

BACKGROUND: Full unloading of the left ventricle (LV) in chronic heart failure (CHF) induces reversal of LV dilation and geometric distortion. In this study we describe the partial unloading effects in ischemic CHF.

METHODS: Six weeks after myocardial infarction, sheep were randomized to partial support (“pump,” n = 5), as provided by the CircuLite Synergy micro-pump, or to no therapy (“sham,” n = 6) for an additional 6 weeks. At baseline, and at 6 and 12 weeks after infarction, pressure–volume (PV) recordings were made. Systolic and diastolic functions were characterized by the end-systolic volume (ESV) where LV end-systolic pressure reached 90 mm Hg (V90), and the end-diastolic volume (EDV) where LV end-diastolic pressure reached 15 mm Hg (V15), respectively. Magnetic resonance imaging (MRI) was performed 6 and 12 weeks after infarction. During autopsy at 12 weeks, isolated LVs were weighed. Histologically, the degree of fibrosis in the non-infarcted area was assessed using systematic randomized sampling, and myocyte hypertrophy was measured by the mean linear intercept method.

RESULTS: At 6 weeks, PV measurements showed a V90 and V15 increase (p = NS between groups). Six weeks later, V90 and V15 increased in the sham group. In the pump group, V90 decreased but V15 did not change significantly. At 6 weeks, MRI indicated no significant difference between groups. Six weeks later, in the sham group, EDV and ESV increased significantly. In the pump group, EDV decreased significantly and ESV trended to decrease. Sphericity index increased in the sham group and decreased in the pump group, although not significantly. Explanted LV masses were significantly higher in the sham group than in the pump group. The pump group had a decrease in fibrosis and less myocyte hypertrophy.

CONCLUSION: Partial support 6 weeks after major myocardial infarction halts and reverses ventricular dilation and hypertrophy.

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Chronic heart failure (CHF) is a major health problem in industrialized countries. Regardless the CHF etiology, remodeling and neurohormonal activation are key components of disease progression. Ventricular remodeling comprises changes ranging from structural (e.g., increased sphericity) to histologic (e.g., myocyte hypertrophy) to sub-cellular (e.g., decreased sensitivity of contractile proteins to Ca2+). Ventricular assist devices (VADs) are now in common use in patients with end-stage heart failure (HF). VADs provide hemodynamic unloading of the left ventricle (LV) and normalize the neurohormonal milieu. This breaks
the vicious circle of CHF progression, and induces a process known as reverse remodeling, which includes a variety of changes “back to normal,” from the sub-cellular to the structural level.\textsuperscript{3} Although this approach rarely results in recovery of native heart function to the point where the VAD can be explanted,\textsuperscript{4-10} even modest improvements in LV strength have the potential to provide clinical benefit. This is particularly the case when a partial ventricular support device is used, because, by definition, body perfusion still depends partially on blood flow from the native heart. However, as the degree of LV unloading achieved during partial support is less than during full ventricular support, it is unclear whether partial support induces significant reverse remodeling.

The Synergy micro-pump is a small, continuous mixed-flow pump that pumps at between 1.5 and 4.2 liters/min, depending on the pressure gradient and the rotational speed. In the clinical setting, the pump is generally set to supply \textasciitilde 3 liters/min and thus offers partial support, as evidenced by the fact that the aortic valve opens with every beat. Hemodynamic recordings from patients supported with this device show improvements in cardiac output (CO) and pulmonary arterial and capillary pressures that appear greater than could be expected by this degree of pump flow. It has therefore been hypothesized that reverse remodeling and some degree of functional recovery is achieved by partial support.\textsuperscript{11}

To directly test this hypothesis, we developed an ovine model of post-myocardial infarct HF and implanted the Synergy pump. We quantified ventricular systolic and diastolic pump properties through pressure–volume analysis and compared the results to those of a control group with the same degree of post-infarct HF but did not receive a pump. Pressure–volume analysis has been shown to yield load-independent indexes of heart size and function that are sensitive for quantifying ventricular remodeling in the setting of HF, and reverse remodeling in the setting of effective therapies such as VADs.\textsuperscript{12,13}

Other parameters that would support the presence and degree of reverse remodeling were obtained using magnetic resonance imaging (MRI), ex vivo passive diastolic pressure–volume analysis and heart weight.

Methods

This study was performed with the approval of and adherence to the guidelines of the animal ethics committee of the KU Leuven and according to the “Principles of Laboratory Animal Care,” formulated by the National Society for Medical Research, and the Guide for the Care and Use of Laboratory Animals, prepared by the Institute of Laboratory Animal Resources (National Institutes of Health). Twenty-five female sheep (Texal crossbred), weighing 52.3 ± 2.8 kg, were studied. Animals were sedated (15 mg/kg ketamine intramuscularly [IM]), induced (5% isoflurane, via face mask), intubated and mechanically ventilated. General anesthesia was maintained by isoflurane inhalation (2.5%). Peripheral arterial pressure was measured invasively with a catheter in an ear artery via a fluid-filled line connected to a pressure transducer (Maquet GmbH, Rastatt, Germany). Venous access was obtained via a deep venous line in the external jugular vein.

By way of an overview of the protocol (Figure 1), CHF was induced in all animals by acute coronary ligation. Six weeks after infarct, animals underwent invasive hemodynamic testing and MRI. Animals were then divided into 2 groups. The control group (\(n = 6\)) was observed for an additional 6-week period and did not receive any form of treatment. The partial support group (\(n = 5\)) underwent implantation of the Synergy pump and were also followed for 6 weeks. At the end of the 6-week follow-up period, the pump was explanted from the active group and all animals underwent repeat MRI, followed by invasive hemodynamic testing. Hearts were then explanted, and left and right ventricles were isolated and weighed.

Creation of myocardial infarction

Prior to the infarction procedure, the following anti-arrhythmics were administered: amiodarone (150 mg in 200 ml of 5% glucose) and lidocaine (250 mg in 200 ml of 0.9% NaCl) infused intravenously (IV) over 30 minutes plus MgSO\(_4\) (2 g), given in a bolus injection. The heart was exposed via left thoracotomy. Then, 10,000 IU of heparin was administered. The left anterior descending artery (LAD) was ligated permanently (using polypropylene 3/0) at the midpoint between the apex and base. The second diagonal was also ligated permanently at the same level. After a 15-minute equilibration period, the proximal LAD was occluded with a 3/0 Prolene snares for 1 hour. After hemodynamic stabilization, the thorax was closed. Animals were weaned from ventilation. Post-operative hypotension was treated with phenylephrine and, in some cases, milrinone (0.125 to 0.500 mg/kg/min). When present, ventricular ectopic beats were treated with lidocaine (2 mg/kg/h, IV) and amiodarone (0.5 mg/kg/h, IV). Piritramide (10 mg intramuscularly) was used for post-operative analgesia.

Pump implantation and sham thoracotomy 6 weeks after infarction

Six weeks after infarction, all animals underwent redo left thoracotomy. In control animals, the thoracotomy was immediately closed. Animals in the partial support group were implanted with a Synergy system. After exposure of the heart, 10,000 IU of heparin was administered. The thorax was closed. Animals were weaned from ventilation. Post-operative hypotension was treated with phenylephrine and, in some cases, milrinone (0.125 to 0.500 mg/kg/min). When present, ventricular ectopic beats were treated with lidocaine (2 mg/kg/h, IV) and amiodarone (0.5 mg/kg/h, IV). Piritramide (10 mg intramuscularly) was used for post-operative analgesia.

Figure 1  Time-points of surgical intervention and MRI. Pump group–specific events are indicated in gray. In both groups, PV measurements were performed before the infarction, at week 0. Six weeks after the infarction (i.e., “6 weeks”), PV measurements were repeated and MRI was performed. Subsequently, a thoracotomy and MRI were performed: in the pump group, the pump had been explanted 0.5 to 1 day prior to these studies. Right heart catheterization was performed during pump removal.
was given. The inflow cannula, equipped with a flow probe, was inserted through the left atrial dome. The outflow graft was anastomosed to the descending aorta (5/0 polypropylene). Pump speed was set so that its flow rate, measured by the flow probe, was approximately half of the CO measured by thermodilution.

Brain natriuretic peptide measurements

Blood samples were taken on ice-cooled ethylene-diamine tetraacetic acid (EDTA)-containing tubes at baseline and at 6 and 12 weeks. After centrifugation at 4°C (15 minutes at 6,000 rotations/min), plasma was immediately frozen at −80°C. After SepPak extraction, a radioimmunoassay procedure with 125I porcine brain natriuretic peptide (BNP; ovine BNP26 is identical to ovine BNP) was performed.5,14,15

Pressure–volume loop recordings

Hemodynamic measurements were obtained at baseline and at 6 and 12 weeks after the infarction. A 7-French sheath (Cordis Corporation, Miami Lakes, Florida) was placed in the common carotid artery. An 8-French sheath (Cordis) and a custom-made balloon were inserted into the external jugular. The balloon is docked in the inferior vena cava. A Swan–Ganz catheter (Edwards Lifesciences Corporation, Irvine, California) was advanced to the pulmonary artery via the venous sheath. CO was measured by thermodilution; saline injections were repeated until at least 4 recordings within a 10% range of variation were obtained. A 12-electrode conductance catheter (Millar Instruments, Houston, Texas) was introduced via the arterial sheath and advanced to the LV apex. The catheter was connected to an Inca (CD Leycom, Zoetermeer) conductance signal conditioner. Pressure–volume loops were recorded during vena cava occlusion achieved by balloon inflation. Parallel conductance was estimated by bolus injection of hypertonic saline. The proportionality constant was determined by determining the ratio between thermodilution and conductance stroke volume.

In the pump group, right heart catheterization was performed at 12 weeks during surgery for pump removal. PV measurements at 12 weeks were performed 0.5 to 1 day after pump stoppage (after MRI; followed by killing and autopsy).

Magnetic resonance imaging

MRIs were performed under general anesthesia at 6 and 12 weeks after infarction. Animals were scanned in the right lateral decubitus with 3.0-Tesla MRI (Magnetom, Trio Tim; Siemens Medical Solutions, Erlangen, Germany) with a phased-array body coil wrapped over the heart. Images were acquired with electrocardiographic (ECG) gating and during suspended respiration. Cine images were acquired in vertical and horizontal long- and short-axis planes.

In the pump group, measurements at 12 weeks were performed 0.5 to 1 day after pump stop.

Ex vivo passive EDPVR

After explantation of the heart, a custom-made balloon was fitted into the LV and the mitral annulus was closed with a purse-string ligature. The balloon was progressively inflated while monitoring the pressure inside the balloon. Pressure was then plotted as a function of volume to assess ex vivo passive end-diastolic pressure–volume relations. Hearts of 5 healthy, weight-matched animals served as controls.

LV and RV mass

The right ventricular (RV) free wall was separated from the LV and both parts weighed. Hearts of 4 sheep that died at 6 weeks after myocardial infarction and 5 healthy, weight-matched animals were analyzed as well.

Fibrosis

An LV slice at the basal and the mid-ventricular level was fixed in 10% formalin followed by paraffin embedding, sectioning at 5-μm thickness and hematoxylin and eosin staining. If infarction was present, a region remote from the infarction was chosen. An 8-point grid with an area of 0.0625 mm² at 400× magnification was projected at 8 randomly chosen quadrants. The proportion of points hitting connective tissue equals the volume occupied by this compartment according to the principle of Delesse.6 The hearts in the pump and sham groups, harvested at autopsy, were analyzed, as were the hearts of 4 sheep that died at 6 weeks after myocardial infarction.

Myocyte hypertrophy

Hematoxylin and eosin sections were analyzed by using the mean linear intercept method at the basal level in the remote area, free of fibrosis.15 In brief, the number of myocytes transsected by a probe with a length of 500 μm at 200× magnification was counted on 10 fields per heart and then averaged. The number of transsected myocytes correlates with the inverse of myocyte volume and thus indexes myocyte hypertrophy. Sections of the pump and sham group were analyzed as were the 4 hearts harvested at 6 weeks after infarction.

Data analysis and statistics

Continuous variables were summarized by group using mean and standard deviation. Group differences were assessed by t-tests, with p-values adjusted for multiple comparisons when made. Conductance-derived pressure–volume loops were analyzed to obtain beat-by-beat pressure–volume points at end-diastole and end-systole (Pes, VEs, Pes, VEd) for construction of end-diastolic pressure–volume relations (EDPVRs) and end-systolic pressure–volume relations (ESPVRs), respectively. ESPVR data were fit by linear regression analysis to arrive at the slope (Ees, end-systolic elastance) and volume–axis intercept (V0); Pes = Ees(Ves – V0). In addition, we calculated the volume on the ESPVR at which the pressure was 90 mm Hg (V90/Ees) for construction of end-diastolic and end-systolic pressures and for sphericity index using MATLAB (The MathWorks, Inc., Natick, Massachusetts).

Results

Mortality

Myocardial infarction was induced in 25 sheep, of which 11 completed the study. Nine sheep died peri-operatively due to
intractable arrhythmias. At the 6-week time-point, 1 sheep died at induction of anesthesia, 2 died at pump implantation, and 1 was found dead the day after sham thoracotomy. At 12 weeks, 1 sheep died at induction and another sheep died during pump removal (prior to hemodynamic measurements). One sheep had a superficial wound infection at the site of the pump pocket, which was successfully treated with amoxicillin (Duphamox; Pfizer) 750 mg/day intramuscularly for 10 days.

Hemodynamics and acute hemodynamic effects of partial support

Hemodynamic characteristics at baseline and 6 weeks after myocardial infarction are summarized in Table 1. Although baseline parameters were similar between the 2 groups, the HF degree in the partial support group was slightly worse, yet not statistically significant.

The acute effects of instituting partial support are illustrated in typical pressure–volume loops obtained from a representative animal (Figure 2). The blue loop was obtained in the HF state just prior to turning on the pump. The presence of HF is evidenced by the low systolic blood pressure (~60 mm Hg), the high end-diastolic pressure (just over 20 mm Hg), and the fact that the pressure–volume loop is situated on the steep portion of the EDPVR. The CO in this case was 2.7 liters/min. Upon initiation of pumping at 1.7 liters/min (i.e., 50% of the native cardiac output), the total CO determined by the Swan–Ganz catheter increased to 3.5 liters/min and there were significant changes in the pressure–volume loop. First, the end-diastolic pressure and volume decreased significantly (diastolic unloading), tracking down the EDPVR. Second, the loop was taller, indicating that the pump partially supported the circulation.

In the partial support group, native CO averaged 3.1 ± 1.8 liters/min and pump speed was set so that pump flow averaged 1.8 ± 0.2 liters/min. The resulting total CO averaged 3.8 ± 0.9 liters/min (p < 0.001 vs CO pre-pump). Thus, the net increase in total CO (which averaged 0.7 liter/min, or a 22% increase) amounted to 40% of the flow rate of the pump, totally consistent with expectations. The less than 1:1 ratio between change in total CO and pump flow was because the pump shunts blood away from the LV; with decreased filling, intrinsic LV output was decreased through the Frank–Starling relationship. Along with the changes in total CO, there were trends for reductions in pulmonary capillary wedge pressure (PCWP; 17.4 ± 4.2 vs 13.6 ± 2.1 mm Hg, p = 0.1) and increases in mean arterial blood pressure (MAP; 56.1 ± 11.5 vs 62.3 ± 13.7 mm Hg, p = 0.15). End-diastolic volume (EDV) decreased from 118 ± 27 to 107 ± 28 (p = 0.001), further evidence of partial unloading of the ventricle.

At the time of pump explant, total CO during pumping was higher. When the pump was turned off, CO decreased to 2.5 ± 0.4; this means that, similar to what was measured during the implant, the increase in CO due to partial support was ~32% of the pump’s flow rate. With termination of pumping there were no detectable changes in PCWP (10.2 ± 3.6 vs 10.4 ± 2.4 mm Hg), but a trend for MAP to decrease (85.5 ± 10.3 vs 68.7 ± 14.9 mm Hg, p = 0.07).

Repeated right heart catheterization at the moment of PV measurement revealed no significant hemodynamic changes.

Table 1 Hemodynamic Parameters at Baseline and 6 Weeks After Induction of Heart failure

<table>
<thead>
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<th>Control group (n = 6)</th>
<th>Partial support group (n = 5)</th>
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<tr>
<td></td>
<td>Baseline 6 wk p</td>
<td>Baseline 6 wk p</td>
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<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>60.1 ± 7.0 0.264</td>
<td>65.5 ± 15.4 0.513</td>
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<tr>
<td>Mean pulmonary pressure (mm Hg)</td>
<td>13.1 ± 2.4 0.337</td>
<td>15.8 ± 3.7 0.006</td>
</tr>
<tr>
<td>Mean pulmonary capillary wedge pressure (mm Hg)</td>
<td>8.3 ± 2.2 0.004</td>
<td>10.1 ± 3.2 0.000</td>
</tr>
<tr>
<td>Cardiac output (liters/min)</td>
<td>3.6 ± 0.9 0.146</td>
<td>3.9 ± 0.5 0.011</td>
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</table>

BNP measurements

Baseline BNP values were 3.76 ± 0.34 pmol/liter and 3.54 ± 0.48 pmol/liter in the sham and pump groups, respectively. At 6 weeks after myocardial infarction, BNP values were significantly increased compared with baseline.
At 12 weeks, BNP increased further in the sham group, but did not change significantly in the pump group (10.07 ± 1.65 pmol/liter \(p = 0.03\) and 7.85 ± 0.06 pmol/liter \(p = 0.60\)) compared with 6 weeks.

Pressure–volume relations

The main findings of this study are summarized in Figure 3 and Table 2. The average results from the control group are shown in Figure 3A. Compared with baseline (shown in black) both ESPVR and EDPVR shift towards significantly larger volumes at 6 weeks after infarct induction (shown in red). \(E_{es}\) increased slightly, but \(V_o\) increased markedly, an indication of the decrease in contractile strength. The average EDPVR also shifted rightward, an indication that the heart had remodeled. After the additional 6-week follow-up period in the control group, both ESPVR and EDPVR shifted further rightward (shown in blue), indicative of additional remodeling and deterioration of systolic function. The degree of shifting of the EDPVVs and ESPVVs is further indexed in the progressive and significant increases in the values of \(V_{15}\) and \(V_{90}\), respectively.

The findings in the partial support group are essentially the same as those for the baseline and 6-week follow-up measurements. The impact of 6 weeks of partial support is revealed by the pressure–volume relations, namely a leftward shift of the ESPVR (mainly due to an increase in \(E_{es}\) and minimal change in \(V_o\)). Consequently, there was a significant reduction in \(V_{90}\). The EDPVR tends to shift towards lower volumes, but the reduction in \(V_{15}\) was not statistically significant. Note that these measurements were made after we explanted the pump, with the native heart fully supporting the circulation.

Magnetic resonance imaging

MRI was performed on animals at the 6- and 12-week follow-up time-points (after explantation of the pump in the treatment group). The results (Table 3) show that, in the control group, EDV, ESV and sphericity index increased substantially between 6 and 12 weeks, indicative of remodeling; there was no appreciable change in ejection fraction. In the partial support group, these volumes decreased, as did the sphericity index. Again, there was no appreciable change in ejection fraction.

Ex vivo passive EDPVR

The ex vivo passive EDPVR curve of the hearts that underwent 6 weeks of partial support is situated at lower volumes compared with the sham group, but at higher volumes than healthy controls (Figure 4).
LV and RV mass

LV and RV mass was significantly higher at 6 weeks after the infarction, compared with healthy controls. At 12 weeks, LV mass was significantly lower in the partial support group. RV mass was also lower, but not as significantly reduced as in the LV (Table 4).

Fibrosis

The degree of fibrosis was $5.6 \pm 1.7\%$ of the non-infarcted LV mass in the 4 sheep at 6 weeks after infarction. At 12 weeks, fibrotic tissue accounted for $2.9 \pm 1.9\%$ and $6.4 \pm 2.3\%$ in the pump and sham groups, respectively ($p = 0.031$ between groups).

Myocyte hypertrophy

The number of transsected myocytes was $23.2 \pm 2.6$ and $19.1 \pm 0.6$ per $0.5$ mm in the non-fibrotic areas of the pump and sham groups, respectively ($p = 0.004$). This was $18.3 \pm 1.3$ in the 4 sheep at 6 weeks after infarction ($p = 0.011$ vs pump group, $p = \text{NS}$ vs sham group).

Discussion

We have created an infarct-related ovine model of CHF, as evidenced by hemodynamics (increased wedge pressure and decrease in CO) and a significant increase in BNP, to test whether partial support provided by the Synergy micro-pump results in reverse remodeling. Six weeks after myocardial infarction, significant rightward shifts of ESPVR and EDPVR were observed, indicating remodeling. The significantly increased LV mass of 4 sheep at 6 weeks after infarction compared with 5 healthy controls supports this finding. After a sham thoracotomy and another 6 week observation period in the control group, both ESPVR and EDPVR shifted further rightward, particularly the ESPVR. In the partial support group, pump flow rates were adjusted at the time of implant to $\sim50\%$ of each animal’s native heart CO.

Measurements made both at the time when support was initiated and at the end of the follow-up period when support was terminated showed the characteristic, expected impact of left atrial-to-arterial partial support on the pressure–volume loop. These consisted of reductions in end-diastolic pressures and volumes (diastolic unloading), narrowing of the loop (indicating decreased stroke volume of the native LV) and increases in peak pressure (due to the increased total output). These changes in the pressure–volume loop are significantly different from what is observed when blood is pumped directly from the ventricle, such as in the currently used VADs, during which there is generally more pre-load reduction, less increase in arterial pressure, and loss of isovolumic periods due to continuous pumping of blood throughout the cardiac cycle. Thus, the nature and magnitude of ventricular unloading achieved with the Synergy system differ from what is achieved with the majority of currently used VADs. It was previously unknown whether partial support with a left atrial-to-arterial flow path induces reverse remodeling.

After 6 weeks of partial support, there was indeed a leftward shift of the in vivo ESPVR and, even after removal of the pump, there were significantly lower values of EDV by MRI. Ex vivo passive EDPVRs showed a shift to the left in the partial support group compared with the control group; LV mass was decreased and, histologically, there

**Table 3** Magnetic Resonance Imaging

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<th>Control group</th>
<th>Partial support group</th>
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<tr>
<td></td>
<td>6 wk</td>
<td>12 wk</td>
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<td></td>
<td>12 wk</td>
<td>Delta$^a$</td>
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<td></td>
<td>Delta$^a$</td>
<td>$p^b$</td>
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<tr>
<td>EDV (ml)</td>
<td>131.2 ± 24.9</td>
<td>153.8 ± 33.4</td>
</tr>
<tr>
<td>ESV (ml)</td>
<td>95.8 ± 23.8</td>
<td>115.4 ± 26.4</td>
</tr>
<tr>
<td>EF (%)</td>
<td>27.8 ± 7.9</td>
<td>25.0 ± 2.9</td>
</tr>
<tr>
<td>Sphericity</td>
<td>0.54 ± 0.08</td>
<td>0.60 ± 0.13</td>
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$^a$Delta, change between 12 wk and 6 wk within each group.  
$^b$p for comparison of delta values between groups.  
$^p$ for comparison between 6 wk and 12 wk within each group.

Figure 4 Ex vivo passive EDPVRs of explanted hearts. The mean ex vivo end-diastolic pressure–volume relationship of the pump group (dotted line) is situated at lower volumes compared with the sham group (solid line), but at higher volumes when compared with healthy control hearts (broken line).
was less hypertrophy with partial support. Taken together, these findings indicate reverse remodeling.

At the level of the extracellular matrix, we found a lower degree of fibrosis in the pump group. Studies concerning connective tissue changes after mechanical support in patients yielded conflicting results: some reported an increase in fibrosis; some reported a decrease in fibrosis; and others reported no change in the total collagen content.3

We consider the reverse remodeling effects as probably not durable. Because it is highly unlikely that the pump induced changes in infarct mass, we expect that the spontaneous evolution after explantation of the pump would be a progressive loss of this reverse remodeling effect in a process called recurrent remodeling.19

Earlier studies of reverse remodeling during mechanical support have been primarily derived from retrospective studies of biologic material obtained from patients with devices that provide full support and more significant LV unloading.3 Performing these studies in animals offers several advantages over human studies, including ability to have a more uniform HF degree between animals, the availability of a concurrent control group, and capacity to regulate background medical therapies (in the present study no other therapy was provided). However, studies have been limited by the lack of a suitable animal model in which VADs can be implanted for long periods. The current studies were facilitated by the small size of the Synergy pump, which was suitable for long-term studies.

Naturally, there are several limitations of this model and of the present study. First, there was a small number of animals that completed the study due to the high rate of mortality. This high mortality (≈50%) is typical for large-animal HF models.20–22 Second, compared with a clinical setting, the current study was conducted over short time periods, both with regard to the period allowed for establishing the HF state (6 weeks) and for the duration of support. The results from the control group show that there was still progressive remodeling between 6 and 12 weeks and, therefore, the Synergy system was introduced at a time when the heart was still actively remodeling. Studies of the time dependence of various aspects of reverse remodeling during full VAD support suggest that 6 weeks may be enough time to establish a near steady state for molecular and structural reverse remodeling, but not likely long enough to see the final degree of changes in the extracellular matrix. It is unknown whether the time course of reverse remodeling is slower with partial support. Because of these limitations, the current results should not be translated quantitatively to the clinical setting but should instead be considered a proof of concept that partial support can result in reverse remodeling.

In summary, left atrial-to-aortic partial ventricular support unloads the heart, improves blood pressure and CO and induces reverse remodeling. It is unknown how the degree of reverse remodeling achieved with this approach compares with what could be achieved in this model by full support.

Because the control group exhibited active remodeling (further ventricular dilation and increase in LV mass at 6 weeks after the infarction) and no third group receiving full support was included, we are unable to draw definitive conclusions regarding the inherent effect of the partial support modality of mechanical circulatory support. Nevertheless, the current model offers the possibility to study, in a large-animal model, the impact of concomitant pharmacologic and device-based treatment on reverse remodeling.

**Disclosure statement**

D.B. is Chief Medical Officer of CircuLite, Inc. The other authors have no conflicts of interest to disclose. This work was partially supported by the Belgian Fund for Cardiac Surgery and the European Union Seventh Framework Programme “Sensorart.”

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