Effect of Direct Cardiac Compression on Left Ventricular Axial Dynamics in Sheep

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The HeartPatch direct cardiac compression device consists of two separate, nonsurround patches placed on the left and right ventricular free walls. Although the device has been shown to effectively restore circulatory parameters in acute heart failure sheep, the impact of device inflation on left ventricular geometry is yet to be elucidated. This study used sonomicrometer crystal transducers to examine three orthogonal left ventricular dimensions under various cardiac states and assessed the feasibility of determining stroke volume from these dimensions. Seven sheep (weight, 51 ± 5 kg) were implanted with six sonomicrometer crystals, and a heart patch was placed on each of the ventricles. The crystals were positioned to measure anterior-posterior, septal-lateral, and apex-base (long-axis) dimensions. Sheep were studied under both awake and anesthetized conditions. Septal-lateral shortening was increased with direct cardiac compression assist, whereas anterior-posterior and long-axis dimensions were either unchanged (awake) or decreased (anesthetized). Estimation of stroke volume, using the ellipsoid volume model, correlated well with stroke volume measured from an aortic flow probe; however, absolute stroke volumes were lacking in agreement. *ASAIO Journal* 2007; 53:292–297.

Direct cardiac compression (DCC) devices externally compress the heart to restore or augment ventricular pump function. The HeartPatch pump is a DCC device consisting of two, separate, nonsurround patches placed on the left and right ventricular free walls. Previous studies have shown the device is capable of restoring hemodynamic parameters in sheep with acute, pharmacologically induced heart failure.[1]

Because of the unique, nonsurround shape of the HeartPatch Pump, however, little is known about its impact on the geometry of the ventricles. Furthermore, because the device is unlikely to compress the ventricles in a uniform manner, usual methods of left ventricular (LV) volume calculation assuming an ellipsoid shape may no be longer valid. To understand the changes in the various ventricular axes and to assess the impact of these changes on stroke volume calculation, sonomicrometer crystal transducers were embedded in the myocardium of sheep undergoing DCC assist studies and their dimensions were examined under various cardiac conditions.

The aims of this study were thus 1) to examine the axial dimension dynamics with HeartPatch DCC assist and 2) to assess the feasibility of predicting cardiac function (stroke volume) from these dimensions.

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Materials and Methods

Seven Merino ewes (body weight, 51 ± 5 kg) were used in this study approved by the institutional animal care and ethics committee. All animals received humane care in compliance with the "Guide for the Care and Use of Laboratory Animals" prepared by the Institute of Laboratory Animals Resources, National Research Council, and published by the National Academy Press, revised 1996.

HeartPatch DCC Device

The device consists of two inflatable silicone patch elements biointegrated to the left and right ventricular epicardium by means of a porous silicone material on the visceral patch surface. Each patch has a heart-contacting (visceral) membrane that is more distensible than the outer (parietal) wall, with the two enclosing an air chamber. Inflation and deflation of the patches are driven by an extracorporeal pneumatic pump, using the ECG R-wave to trigger a computer-based control and monitoring system (Amlab Technologies, Sydney, NSW, Australia). The epicardial adhesion of the patches also allows the application of negative (suction) pressure to the surface of the heart during diastole. An illustration of the patches on the heart and histological evidence of biointegration is shown in **Figure 1**.

Sonomicrometer Crystals

Three pairs of 2-mm piezoelectric ultrasonic crystal transducers (Sonometrics Corporation, Ontario, Canada) were implanted into the endocardium of the left ventricle to measure the anterior to posterior, septal to lateral and apex to base, or long-axis dimensions (**Figure 2**). Crystals were secured with Prolene sutures, and their position was confirmed at autopsy. Dimensions were recorded at 200 Hz on an IBM computer, using SonoVIEW software and analyzed offline with CardioSOFT (Sonometrics Corporation, Ontario, Canada). Advanced circuitry within the sonomicrometer unit allows for automatic calibration of sonomicrometer signals, and each measurement has a relative error (dynamic resolution) of 0.024 mm.

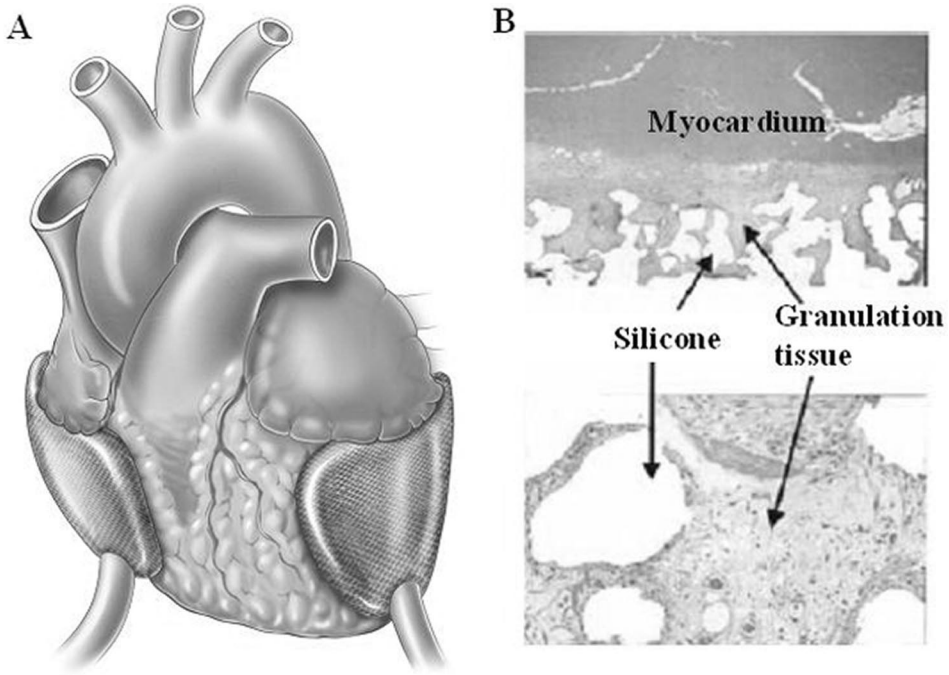

Figure 1. (A) Illustration of the HeartPatch DCC device applied to the heart. (B) Hematoxylin and eosin–stained sections showing adhesion of the Biomatrix to the heart surface, 1 week after implantation. Processing of the samples leads to silicone material being dissolved away, leaving lacunae between freshly formed granulation tissue.

Animal Preparation

Sheep were implanted with sonomicrometer crystals and the DCC patches under general anesthesia induced with 15 to 20 mg/kg thiopentone and maintained with 1.5% to 2% isoflurane in 40% oxygen. Ventilation was maintained with a respirator (Bird Model 8, Bird Corporation, Palm Springs, CA) and expired CO_2 was maintained at 5%, which was monitored with a POET II monitor (Criticare Systems Inc., Milwaukee, WI). Hartmann's solution was given intravenously as maintenance fluid. After left lateral thoracotomy at the 5th rib level with partial removal of the rib and pericardiotomy, a size 16 or 20A Transonic flow probe (Transonic Systems Inc., Ithaca NY) was placed around the ascending aorta.

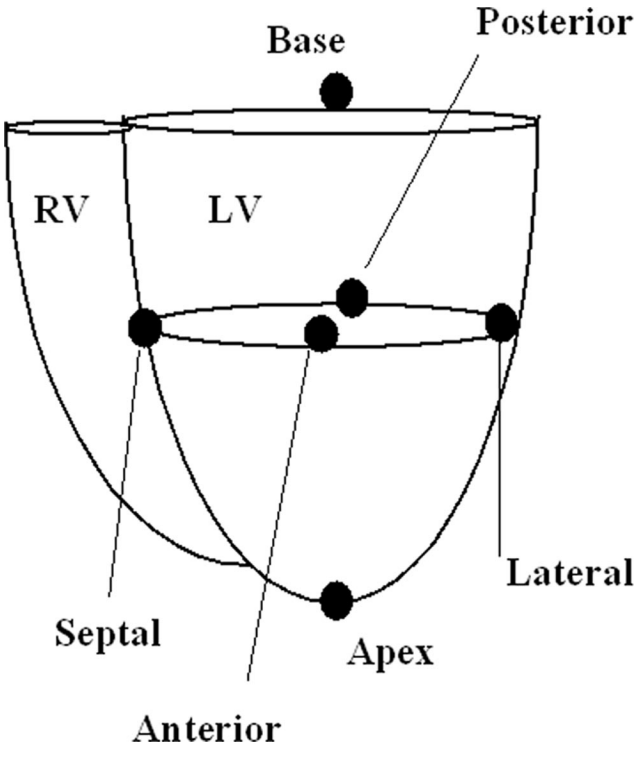

Figure 2. Position of the sonomicrometer crystals in the left ventricle. Three orthogonal axes were measured; anterior-posterior, septal-lateral, and apical-basal (long axis).

The six sonomicrometer crystals were then implanted into the myocardium and the DCC patches were positioned over the left and right ventricular free walls, secured to the visceral pericardium by stay sutures (4–0 Prolene, J&J Medical, NSW, Australia). Driving conduits and ECG, sonomicrometer crystal and flow probe cables exited the chest wall through the 7th intercostal space and were tunneled subcutaneously to exit on the sheep's dorsum at the costal margin.

After intercostal nerve blockade with 0.5% bupivacaine (Astra Pharmaceuticals Pty Ltd, NSW, Australia), the chest incision was closed in layers after inflation of the lungs. Sheep were recovered from anesthesia followed by postoperative pain management with the use of buprenorphine (0.3 mg/6 h i.m., Reckitt & Colman Products Ltd, HVS 70S, UK). Ampicillin (1 g/d i.m. for 3 days) was used during surgery for prevention of infection.

Cardiac Assist Studies

The first study was performed in awake sheep 1 week after DCC patch implantation, with the animals standing in a metabolic crate. The second study was performed the following week under general anesthesia. Acute cardiac depression was induced in both studies by using β-blockade with intravenous esmolol (esmolol hydrochloride, Boots Health care Australia Pty. Ltd., North Ryde, NSW, Australia) (2.5 g diluted in 500 mL normal saline). The drug was infused with an IVAC 591 infu-

sion pump (IVAC Corporation, San Diego, CA) to achieve a stable reduction of 50% in CO. During the anesthetized study, ventricular fibrillation was also induced at the end of the study with 2 g KCl.

DCC assist was timed to commence 2 ms after the ECG R-wave (or at a fixed rate during ventricular fibrillation), with systolic assist duration 35% of the R-R interval and driving pressure of 176 ± 37 mm Hg and diastolic suction of –14 ± 12 mm Hg. Persistence of stable β-blockade was always confirmed by repeat hemodynamic recording after cessation of DCC.

A Mikro Millar catheter-tipped, solid-state pressure transducer (Millar Instruments, Inc., Houston, TX) placed in the driveline in close proximity to the patch monitored driving pressure (Dri P). Pressure signals were amplified by Triton System 6 pressure amplifiers (Triton Technology, Inc., San Diego, CA), whereas instantaneous aortic blood flow velocity was monitored by the Transonic flowmeter. The integral of the flow curve describes CO and heart rate was calculated from the ECG recordings. Hemodynamic data were recorded on an IBM computer, using the PowerLab system (ADInstuments Pty. Ltd., Castle Hill, NSW, Australia).

Data Analysis

Sonomicrometer crystal dimensions were analyzed at end-diastole and end-systole, with the average of five beats taken for each recording. During normal sinus rhythm, end-diastole was defined as the time of ECG R-wave and end-systole as the point of zero aortic flow. During ventricular fibrillation, end-diastole and end-systole were undefinable; the average axial length for the recording was assigned to both dimensions. During DCC assist with ventricular fibrillation, end-diastole and end-systole were defined as minimum and maximum driving pressure, respectively.

The systolic percentage shortening (%S) was calculated by using the formula (end-diastolic dimension – end-systolic dimension)/end-diastolic dimension × 100. During the awake study, the following conditions were examined: baseline, β-blockade–induced cardiac depression (BB), and β-blockade with DCC assist (BB+DCC). During the anesthetized study, the conditions examined were: baseline, normal heart with DCC assist (BL+DCC), BB, BB+DCC, ventricular fibrillation (VF), and VF+DCC. SV was estimated from axial dimensions, using the ellipsoid model to calculate end-diastolic and end-systolic volume (and hence SV), using the formula $V = (\pi/6)$ anterior-posterior dimension (mm) × septal-lateral dimension (mm) × long-axis dimension (mm)/1000. Data are expressed as mean ± standard deviation. Repeated-measures ANOVA followed by *post hoc* testing (Tukey t test) was used for statistical analysis, performed with SigmaStat software (SPSS, Chicago, IL).

Results

Awake Acute Heart Failure Study

Cardiac output decreased with the administration of β-blockade from 4.6 ± 0.7 to 2.2 ± 0.2 L/min (50% ± 7% of baseline, $p < 0.001$) and was due to reductions in both heart rate (142 ± 17 to 106 ± 12 beats/min, $p = 0.001$) and stroke volume (32 ± 5 to 21 ± 3, $p < 0.001$). Activation of DCC assist did not affect heart rate but increased stroke volume 173% ± 22% ($p < 0.001$) and cardiac output 161% ± 22% ($p < 0.001$).

A representative trace of sonomicrometer dimensions and aortic blood flow in the three study conditions is displayed in **Figure 3**. The end-diastolic and end-systolic dimensions for all sheep are summarized in **Table 1**. β-Blockade significantly increased the end-diastolic and end-systolic dimensions of

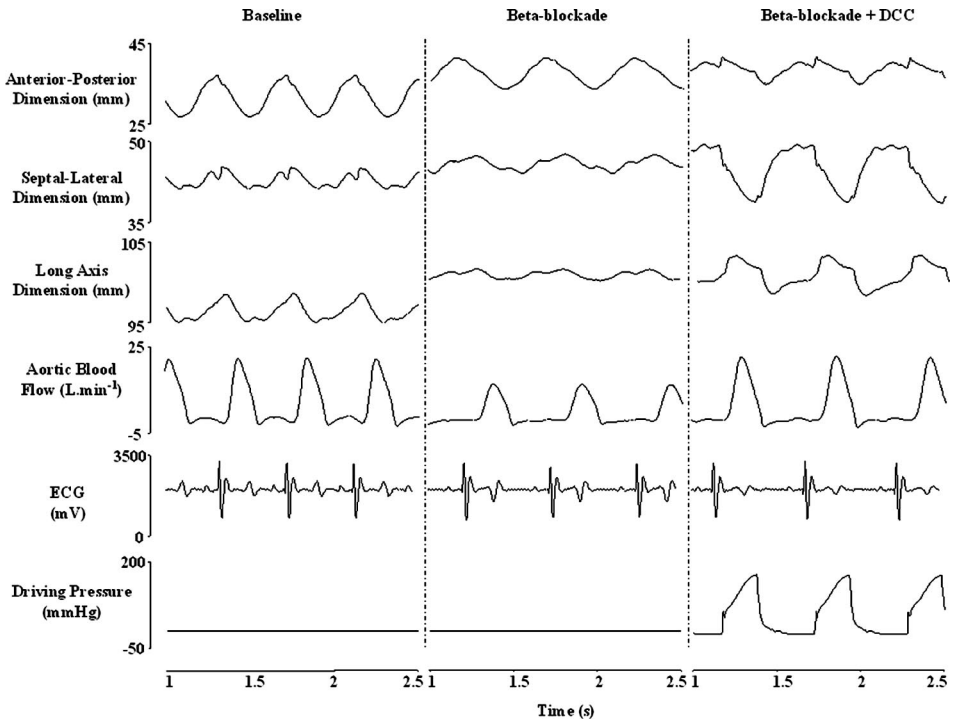

Figure 3. Representative sonomicrometer recordings of the three orthogonal dimensions under awake conditions during baseline, β-blockade, and β-blockade with DCC assist.

Table 1. End-Diastolic Dimension and End-Systolic Dimension of the Three Axes in Response to Direct Cardiac Compression in the Normal Baseline, β -Blocked, and Fibrillating Heart Under Awake and Anesthetized Conditions

	Dimension (mm)					
	Anterior-Posterior		Septal-Lateral		Long Axis	
	ED	ES	ED	ES	ED	ES
Awake study						
Baseline	44 ± 9	39 ± 11	50 ± 8	45 ± 10	96 ± 12	92 ± 12
BB	48 ± 9*	45 ± 9*	55 ± 8	49 ± 9	98 ± 12*	96 ± 12*
BB+DCC	51 ± 10*†	49 ± 12*†	49 ± 8	41 ± 8*†	100 ± 12*†	97 ± 12*
Anesthetized study						
Baseline	52 ± 6	46 ± 6	50 ± 10	47 ± 11	99 ± 15	95 ± 14
BL+DCC	51 ± 6	50 ± 8	51 ± 11	40 ± 11	98 ± 15	96 ± 13
BB	50 ± 5	46 ± 6	50 ± 12	47 ± 12	95 ± 12	92 ± 11
BB+DCC	52 ± 7	53 ± 9*†	50 ± 11	42 ± 9	99 ± 15	100 ± 14*†
VF	56 ± 8	56 ± 8*	44 ± 10	44 ± 10	101 ± 18	101 ± 18*
VF+DCC	55 ± 7	59 ± 8*	51 ± 9†	43 ± 8	98 ± 12	101 ± 11*†

DCC, Direct cardiac compression; BL, baseline; BB, β -blocked (BB); VF, ventricular fibrillation.
* $p < 0.05$ compared with baseline.
† $p < 0.05$ compared with preassist values.

both the anterior-posterior ($p = 0.013$ and $p = 0.006$) and long ($p < 0.001$ and $p < 0.001$) axes. The end-diastolic and end-systolic dimensions of the anterior-posterior axis were further increased with DCC assist ($p = 0.037$ and $p = 0.017$), and the end-diastolic dimension of the long axis was also further increased with DCC assist ($p = 0.015$). The septal-lateral axis end-diastolic dimension did not differ among the three conditions; however, the end-systolic dimension was significantly shortened with DCC assist when compared with both baseline ($p = 0.024$) and β-blockade ($p < 0.001$). Axial shortening in the three study conditions is shown in **Table 2**. DCC assist significantly increased shortening of the septal-lateral axis ($p = 0.003$), whereas anterior-posterior and long-axis shortening remained unchanged with DCC activation.

Table 2. Left Ventricular Axial Shortening of the Three Orthogonal Dimensions in Response to Direct Cardiac Compression in the Normal Baseline, β -Blocked, and Fibrillating Heart Under Awake and Anesthetized Conditions

	Axial Shortening (%)		
	Anterior-Posterior	Septal-Lateral	Long Axis
Awake study			
Baseline	12 ± 7	11 ± 8	4 ± 1
BB	7 ± 3	6 ± 4	2 ± 1*
BB+DCC	4 ± 7*	16 ± 6†	3 ± 1
Anesthetized study			
Baseline	12 ± 3	8 ± 5	4 ± 2
BL+DCC	3 ± 7*†	21 ± 11*†	1 ± 4*†
BB	9 ± 4	6 ± 3	3 ± 2
BB+DCC	0 ± 6*†	15 ± 9	0 ± 3*†
VF	0 ± 0*	0 ± 0	0 ± 0*
VF+DCC	–8 ± 3*†	15 ± 10†	–3 ± 2*†

DCC, Direct cardiac compression; BL, baseline; BB, β -blocked (BB); VF, ventricular fibrillation.
* $p < 0.05$ compared with baseline.
† $p < 0.05$ compared with preassist values.

Anesthetized Acute Heart Failure Study

Cardiac output tended to increase ($p = 0.065$), from 3.3 ± 0.9 at baseline to 4.1 ± 1.0 L/min with activation of DCC (BL+DCC). β-Blockade reduced cardiac output to 1.6 ± 0.3 L/min (51% ± 8% of baseline, $p < 0.001$) and was subsequently restored to 2.7 ± 0.6 L/min with DCC activation ($p = 0.018$). The induction of ventricular fibrillation with KCl abolished CO to 0.0 L/min. This was restored to 2.5 ± 0.7 L/min with DCC assist ($p < 0.001$). Assist rate was 116 ± 8 beats/min, and stroke volume was 22 ± 7 mL.

The end-diastolic and end-systolic dimensions for all sheep during the anesthetized study are summarized in **Table 1**. DCC assist in the normal heart tended to shorten the end-systolic dimension of the septal-lateral axis ($p = 0.092$) and lengthen end-systolic dimension of the anterior-posterior axis ($p = 0.063$). In contrast to the awake studies, β-blockade did not alter end-diastolic or end-systolic dimensions of any axis. Similar to the awake studies, however, end-systolic dimensions of the anterior-posterior and long axes were increased with DCC activation ($p = 0.032$ and $p = 0.011$, respectively). Induction of VF was associated with further increases in these axes, which was maintained with VF+DCC.

Axial shortening in the six study conditions is shown in **Table 2**. Again, DCC assist increased septal-lateral shortening, significant for BL+DCC ($p = 0.035$) and VF+DCC ($p = 0.045$). Anterior-posterior and long-axis shortening, however, were significantly reduced with DCC activation in the normal, failing, and fibrillating heart. HF+DCC abolished anterior-posterior and long axis shortening. Under VF+DCC, paradoxical wall movement was observed, with this dimension lengthening as the heart was assisted.

SV Estimation From Axial Dimensions

Assuming an ellipsoid shape of the left ventricle, the end-diastolic, end-systolic, and hence, stroke volumes, were calculated under all conditions (**Table 3**). With this method, stroke volume with DCC assist tended to be underestimated,

Table 3. Stroke Volume Calculated Using the Ellipsoid Model of the Left Ventricle and Measured with the Aortic Flow Probe

	SV (Ellipsoid Volume Calculation) (mL)	SV (Aortic Flow Probe Measurement) (mL)
Awake study		
Baseline	30 ± 9	32 ± 5
BB	18 ± 5	21 ± 3
BB+DCC	30 ± 3	37 ± 4
Anesthetized study		
Baseline	32 ± 10	33 ± 13
BL+DCC	40 ± 23	41 ± 18
BB	22 ± 9	20 ± 6
BB+DCC	24 ± 17	34 ± 8
VF	0 ± 0	0 ± 0
VF+DCC	4 ± 12	22 ± 7

SV, Stroke volume; DCC, direct cardiac compression; BL, baseline; BB, β -blocked (BB); VF, ventricular fibrillation.

presumably because stroke volume generation is primarily governed by septal-lateral shortening in DCC assist rather than an equal contribution of all three axes.

The correlations between calculated stroke volume and that measured with the aortic flow probe are displayed in **Figure 4A** (unassisted states) and **Figure 4B** (DCC assisted states). When agreement between the stroke volumes was assessed according to the method of Bland and Altman,[2] the limits of agreement were –15 to 10 mL for unassisted states (**Figure 4C**) and –32 to 12 mL for DCC-assisted states (**Figure 4D**), suggesting that for estimation of DCC effect, sonomicrometer axial dimensions could not be applied to the ellipsoid volume calculation as a surrogate of aortic flow measurement.

Discussion

This study shows that HeartPatch DCC assist of the normal, depressed, and fibrillating heart results in unique geometric changes of the anterior-posterior, septal-lateral, and long-axis dimensions. The septal-lateral axial shortening is always increased with DCC assist, which is expected because the patches are placed on the left and right ventricular free walls. The anterior-posterior and long-axis shortening are either unchanged or decreased with DCC assist and actually lengthen when the myocardium does not provide natural systolic contraction, such as during ventricular fibrillation. Because of these unique geometric dynamics, application of the ellipsoid volume model for SV calculation tended to underestimate, suggesting an alternative volume calculation specific for DCC assist may be required.

The present study used sonomicrometry for measurement of cardiac dimensions, but several alternative techniques are available. The most common is transthoracic echocardiography; however, this is not suitable for conditions of DCC activation because of the air used to inflate device patches. Computed tomography and magnetic resonance imaging would be suitable but have other shortcomings in situations requiring continuous tracking. Sonomicrometry has been used to study cardiac geometry since 1956, when Rushmer *et al.*[3] measured the dynamic diameter of the heart. Although this technique is not currently applicable to the clinical setting, the advantages of its high resolution, continuous measurement, and ability to determine 3D coordinates have made it a useful tool in cardiac research.[4,5] In terms of LV geometry, it is most widely applied to calculate LV volume by using three orthogonal dimensions and the ellipsoid volumetric model. Although this method has been validated for the normal heart,[6] it is recognized that severe abnormalities in wall motion and marked changes in LV shape will affect the accuracy of this technique.

To date, little data have been published that investigate the impact of a direct cardiac compression device on LV geometry. One previous study did, however, examine cardiac dimension changes during cardiopulmonary resuscitation (CPR) in dogs.[7] This study reported that whereas all axes shortened

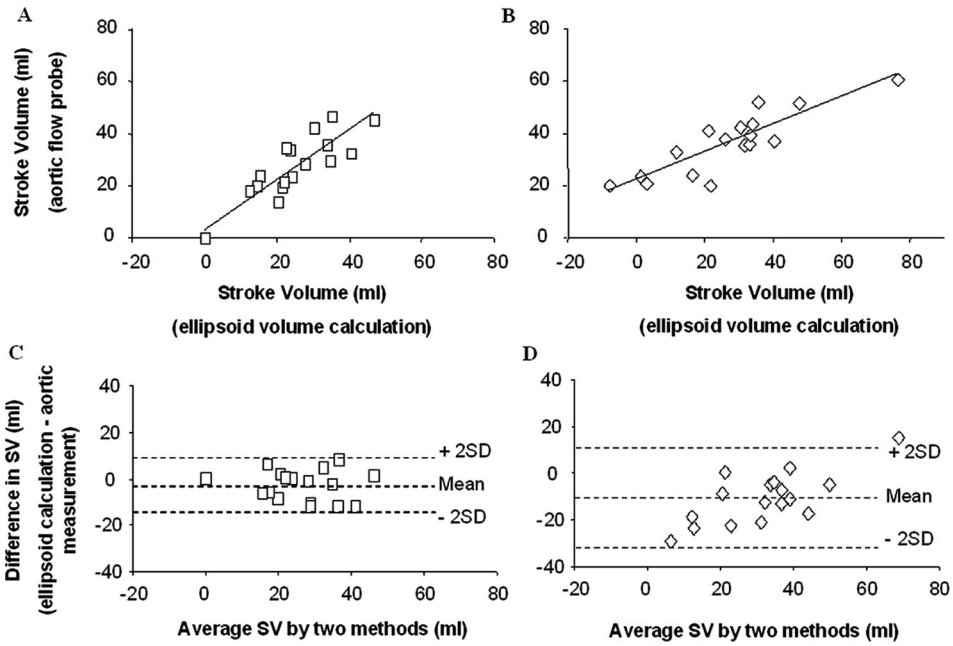

Figure 4. Correlation between stroke volume (SV) calculated by using axial dimensions and application of the ellipsoid volume model and SV measured from an aortic flow probe (A, B) and assessment of agreement between the two methods (C, D). Data points representing unassisted and DCC-assisted states are represented with squares and diamonds, respectively. For unassisted states (4A), SVmeas = 0.966 × SVcalc + 3.048, $R = 0.900$, $p < 0.001$; for DCC-assisted states (4B), SVmeas = 0.527 × SVcalc + 22.657, $R = 0.867$, $p < 0.001$.

during systole under control conditions, the onset of ventricular fibrillation and CPR in the supine position caused shortening of the septal-lateral axis and long ("major") axis but lengthening of the anterior-posterior ("minor") axis. CPR of the dog lying in the lateral position resulted in shortening of the anterior-posterior axis yet lengthening of the septal-lateral and long axis. The results of this study are consistent with those found with the fibrillating heart of the present study, that is, the compression of one axis in a weak, asystolic heart, will lead to lengthening of either one or both of the orthogonal axes.

In addition to defining the geometric changes that occur with HeartPatch DCC assist, the present study highlighted the importance of native heart function when examining such dimension changes. In this study, it was observed that whereas shortening of the anterior-posterior and long axes was reduced during DCC assist under awake conditions, shortening of these axes during DCC assist under anesthesia was completely abolished. As the assist pressure was unchanged, it appears the difference lies in the native myocardial function, weakened by anesthesia. Indeed, when the heart was asystolic and wall motion was the result of DCC assist alone, these two axes were lengthened by device activation.

The long-term consequences of nonuniform cardiac compression are not yet known. Paradoxical movement of cardiac walls may result in increased wall tension, energy wasting, and suboptimal stroke volume. It is also recognized that the ventricular wall movements observed in this study are likely to differ from DCC application in ischemic heart failure with extensive fibrosis.[8] Placement of the heart patches may need to be customized according to location of infarcted or weakened myocardium. A shortcoming of the present study is that results observed in normal hearts with acute, esmolol-induced failure may differ from those with chronic, ischemic failure. Further studies of longer duration, using a more clinically relevant model, are required to address these issues.

In conclusion, the HeartPatch DCC device alters LV geometry, increasing shortening of the septal-lateral axis but compromising that of the anterior-posterior and long axes. Despite this, DCC assist results in effective restoration of stroke volume in the failing and fibrillating heart. Traditional stroke volume measurement derived from flow probe (or thermodilution) cardiac output is recommended, as calculation using axial dimensions may require a new algorithm specific for DCC assist states.

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