

Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION



Physiological and Hemodynamic Evaluation of Nonuniform Direct Cardiac Compression

John H. Artrip, Geng-Hua Yi, Howard R. Levin, Daniel Burkhoff and Jie Wang
Circulation 1999;100;II-236-II-243

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 72514

Copyright © 1999 American Heart Association. All rights reserved. Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:

http://circ.ahajournals.org/cgi/content/full/100/suppl_2/II-236

Subscriptions: Information about subscribing to *Circulation* is online at
<http://circ.ahajournals.org/subscriptions/>

Permissions: Permissions & Rights Desk, Lippincott Williams & Wilkins, a division of Wolters Kluwer Health, 351 West Camden Street, Baltimore, MD 21202-2436. Phone: 410-528-4050. Fax: 410-528-8550. E-mail:
journalpermissions@lww.com

Reprints: Information about reprints can be found online at
<http://www.lww.com/reprints>

Physiological and Hemodynamic Evaluation of Nonuniform Direct Cardiac Compression

John H. Artrip, MD; Geng-Hua Yi, MD; Howard R. Levin, MD;
Daniel Burkhoff, MD, PhD; Jie Wang, MD, PhD

Background—Biventricular direct cardiac compression (DCC) has the potential to support the failing heart without the complications associated with a blood/device interface encountered with the use of current ventricular assist devices. A clinically designed DCC device that provides compression pressure around the base of the heart in synchrony with native ventricular contractions was evaluated with the use of an ex vivo and in vivo canine model of heart failure.

Methods and Results—The device was tested over a series of ventricular preloads with the use of an ex vivo canine heart preparation and computerized afterload system that mimicked the conditions of heart failure. The end-systolic pressure-volume relation of the left and right ventricles was shifted upward in parallel by DCC, with the magnitude of the shift averaging 40% of the device compression pressure. The device was tested in vivo with the use of a canine model of acute ischemic heart failure in which graded reductions in ventricular function were created through serial coronary artery embolizations. Under the most severe condition of heart failure, DCC improved cardiac output (CO) by 104% (0.80 ± 0.33 to 1.63 ± 0.40 L/min) and mean arterial pressure by 95% (45.6 ± 11 to 89.0 ± 18.2 mm Hg). The CO was typically restored to $\approx 60\%$ of the normal baseline value, despite attempts to further increase CO by increasing the amount or duration of compression pressure.

Conclusions—Nonuniform DCC significantly improves the left and right ventricular pressure-generating capability and, in the setting of acute heart failure, can increase CO and mean arterial pressure. Such DCC devices can potentially avoid the complications associated with currently available ventricular support devices that involve a blood/device interface. (*Circulation*. 1999;100[suppl II]:II-236–II-243.)

Key Words: heart failure ■ hemodynamics ■ ischemia ■ physiology ■ cardiac assist devices

The effective treatment of acute cardiogenic shock often requires circulatory support with the use of mechanical left ventricular (LV) assist devices. However, these support devices require direct contact with the patient's blood; thus, thromboembolic events, the need for anticoagulation, hemolysis, and immune reactions are frequently encountered problems. Ventricular assistance achieved through direct mechanical compression of the surface of the heart in synchrony with native ventricular contraction has the potential to support the failing heart without the complications associated with a blood/device interface.

The effects of synchronized direct cardiac compression (DCC) on ventricular mechanics have been previously studied with the use of isolated canine heart preparations.^{1–4} Results of those studies showed that for isovolumic contractions at a given volume, net ventricular pressure-generating ability for both ventricles could be augmented with external pressure and that the magnitude of this effect was similar for the LV and right ventricle (RV). Importantly, the increase in ventricular pressure-

generating ability was achieved without an increase in myocardial oxygen demand.⁴ Under computer-simulated ejection conditions, such as those encountered in situ, the increase in ventricular function afforded with DCC manifested as significant increases in stroke volume (SV).⁴

In these earlier studies, the isolated heart was placed into a compression chamber, and uniform compression pressure was provided that could be varied in synchrony with native systole. Because of their physical size and configuration, these compression chambers cannot be used on a heart in vivo. Recently, DCC devices have been developed that have the potential to be used clinically to administer biventricular compression to a failing heart. These devices provide nonuniform compression to the heart such that the net forces form a circumference around the base of the heart, excluding the apex. The physiology and hemodynamic effects of nonuniform compression devices have not been studied systematically.

The purpose of the study was 2-fold: (1) to study the effects of nonuniform DCC on ventricular physiology and 2) to test

From the Department of Surgery, Division of Cardiothoracic Surgery (J.H.A.), and Department of Medicine, Division of Circulatory Physiology (G.-H.Y., D.B., J.W.), College of Physicians and Surgeons, Columbia University, New York, NY; and Cardio Technologies Inc (H.R.L.), Pine Brook, NJ.

Presented in part at the 71th Scientific Sessions of the American Heart Association, Dallas, Tex, November 8–11, 1998.

Correspondence to Jie Wang, MD, PhD, Department of Medicine, Division of Circulatory Physiology, College of Physicians and Surgeons, Columbia University, MHB 5-435, 177 Fort Washington Ave, New York, NY 10032. E-mail jw147@columbia.edu

© 1999 American Heart Association, Inc.

Circulation is available at <http://www.circulationaha.org>

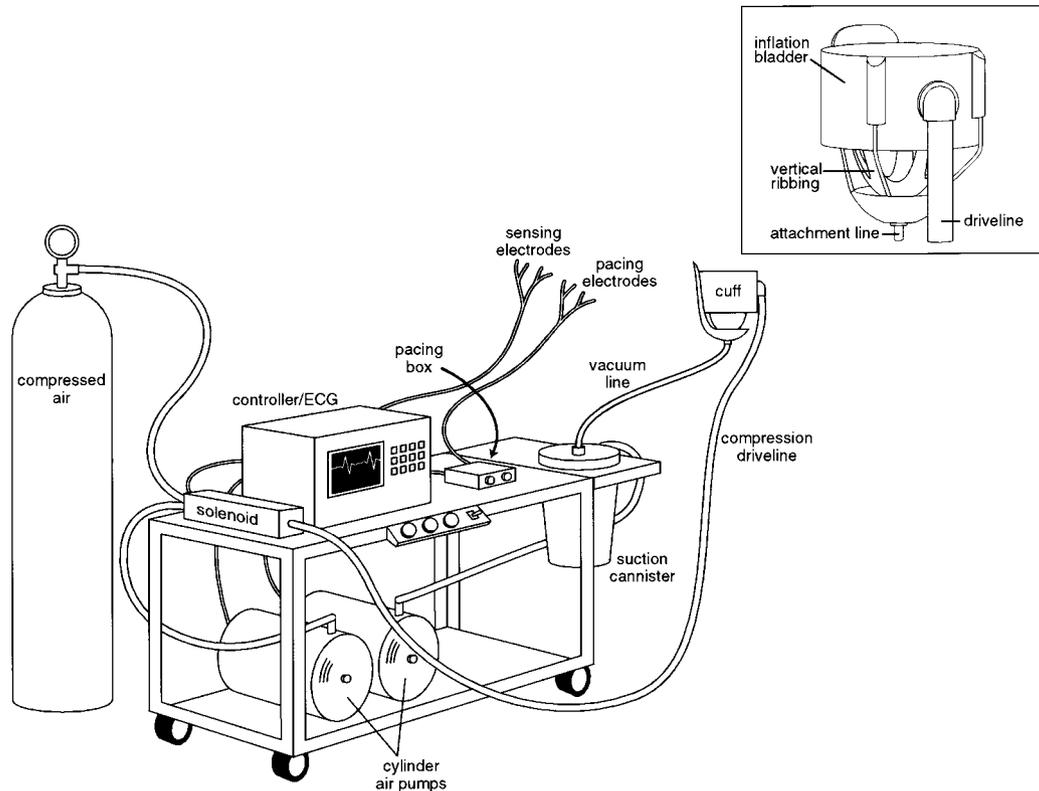


Figure 1. Schematic of pneumatic compression device. Cuff extends from apex of heart to outflow tract heart with inflation bladder surrounding LV and RV at base. Inset, cuff details. Vertical ribbing extends from apex of cuff to outer lip of inflation bladder.

the hemodynamic effects of nonuniform DCC in the setting of acute heart failure. First, an ex vivo isolated canine heart preparation was used with which LV and RV pressure-volume relations could be controlled and accurately measured. DCC was tested over a series of ventricular preload volumes and under conditions mimicking heart failure. Next, the hemodynamic effects of DCC were tested in an in vivo canine model of ischemic heart failure in which graded reductions of cardiac function could be achieved. The DCC device was tested in the setting of 3 levels of reduced cardiac function to simulate various degrees of heart failure encountered clinically.

Methods

General Surgical Preparation

A total of 23 adult male mongrel dogs (Team Associates) weighing between 34.8 and 22.0 kg (mean 26.7 ± 4.2 kg) were used for the study. All animals received humane care in compliance with the "Guide for the Care and Use of Laboratory Animals" published by the National Institutes of Health (NIH publication No. 85-23, revised 1985). For all studies, dogs were anesthetized with pentobarbital sodium (30 mg/kg IV), intubated with an 8F endotracheal tube, and maintained with mechanical ventilation with humidified room air (Harvard Apparatus Inc).

DCC Device

Nonuniform DCC was provided by the CardioSupport System (Cardio Technologies Inc). This device, which is illustrated in Figure 1, consisted of an inflatable plastic cuff, 2 air pumps, an epicardial ECG sensor, and a computer controller. The cuff fits around the heart with an inflation bladder that circumscribes both ventricular chambers and extends from the midwall of the heart to the outflow tract.

The cuff was held to the heart with negative attachment pressure (≈ 200 mm Hg) applied to the cardiac apex. Vertical ribbing extended from the apex of the cuff to the inflation bladder and was used to prevent migration of the inflation bladder. One pump was used to generate the attachment pressure, and the other pump was used to generate the bladder inflation pressure. A valved solenoid physically regulated the amount, onset, and duration of cardiac compressions and was digitally controlled with the computer console. A solid microtipped-catheter (Millar Instruments Inc) placed in the driveline near the device was used to measure the pressure inside the inflation bladder. The ECG sensor was connected to pacing leads sewn in the heart, and the pneumatic pump was synchronized to the native QRS complex with the computer controller. The device could generate >200 mm Hg of compression pressure with inflation periods varying between 10% and 50% of the cardiac cycle; however, an inflation pressure of 100 mm Hg and a duration of 40% were typically used throughout the experiment.

Ex Vivo Canine Heart Study

Preparation

Six isolated cross-perfused canine hearts were studied according to methods that were similar to those described previously.⁵ Briefly, the femoral arteries and veins of a dog ("support dog") were cannulated and connected to a perfusion system that was used to supply oxygenated blood to the isolated heart. The heart from the second dog ("heart donor dog") was removed while metabolically supported with arterial flow from the support dog. Two metal adapters were sutured to atrioventricular valve rings and were used to hold the isolated heart to individual ventricular volume servopump systems. Water-filled balloons of the servopump systems were then placed inside the ventricular cavities. A Millar pressure transducer was placed inside each balloon to measure the respective ventricular pressure. The ventricular volume servopump systems were controlled with a computer system that simulated hemodynamic properties of the systemic and pulmonary circuits and allowed the

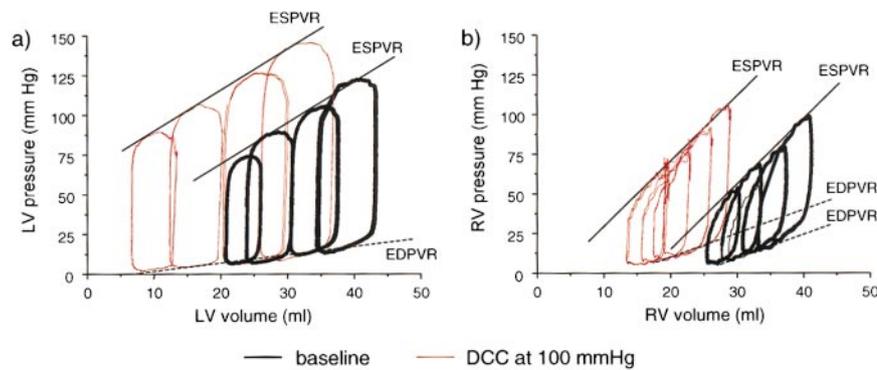


Figure 2. PV tracings from representative experiment showing effects of non-uniform DCC on ESPVR and EDPVR for both (a) LV and (b) RV.

ventricles to eject against physiological afterloads.^{6,7} A bipolar surface ECG was measured between 2 electrodes sutured to the surface of the heart.

Protocol

The ex vivo experimental protocol was designed to determine the effects of nonuniform DCC on LV and RV systolic and diastolic functions. The heart rate was set between 100 and 140 bpm with the use of atrial pacing, and the values of the simulated vascular systems were adjusted to approximate the hemodynamics of the heart failure state (RV end-diastolic pressure 5 to 15 mm Hg, LV end-diastolic pressure 15 to 20 mm Hg, SV 5 to 10 mL, and peak arterial pressure 80 to 100 mm Hg). Under these conditions, baseline LV and RV end-systolic and end-diastolic pressure-volume (PV) relations (ESPVR and EDPVR, respectively) were obtained through the recording of PV data at 4 to 6 different filling volumes. The series of preloads was obtained through simulation of increasingly severe degrees of inferior vena caval occlusions in the computerized vascular system. After the establishment of baseline steady-state conditions at each preload setting, ≈ 5 s of data (ventricular pressures and volumes) were recorded on the computer system. The DCC device was then placed on the heart, and compressions were initiated. Hemodynamic data were recorded after a new hemodynamic steady state was established.

In Vivo Canine Heart Study

Preparation

For each in vivo experiment (n=11), the right carotid artery was cannulated with a Millar pressure transducer that was introduced into the LV for the measurement of LV pressure. The right internal jugular vein was similarly cannulated with a Millar pressure transducer that was introduced into the RV for the measurement of RV pressure. The left carotid artery was cannulated with a Tygon catheter pressure transducer (Statham P32, Gould) to measure arterial pressure. The animal was placed in the left lateral decubitus position, and a standard lateral thoracotomy was performed through the 5th intercostal space. The incision remained open for the duration of the experiment. A flow probe (Transonic Systems Inc) was placed around the ascending thoracic aorta to measure cardiac output (CO). Temporary cardiac pacing leads were sewn into the LV apex and right atrial appendage to record the epicardial ECG. A custom-made silicon catheter was then introduced into the dominant coronary artery (left anterior descending or left circumflex) and was used for coronary microembolizations to gradually induce more severe levels of heart failure.

Coronary Microembolization

As described previously,^{8,9} aliquots of 90- μ m glass beads (≈ 25 000) were injected into the coronary artery every 3 to 5 minutes until the desired level of acute heart failure was achieved. Three levels of heart failure were attempted in each animal, with the degree of failure based on the approximate percent reduction in CO. Mild heart failure was defined as a $\approx 30\%$ reduction in CO from baseline, moderate heart failure was defined as a 30% to 60% reduction in CO, and severe heart failure was defined as a $>60\%$ reduction in CO.

Ventricular ectopy was treated with intravenous lidocaine (20 mg/kg loading dose followed by a constant infusion of $1 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$). Ventricular fibrillation was treated with cardioversion with internal paddles set at 10 to 50 J.

Protocol

A total of 8 dogs were used to test the effects of nonuniform DCC in vivo. The experimental protocol was designed to address (1) the impact of the placement of the device on baseline hemodynamic function and (2) the ability of the device to augment blood pressure and CO in an acutely failing heart.

Impact of Placement of DCC Device on Baseline Hemodynamic Parameters

Hemodynamic data (pressure and flow) were obtained at the baseline condition; an appropriately sized device was then placed on the heart and fixed with negative attachment pressure. Without turning on the device, hemodynamic data were recorded after a stable state was reached. To test whether cuff placement had any impact on baseline hemodynamics, these data were compared with the data obtained before the placement of the cuff on the heart.

Ability of Nonuniform DCC to Augment an Acutely Failing Heart

Once the appropriate level of heart failure was achieved and baseline data were obtained, the DCC device was placed on the heart, and synchronized ventricular compressions were initiated. DCC was sustained until hemodynamic signals attained a stable state. After the completion of data acquisition, the device was removed from the heart and additional embolizations were performed to create the next desired level of failure. This cycle was repeated so that data were obtained in states of mild, moderate, and severe heart failure.

To exclude the possibility of any observed beneficial effect of DCC being attributed to spontaneous ventricular recovery, 3 dogs served as internal controls. They underwent the placement of hemodynamic monitors and coronary microembolization as described above, but DCC was not performed.

Data Collection and Statistical Analysis

All monitored signals were calibrated and zeroed before each experiment. Data were recorded on an 8-channel charted recorder (30-V8808-10; Gould electronics equipped with a National Instruments Analog-In-Digital Conversion System), and periods of interest were digitally sampled (1000 Hz) and analyzed offline with the use of a data analysis program written in Microsoft BASIC. Measurements were averaged over 3 to 5 beats.

For the ex vivo heart study, the end-systolic pressure (P_{es}) and volume (V_{es}) of each ventricular beat were determined through identification of the top left corner of each PV loop, whereas the end-diastolic pressure (P_{ed}) and volume (V_{ed}) points were determined through identification of the bottom right corner. The ESPVR was determined through linear regression analysis with the formula $P_{es} = E_{es}(V_{es} - V_0)$. The EDPVR was analyzed with nonlinear regression analysis according to the equation $P_{ed} = P_0 + \alpha V_{ed}^\beta$. Statistical comparisons of the ESPVR and EDPVR between control and active compression states were accomplished with the use of ANCOVA.

TABLE 1. Nonuniform DCC Tested in an Ex Vivo Canine Heart Preparation: Summary of Values for ESPVR and EDPVR

	LV		RV	
	E_{es}	V_0	E_{es}	V_0
ESPVR				
Baseline	3.1 ± 1.2	4.3 ± 3.7	2.9 ± 2.5	5.3 ± 8.3
DCC	4.5 ± 2.6	-8.5 ± 10.6	2.0 ± 1.2	-24.7 ± 19.3
P^*	0.11	<0.001	0.24	<0.001
EDPVR				
	β	α	β	α
Baseline	$4.9 \times 10^{-3} \pm 1.3 \times 10^{-2}$	4.0 ± 1.5	$2.1 \times 10^{-3} \pm 3.3 \times 10^{-2}$	3.1 ± 0.9
DCC	$2.1 \times 10^{-2} \pm 3.1 \times 10^{-2}$	2.9 ± 1.3	$3.2 \times 10^{-3} \pm 8.0 \times 10^{-3}$	3.6 ± 2.6
P	0.03	<0.001	0.06	0.03

All values are mean \pm SD.

ESPVR and EDPVR were obtained from PV loops of 6 isolated canine heart experiments. Data from different heart rates were pooled for analysis.

*All P values were derived from ANCOVA.

For the nonlinear EDPVR, the data relation was first linearized by plotting $\ln(P_{es} - P_0)$ versus $\ln(V_{ed})$ before the application of ANCOVA.

For the in vivo studies, ANOVA was performed to detect statistically significant differences between groups, and paired t tests with Bonferroni's corrections were performed to detect statistical differences between control and test conditions.

All statistical analyses were performed with commercially available software (SYSTAT). In all cases, a P value of <0.05 was considered statistically significant.

Results

Ex Vivo Studies

Effects of DCC on Ventricular ESPVRs and EDPVRs

The effects of DCC on the PV relations of a representative experiment are shown in Figure 2. The average ESPVR and EDPVR parameter values obtained from the 6 experiments are summarized in Table 1.

As determined with ANCOVA, DCC with the device shifted the ESPVR of both the LV and RV upward in a parallel manner; there was no statistically significant effect on the slope (E_{es}), but there was a large decrease in the extrapolated volume-axis intercept (V_0). The magnitude of

the upward shift of the ESPVR, which indexes the amount of pressure support provided with the DCC device, averaged 39.8 ± 16.4 mm Hg for the LV and 40.3 ± 12.9 mm Hg for the RV. Thus, $\approx 40\%$ of the 100 mm Hg of DCC pressure applied with the device was transmitted to the heart. The effect of DCC on the EDPVR varied somewhat among hearts and between the LV and RV. The representative PV loops plotted in Figure 2 show that although LV EDPVR is little affected, there is a leftward shift in the RV EDPVR. Data pooled from all hearts analyzed with ANCOVA demonstrated statistically significant differences between the parameter values α and β for the EDPVR of both ventricles, suggesting, on average, small leftward shifts in both RV and LV curves.

Effects of DCC on Steady-State Hemodynamics

To investigate the effects of DCC on steady-state hemodynamics, baseline ventricular pressures and volumes were determined with LV filling pressure adjusted to ≈ 15 to 20 mm Hg. DCC was then initiated, and hemodynamic parameters were reassessed after the achievement of steady-state conditions. The results are summarized in Table 2 and demonstrate significant improvements in RV and LV pressures and volumes that amount to an average $26.7 \pm 18.6\%$ increase in SV.

TABLE 2. Nonuniform DCC Tested in an Ex Vivo Canine Heart Preparation: Summary of Steady-State Hemodynamic Data

	LV		RV	
	P_{es}	P_{ed}	P_{es}	P_{ed}
Pressure, mm Hg				
Baseline	73.1 ± 15.1	16.6 ± 5.0	44.6 ± 11.2	19.3 ± 5.4
DCC	82.1 ± 18.0	11.2 ± 3.8	61.0 ± 10.7	14.8 ± 5.4
P^*	<0.01	<0.01	<0.01	<0.01
Volume, mL				
	V_{es}	V_{ed}	SV	V_{ed}
Baseline	31.4 ± 8.4	38.5 ± 7.3	9.6 ± 4.1	29.3 ± 5.4
DCC	17.5 ± 6.7	27.4 ± 7.2	11.7 ± 4.2	21.0 ± 11.3
P	<0.01	<0.01	<0.01	<0.01

All values are mean \pm SD.

Data from different heart rates were pooled for analysis.

*All P values were derived from a paired t test.

TABLE 3. Impact of Placing DCC Device on In Vivo Heart With Attachment Suction but Not Actively Assisting Cardiac Function

	Baseline Normal Cardiac Function (n=7)	
	Cuff Off*	Cuff Placed†
Average CO, L/min	2.93±0.64	2.64±0.53‡
Heart rate, bpm	127.8±19.8	133.4±21.5
SV, mL	23.3±5.8	20.1±0.4‡
Peak aortic flow, L/min	8.17±2.39	7.39±2.33‡
LV systolic pressure, mm Hg	125.4±18.8	119.6±21.6
LV diastolic pressure, mm Hg	8.3±4.0	8.6±4.5
LV dP/dt _{max} , mm Hg/s	1835±481	1730±340
Negative LV dP/dt _{max} , mm Hg/s	-1804±389	-1895±436
Systolic arterial pressure, mm Hg	135.3±23.6	128.0±25.3‡
Mean arterial pressure, mm Hg	119.0±19.7	110.6±23.6
Diastolic arterial pressure, mm Hg	105.9±17.7	100.4±22.2

All values are mean±SD.

*Cuff Off implies that the device was not placed on the heart.

†Cuff Placed implies that the device was placed on the heart but not actively assisting the heart.

‡P<0.05. Values were obtained with a paired t test and in a comparison of the 2 positions.

In Vivo Studies

Impact of Placement of DCC Device on Baseline Hemodynamic Function

The potentially adverse effects of simply placing the DCC device on heart function were studied in 7 dogs, as outlined in "Methods." Data summarized in Table 3 indicate that placement of the cuff on the heart caused a slight but statistically significant reduction in both peak aortic flow and CO. The reduction in CO

was ≈10% and was not influenced by the amount of attachment pressure (data not shown), nor was this consistently observed in the 3 levels of heart failure. No other hemodynamic parameter was influenced by placement of the device.

Effect of DCC in Acute Ischemic Heart Failure

The effects of nonuniform DCC in mild, moderate, and severe acute ischemic heart failure were tested in 8 adult male mongrel dogs. Due to interanimal variability and instabilities, not all animals achieved each level of heart failure. Mild and moderate heart failure was attained in 5 dogs, whereas severe heart failure was attained in all 8 dogs. Baseline data obtained at each level of heart failure and under normal conditions are shown in Table 4. ANOVA demonstrated significant differences between these groups for all of the hemodynamic parameters tested. This model provided no evidence for spontaneous ventricular recovery after microembolization. In fact, the 3 dogs that underwent coronary embolization without the subsequent benefit of ventricular assist demonstrated progressive deterioration in ventricular function, resulting in cardiac arrest within 21±13 minutes of completion of embolization.

In the 8 dogs undergoing the experimental protocol, DCC was performed at each level of ischemic heart failure that was created, and all hemodynamic parameters were compared with values obtained before ventricular assist with the device removed from the heart. Chart recordings from a representative experiment are shown in Figure 3. The average effects of DCC on all hearts studied are summarized in Table 4 and demonstrate significant improvements in all hemodynamic parameters tested with the moderate and severe conditions of heart failure. Plotting of the degree of heart failure (indexed according to the percent reduction in CO from normal) versus the change in SV contributed by DCC (Figure 4a) or versus

TABLE 4. Effect of DCC on 3 Levels of Acute Ischemic Heart Failure

	Normal (n=8)	Mild Heart Failure (n=5)		Moderate Heart Failure (n=5)		Severe Heart Failure (n=8)	
		Baseline	Assisted	Baseline	Assisted	Baseline	Assisted
Average reduction in CO, %	...	22.8±2.0	...	55.6±3.8	...	75.1±9.0	...
DCC pressure, mm Hg	108.6±6.5	...	109.8±4.5	...	114.8±17.7
Average CO, L/min	2.90±0.60*	2.38±0.26	2.12±0.11	1.16±0.27	1.68±0.29†	0.80±0.33	1.63±0.40‡
Heart rate, bpm	126.8±18.5*	134.8±23.2	133.7±25.6	98±20.8	97.1±19.0	113.6±19.2	111.3±14.5
SV, mL‡	23.2±5.4*	18.2±4.4	16.3±2.9	11.9±2.1	17.5±2.9†	7.3±3.5	14.8±3.7†
Pk. aortic flow, L/min	8.09±2.22*	7.36±3.06	6.56±1.92	3.72±0.67	5.63±2.02	2.41±0.99	5.64±2.68†
LV systolic pressure, mm Hg	126.8±17.8*	116.2±9.1	104.8±9.4	72.6±15.4	97.2±11.4†	48.8±14.6	88.8±17.3†
LV diastolic pressure, mm Hg	9.6±5.3*	14.2±7.2	12.8±6.4	18.0±8.4	11.0±6.5†	21.9±11.1	14.9±8.4†
LV dP/dt _{max} , mm Hg/s§	1754±501*	1611±569	2609±171†	690±221	2663±352†	367±117	2059±596†
Negative LV dP/dt _{max} , mm Hg/s	-1777±368*	-1490±347	-1715±160	-639±223	-1901±246†	-321±148	-1453±408†
Systolic arterial pressure, mm Hg	134.4±22.0*	126.8±26.1	124.0±12.7	79.2±17.5	108.2±7.0†	54.4±16.0	102.3±19.4†
Mean arterial pressure, mm Hg	118.6±18.3*	110.4±20.0	105.0±8.9	62.6±12.4	86.0±16.1†	45.6±11.0	89.0±18.2†
Diastolic arterial pressure, mm Hg	106.1±16.4*	99.2±18.9	95.2±11.1	54.4±9.1	85.6±14.0†	41.5±7.6	80.8±16.1†

All values are mean±SD.

*P<0.05. Values were obtained with ANOVA in a comparison of the baseline values for normal heart function with the mild, moderate, and severe heart failure values.

†P<0.05. Values were obtained with a paired t test in a comparison of the baseline (unassisted) values to assisted values.

‡SV was calculated by dividing the CO by heart rate.

§LV dP/dt_{max} and negative LV dP/dt_{max} were calculated by differentiating the LV pressure tracing and by averaging the maximum (or minimum) value obtained for 3 cardiac cycles.

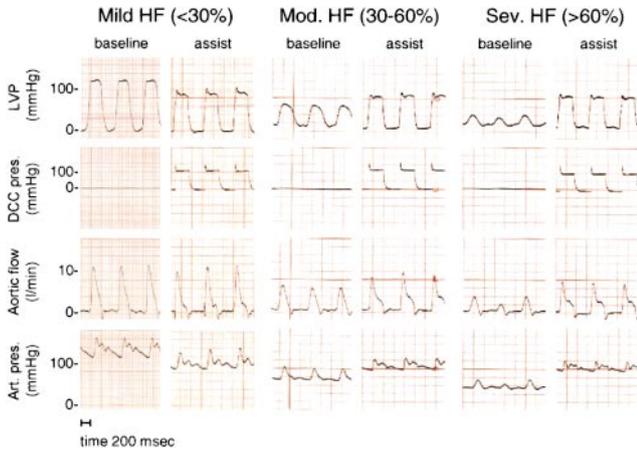


Figure 3. Chart recordings showing LV pressure (LVP), cuff pressure, aortic flow, and arterial pressure tracings from representative experiment. Device was tested in all 3 levels of heart failure (HF) created and compared with respective baseline failure state for each level. Under most severe condition of heart failure that was created, pulsus alternans was occasionally observed, as shown in this representative tracing. This is consistent with profound degree of HF created and should not have affected results because data were averaged over 3 to 5 beats.

the change in LV systolic pressure contributed by DCC (Figure 4b) illustrates the direct correlation between hemodynamic benefit provided by DCC and the degree of ventricular dysfunction.

Although DCC demonstrated significant hemodynamic improvement in the more severe conditions of heart failure, DCC did not restore CO to the baseline control value of 2.90 L/min. This is more clearly illustrated in Figure 5, which shows a plot of the CO during active DCC as a function of unassisted CO. With the line of regression for the data and the line of identity ($x=y$) drawn on the same axis, an approximate upper range of CO obtained with DCC is established (between 1.3 and 2.0 L/min). In addition, the intersection between these 2 lines establishes a point of marginal benefit; at unassisted CO values below this point, DCC improves ventricular function, and at unassisted CO values above this point, DCC reduces ventricular function.

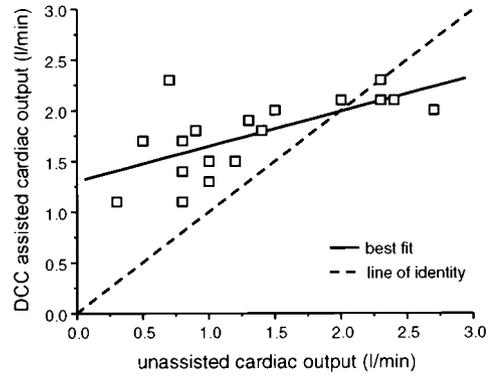


Figure 5. Plot of CO obtained with DCC-assisted hearts versus baseline CO obtained before ventricular assist with device removed from heart. Lines of regression for data are shown (solid line), as well as line of identity (dashed line).

Effect of DCC on Right and Left Heart Function

To investigate the differential effects of DCC on the LV and RV in vivo, in 5 open-chest canine experiments, both the LV and RV were instrumented with pressure transducers, and data from the most severe condition of heart failure were analyzed. RV systolic pressure increased by 132% (28.0 ± 6.3 to 65.0 ± 22.2 mm Hg), and LV systolic pressure increased by 58% (66.6 ± 26.3 to 105.2 ± 16.9 mm Hg). Despite the markedly increased relative pressure changes for the RV, the absolute changes in systolic pressure were similar for both ventricles. The RV end-diastolic pressure decreased by 29% (16.0 ± 7.0 to 11.4 ± 8.1 mm Hg), and the LV end-diastolic pressure decreased by 32% (17.0 ± 8.0 to 11.4 ± 6.8 mm Hg).

Effect of Compression Pressure on CO

To investigate whether additional compression pressure could further augment CO, DCC was performed first with a pressure of 100 and then 150 mm Hg in 6 of the in vivo experiments with animals with severe heart failure. The additional 50 mm Hg of compression pressure increased LV systolic pressure by 11% (from 99.7 ± 26.7 to 110.3 ± 39.2 mm Hg) and peak aortic flow by 20% (from 6.03 ± 3.01 to 7.23 ± 3.24 L/min) and reduced LV end-diastolic pressure by 26% (from 15.3 ± 9.3 to 11.3 ± 7.3 mm Hg). However, CO was further increased by only 4% (from 1.57 ± 0.46 to 1.63 ± 0.50 L/min), and mean arterial

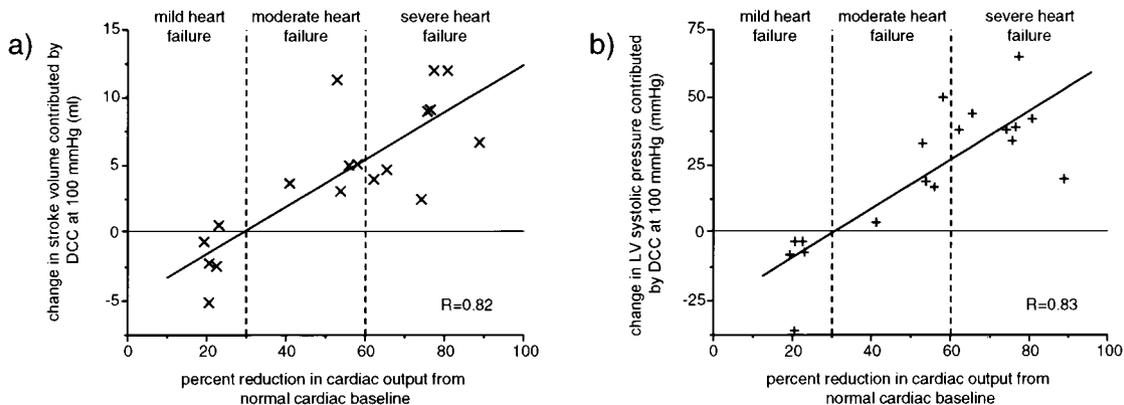


Figure 4. Plot of change in SV (a) and LV P_s (b) produced by DCC versus degree of heart failure indexed as percent reduction in CO from normal baseline value. Respective correlation coefficients are 0.82 and 0.83.

pressure was increased by only 5% (from 92.0 ± 20.6 to 96.5 ± 23.3 mm Hg).

Discussion

Initial investigations into the effects of DCC on ventricular physiology involved the use of a similar *ex vivo* canine heart preparation but included a compression chamber to administer pressure evenly over the surface of both ventricles. Those studies demonstrated that uniform DCC shifts the LV and RV ESPVRs upward in a parallel manner by an amount approximately equal to the compression pressure (P_{DCC}).⁴ In the current set of *ex vivo* experiments, DCC applied with the nonuniform compression device demonstrated similar effects on the ESPVR of both the LV and RV; however, the magnitude of the upward shift in ESPVR (as determined by $\Delta V_o \cdot E_{es}$) was $\approx 40\%$ of P_{DCC} . The difference between P_{DCC} and $\Delta V_o \cdot E_{es}$ reflects the incomplete transmission of the device compression pressure to the ventricular chambers.

The increase in systolic function afforded by nonuniform DCC was accomplished with a small but significant effect on both LV and RV diastolic function. Statistically significant changes in the parameters of the EDPVR (α and β) were observed for both ventricles and likely represent changes in wall characteristics due to physical attachment of the cuff to the heart. These findings are in contrast to the findings from earlier studies in which the idealized compression chamber had little effect on diastolic function.⁴ In terms of impact on overall pump function, this effect on diastolic function will slightly counteract the effects on the systolic properties.

The ESPVR and EDPVR data presented above provide load-independent characterizations of how DCC influences intrinsic ventricular pump function. These data do not, however, reveal the effects of DCC on ventricular pressure and volumes in the physiological setting, where preload volumes vary as a consequence of altered pump function. Earlier studies⁴ and the *ex vivo* data presented in Table 2 demonstrate that DCC increased LV P_{es} ; however, with the increased ventricular pumping capacity, there was a corresponding decrease in V_{es} and V_{ed} . Consequently, the DCC-assisted ventricle is functioning at lower preload volumes, and the increase in P_{es} observed under steady-state conditions is significantly less than the transmitted compression pressure (ie, magnitude of the upward shift in the ESPVR). These findings are predictable on the basis of our previous *ex vivo* studies and explainable within the context of current theories of ventricular/vascular coupling.¹⁰ This theory predicts that the amount of P_{es} and SV augmentation from DCC is dependent on the baseline contractile state, the baseline afterload resistance, and the amount of V_o and V_{ed} shift.⁴ In turn, the shifts in V_o and V_{ed} both depend on the transmission of P_{DCC} to the ventricular chambers.

As predicted on the basis of the *ex vivo* studies, the increased ventricular pumping capacity with DCC manifested as significant increases in LV systolic pressure (P_s), significant decreases in LV P_{ed} , and significant increases in SV with the *in vivo* heart failure model that was used. Also predicted from the *ex vivo* studies was that these hemodynamic benefits were related to the underlying ventricular contractile state and were most apparent with the weakest hearts. Figure 4 illus-

trates the change in SV and LV P_s as a function of ventricular contractile state and demonstrates that ventricular function had to deteriorate by $\approx 30\%$ before DCC actually improved these parameters.

Although DCC was able to significantly improve ventricular pumping capacity under the more severe conditions of heart failure, DCC did not restore CO to the normal baseline value. This is clearly illustrated in Figure 5, which provides a plot of the CO during active DCC as a function of unassisted CO and demonstrates an approximate upper limit to the level of assisted CO. Attempts to increase the inflation pressure by an additional 50 mm Hg only marginally improved CO despite relatively pronounced changes in LV P_s and peak aortic flow. Thus, the inability to normalize CO is not likely to be due to a deficiency in contractile assistance but rather to a limit on ventricular filling. The reduction in CO observed with simple placement of the cuff on the heart (Table 3) and the leftward shift of the EDPVR observed with the *ex vivo* studies support this concept.

Data from the *ex vivo* and *in vivo* studies suggest that DCC pressure is equally distributed across both ventricles; however, the LV and RV function at different levels of contractility and pump into vascular systems with different arterial impedances. Based on the single ventricular analysis presented here, the effects of DCC on the RV will be proportionally greater than the effects on the LV. Under steady-state conditions, however, the SV must be approximately the same for both ventricles, so the proportionally greater effect of DCC on the RV cannot translate into a larger SV for the RV than for the LV. In other words, the amount of ventricular preload shifts and the degree of SV augmentation will depend on the effects of DCC on the unequal pumping capacity and vascular resistance of the LV and RV. Because the RV functions at lower levels of contractility and pumps into vascular beds with lower resistances, the ultimate degree of P_{DCC} to be used will be critically dependent on the effect of DCC on the RV; that is, an increase in P_{DCC} to values above those required to completely empty the RV will fail to further increase LV outputs.

In summary, the present study provides basic information concerning the physiological effects of a novel biventricular support device and demonstrates the effectiveness of this device *in vivo*. Nonuniform DCC with a new assist device that delivers compression forces around the circumference of the heart can increase LV and RV pressure-generating capability and, in the setting of acute ischemic heart failure, can significantly improve systemic hemodynamics and CO. This device has the potential to avoid many of the complications associated with currently available ventricular support devices that involve the use of a blood/device interface. However, future studies will have to address the effects of cardiac compression on underlying ventricular function and the potential damaging effects of compression forces on the myocardium. These studies must be performed over longer periods and use chronic models of heart failure to appropriately address these limitations.

Acknowledgments

This work was supported in part by a grant from Cardio Technologies Inc. Dr Wang was supported in part by an Investi-

gatorship Award from the American Heart Association, New York City Affiliate, and a Grant-in-Aid from the American Heart Association (National Center).

References

1. Kawaguchi O, Goto Y, Futaki S, Ohgoshi Y, Yaku H, Suga H. Mechanical enhancement and myocardial oxygen saving by synchronized dynamic left ventricular compression. *J Thorac Cardiovasc Surg.* 1992; 103:573–581.
2. Kawaguchi O, Goto Y, Futaki S, Ohgoshi Y, Yaku H, Suga H. The effects of dynamic cardiac compression on ventricular mechanics and energetics: role of ventricular size and contractility. *J Thorac Cardiovasc Surg.* 1994;107:850–859.
3. Kawaguchi O, Goto Y, Ohgoshi Y, Yaku H, Murase M, Suga H. Dynamic cardiac compression improves contractile efficiency of the heart. *J Thorac Cardiovasc Surg.* 1997;113:923–931.
4. Artrip JH, Leventhal AR, Tsitlik JE, Levin HR, Wang J, Burkhoff D. Hemodynamic effects of direct bi-ventricular compression studied in isovolumic and ejecting isolated canine hearts. *Circulation.* 1999;99: 2177–2184.
5. Suga H, Sagawa K. Instantaneous pressure-volume relationships and their ratio in the excised, supported canine left ventricle. *Circ Res.* 1974;35:117–126.
6. Burkhoff D, Alexander J Jr, Schipke J. Assessment of windkessel as a model of aortic input impedance. *Am J Physiol.* 1988;255: H742–H753.
7. Tsitlik JE, Halperin HR, Popel AS, Shoukas AA, Yin FCP, Westerhof N. Modeling the circulation with three-terminal electrical networks containing special nonlinear capacitors. *Ann Biomed Engr.* 1992;20: 595–616.
8. Todaka K, Leibowitz D, Homma S, Fisher PE, Derosa C, Stennett R, Packer M, Burkhoff D. Characterizing ventricular mechanics and energetics following repeated coronary microembolization. *Am J Physiol.* 1997;272:H186–H194.
9. Knecht M, Burkhoff D, Yi GH, Popilskis S, Homma S, Packer M, Wang J. Coronary endothelial dysfunction precedes heart failure and reduction of coronary reserve in awake dogs. *J Mol Cell Cardiol.* 1997;29:217–227.
10. Sunagawa K, Maughan L, Burkhoff D, Sagawa K. Left ventricular interaction with arterial load studied in isolated canine ventricle. *Am J Physiol.* 1983;245:H773–H780.