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Hemodynamic Effects of Direct Biventricular Compression Studied in Isovolumic and Ejecting Isolated Canine Hearts

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Background—Biventricular direct cardiac compression (DCC) can potentially support the failing heart without the complications associated with a blood/device interface. The effect of uniform DCC on left and right ventricular performance was evaluated in 7 isolated canine heart preparations.

Methods and Results—A computer-controlled afterload system either constrained the isolated heart to contract isovolumically or simulated hemodynamic properties of physiological ejection. Biventricular DCC was provided by a chamber surrounding the heart that allowed adjustment of the compression pressure, onset time, and duration. Through a series of ventricular preloads, the effect of DCC on the end-systolic pressure-volume relationship (ESPVR) was evaluated under isovolumic and ejecting conditions. Under both conditions, DCC shifted the ESPVR of the left and right ventricles upward by an amount approximately equal to the compression pressure. The augmentation of end-systolic pressure for each initial preload tested, however, was less under ejecting conditions, because reductions in end-systolic and end-diastolic volumes occurred with ejection. Nevertheless, the net effect was to increase stroke volume. Measurement of $M\dot{V}O_2$ demonstrated that at a given ventricular volume, $M\dot{V}O_2$ did not change with DCC; however, peak ventricular pressure increased substantially, so that the effective pressure-volume area increased.

Conclusions—Biventricular DCC can augment end-systolic pressure with no added costs of $M\dot{V}O_2$. Under ejecting conditions, this augmentation of ventricular contracting ability manifests as increases in stroke volume. Thus, DCC represents a feasible alternative form of ventricular assist, and devices that support the heart in this manner should be further explored. **(*Circulation*. 1999;99:2177-2184.)**

Key Words: heart-assist device ■ heart failure ■ physiology ■ hemodynamics ■ ventricles

Treatment of severe, acute cardiogenic shock remains a major clinical challenge. Regardless of whether it is due to an acute myocardial insult or the consequence of decompensation in the setting of long-standing heart failure, the repertoire of available medical and surgical therapies is somewhat limited and frequently ineffective. Although a variety of ventricular assist devices are available, most of these devices require direct contact with the patient's blood. Thus, thromboembolic events, the need for anticoagulation, hemolysis, and immune reactions are ever-present problems. There has been renewed interest in developing techniques to support the circulation by compressing the weakened heart from its external surface.

Some understanding of the impact of external cardiac compression on ventricular performance has been obtained through use of a conditioned muscle wrap, dynamic cardiomyoplasty. Despite little improvement in cardiac output, this procedure has demonstrated underlying physiological benefits of improved myocardial contractility, reduced myocardial O_2 consumption ($M\dot{V}O_2$), and stabilization of the remodeling process of heart failure.[1–3] A significant amount of experience has also been gained previously with the use of pneumatic compression devices in the setting of complete cardiac arrest.[4,5] However, there has been little experience in the use of such mechanical devices to augment contraction of a beating but weakened heart.

To begin exploring the effects of external cardiac compression on ventricular performance, Kawaguchi et al[6–8] studied left ventricular (LV) mechanics of isolated canine hearts placed inside a chamber whose pressure could be varied in synchrony with cardiac contraction. Results of those studies showed that at a given volume, net ventricular pressure-generating capabilities could be augmented by external pressure without increasing myocardial oxygen demand. However, many fundamental questions remain. It has not been determined how external compression affects LV pressure generation at different volumes (ie, on the end-systolic and end-diastolic pressure-volume relationships [ESPVR and

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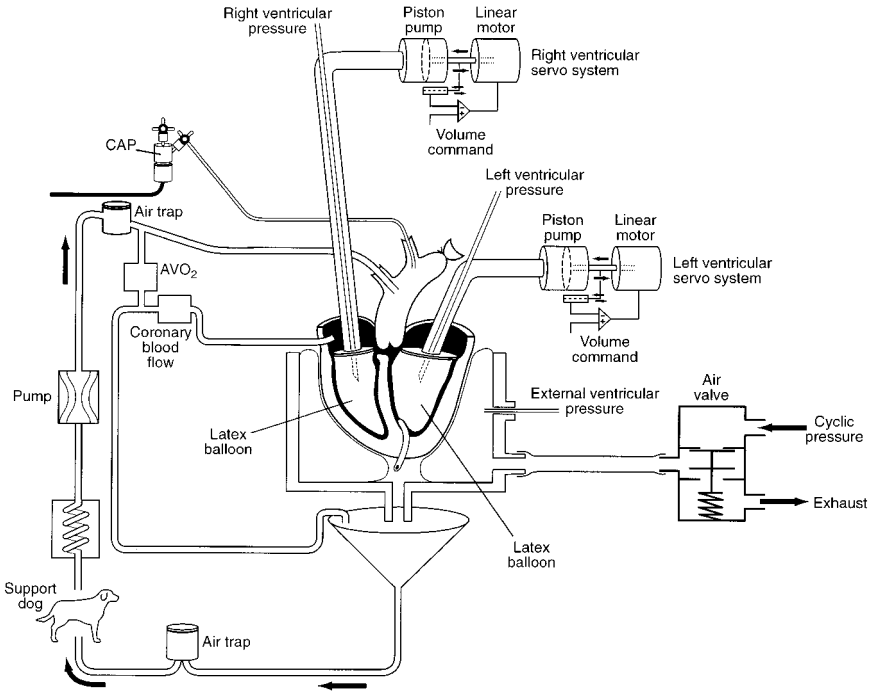

Figure 1. Schematic of isolated canine heart preparation showing donor heart within compression chamber.

EDPVR, respectively]), how right ventricular (RV) mechanics are affected, or how LV and RV filling volumes and stroke volumes (SVs) would be affected under conditions of physiological preloading and afterloading.

The purpose of this study was to evaluate the effects of uniform, biventricular direct cardiac compression (DCC) on LV and RV performance and overall hemodynamics under both isovolumic and ejecting conditions. We used an isolated canine heart preparation in which physiological afterload conditions were imposed on the heart to permit a study of the effects of DCC on preload volumes and cardiac output under conditions that mimic those encountered in situ. Finally, $M\dot{V}O_2$ was measured to assess the relationship between changes in overall hemodynamic performance and energy demands of the heart.

Methods

Surgical Preparation

A total of 14 adult male mongrel dogs weighing between 22.0 and 24.0 kg were used for the study. All animals involved in the study 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).

Seven isolated canine hearts were studied by methods that were similar to those described previously[9] and are shown schematically in Figure 1. In brief, 2 mongrel dogs were anesthetized with pentobarbital sodium 30 mg/kg IV. The femoral arteries and veins of 1 dog ("support dog") were cannulated and connected to a perfusion system used to supply oxygenated blood to the isolated heart. The second dog ("heart donor dog") was mechanically ventilated, a midline sternotomy was performed, and the heart was removed while being metabolically supported by arterial flow from the support dog. The left and right atria were opened, and all the chordae tendineae were freed from the leaflets of both mitral and tricuspid valves. Two metal adapters were sutured to the mitral and tricuspid rings. These adapters hold the isolated heart to individual ventricular volume servopump systems. A cannula was placed into the mouth of the coronary sinus to permit collection of coronary venous blood. When the surgical preparation was complete, water-filled balloons of the servo systems were placed inside the LV and RV cavities. A solid-state pressure transducer (Millar Instruments) was placed inside each balloon to measure the respective ventricular pressure.

Coronary arterial pressure was set to ≈100 mm Hg and held constant by a servo system that regulates blood flow rate out of the support dog. The temperature of the perfusate was maintained at ≈35°C with a heat exchanger. The coronary sinus venous blood flow was measured continuously by a transit-time flow probe (Transonic) positioned at the outlet of the coronary sinus drain. The difference in oxygen content between arterial and coronary venous blood ($SavO_2$) was measured continuously by absorption spectrophotometer (A-VOX Systems).[10] The arterial pH, PO_2, and PCO_2 were measured periodically during each experiment to ensure nearly 100% SaO_2 during periods of data collection. LV O_2 consumption was calculated from the measurements of coronary blood flow and $SavO_2$ as described below.

Pacing electrodes were sutured to the atrial tissue, and the heart was paced at a rate 10 to 15 bpm greater than the spontaneous rate (mean paced rate, 104±4 bpm). A bipolar surface ECG was measured between 2 electrodes sutured to the surface of the heart.

Impedance Loading System

The ventricular volume servo systems were controlled by a computer system that either constrained the hearts to contract isovolumically or simulated hemodynamic properties of the systemic and pulmonic circuits to allow physiological ejection patterns. A digital computer was programmed with the differential equations representing the closed-loop system of systemic and pulmonary circulations.[11] This model provides a reasonable representation of vascular pressure-flow relations of the real circulation for simulating many aspects of coupling of ventricles and their respective vascular loads.[12] The parameter values of each of the resistive and capacitive elements in the model could be specified from the computer keyboard. To implement the loading of ventricles by this model, the computer digitizes the instantaneous LV and RV pressures and calculates the appropriate instantaneous flow into or out of each ventricle. The flow signals are integrated digitally and converted to an analog signal, which is used as the command signal for the respective volume servo system.

External Compression Device

As shown in Figure 1, the heart was placed inside a Lucite compression chamber. A nylon lining inside the chamber contacted the heart and ensured that any blood draining from the heart did not enter the compression tubing but rather drained out the bottom chamber to return to the isolated heart. Cardiac compression pressure (P_{DCC}) was provided to the chamber from a valved compressed-air cell that was regulated by a computer and allowed for adjustment of P_{DCC}, onset, and duration. The amount of pressure was measured by a Millar microtip catheter placed in the driveline near the chamber. The onset of P_{DCC} was synchronized with the QRS complex of the explanted heart.

Experimental Protocol

Four different protocols were performed.

Protocol 1 was designed to determine the effects of external compression on the ESPVR and EDPVR in isovolumically contracting LVs and RVs. To obviate potential confounding effects of interventricular interaction on the results, ESPVR and EDPVR of each ventricle were measured separately with the contralateral ventricle emptied of volume so that there was no developed pressure. Also, coronary blood flow and Sav_{O_2} were measured during the LV ESPVR/EDPVR run. These parameters, along with ventricular pressures, were measured with and without active compression at several volumes. The compressions were performed with a pressure of 50 mm Hg and a duration of 40% of the cardiac cycle.

In protocol 2, the effects of the timing of the onset of compression, the duration of compression, and the amount (pressure) of compression were then studied individually under isovolumic conditions at a single setting of LV and RV volumes.

In protocol 3, the effects of external compression under ejecting conditions were investigated. Parameter values for the simulated vascular systems were set to approximate heart failure conditions: LV and RV end-diastolic pressures of ≈20 and 10 mm Hg, respectively; LV and RV ejection fractions of ≈20%; peak LV pressure less than ≈90 mm Hg; and peak RV pressure greater than ≈35 mm Hg. Because it is not possible to adjust each of these variables (because these variables are interdependent, with a relationship that is heavily dependent on the contractile state of each ventricle), these set points served as guidelines for adjusting parameter variables, not strict criteria. After a group of parameter values had been decided on and hemodynamic conditions had been stabilized, data were recorded. The device was then turned on at a P_{DCC} of 50 mm Hg and a duration of 40% of the cardiac cycle. Once conditions had stabilized with the device on (≈5 minutes), data were recorded.

Finally, in protocol 4, the effects of compression on ESPVR and EDPVR during ejecting conditions were achieved by simulation of a vena caval occlusion, which resulted in a gradual reduction in ventricular end-diastolic volumes (EDVs). This was performed both with and without active compression at a pressure of 50 mm Hg and a duration of 40% of the cardiac cycle.

Data Analysis

All data were digitally sampled at a rate of 1000 Hz for ≈5 seconds and analyzed with a data analysis program written in Microsoft BASIC. Measurements were averaged over 3 to 5 beats and analyzed offline.

End-systolic pressure (ESP, P_{es}) was defined as peak pressure for isovolumic contractions. For ejecting beats, end-systolic volumes (ESVs, V_{es}) and ESPs were defined by the point in the cardiac cycle at which the instantaneous ratio between pressure and volume attained a maximal value. ESPVRs were analyzed by linear regression analysis applied to data from the different volume beats according to the formula $P_{es}=E_{es}(V_{es}-V_o)$, and EDPVRs were analyzed by nonlinear regression analysis according to the equation $P_{ed}=P_o+\beta V_{ed}^{\alpha}$, where E_{es} is end-systolic elastance, V_o is volume axis intercept, P_{ed} is EDP, P_o is pressure when ventricular volume is zero, V_{ed} is EDV, and β and α are constants. The effects on metabolic parameters were assessed by determining the relation between $M\dot{V}_{O_2}$ and total mechanical energy indexed by pressure-volume area (PVA). $M\dot{V}_{O_2}$ was defined as the product of Sav_{O_2} and coronary blood flow. PVA was determined, as detailed previously, as the area contained within the ESPVR and the EDPVR up to the volume of the isovolumic beat.[13]

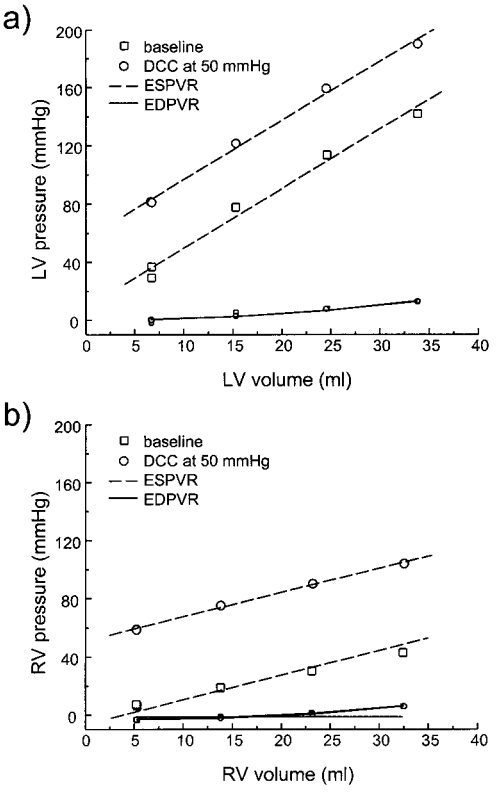

Figure 2. Results from representative experiment showing effects of DCC on ESPVR and EDPVR for both (a) LV and (b) RV.

Statistical comparisons of the linear ESPVRs and $M\dot{V}_{O_2}$-PVA relationships between control and active compression states were done by ANCOVA. The nonlinear EDPVRs were linearized $[\ln(P_{ed}-P_o)=\ln\beta+\alpha \cdot \ln V_{ed}]$ and then compared statistically by ANCOVA. Other parameters were expressed as mean±SD and were compared by paired *t* tests. All statistical analyses were performed with commercially available software (SYSTAT). In all cases, a value of $P<0.05$ was considered statistically significant.

Results

Effects of DCC on Isovolumic ESPVR and EDPVR

Results from a representative experiment are shown in Figure 2; a summary of the average results and statistical compari-

TABLE 1. ESPVR and EDPVR Under Isovolumic Conditions

	ESPVR		EDPVR	
	E_{es}	V_o	α	β
LV				
Baseline	4.0±1.24	1.9±4.43	2.5±0.41	$2.4\times10^{-3}\pm2.39\times10^{-3}$
DCC	4.2±1.05	−7.5±4.29	2.6±0.36	$1.5\times10^{-3}\pm0.82\times10^{-3}$
P	0.18	<0.001	0.84	0.80
RV				
Baseline	2.0±0.91	−0.1±5.84	2.6±0.31	$9.3\times10^{-3}\pm21.3\times10^{-3}$
DCC	2.3±0.68	−19.3±7.75	2.7±0.20	$2.7\times10^{-3}\pm4.87\times10^{-3}$
P	0.03	<0.001	0.46	0.48

TABLE 2. $M\dot{V}O_2$ and Work Relations (PVA)

	A	B
Baseline	$1.6\times10^{-3}\pm0.65\times10^{-3}$	4.9±0.85
DCC	$1.1\times10^{-3}\pm0.39\times10^{-3}$	4.4±0.69
P	<0.001	0.06

sons obtained from 7 hearts is provided in Table 1. DCC shifted the ESPVR of both the LV and RV upward in a parallel manner by an amount approximately equal to the P_{DCC}. In terms of the parameter values, there was little effect on the E_{es} values, but V_o values were decreased. ANCOVA revealed highly significant decreases in V_o for both ventricles ($P<0.001$), with slight increases in E_{es} only for the RV that were statistically ($P=0.03$) but not physiologically significant. The EDPVRs were not affected for either ventricle.

Effect of DCC on $M\dot{V}O_2$-PVA Relationship

At a given ventricular volume, $M\dot{V}O_2$ did not change significantly during active compression. Peak total ventricular chamber pressure was increased substantially, so that the effective PVA also increased significantly. Accordingly, there was a large effect on the $M\dot{V}O_2$-PVA relationship, with a significant decrease in slope (A) but with little influence on the *y* intercept (B): A relates to the oxygen consumption per PVA, whereas B is the oxygen consumption for no external work (ie, PVA=0). These findings were confirmed in the 5 animals in which these measurements were made. The values for A and B, as well as the probability value obtained from the ANCOVA comparing control and DCC values, are summarized in Table 2.

Effect of P_{DCC}, Compression Onset Time, and Compression Duration

Representative pressure waveforms for the LV, RV, and compression device with P_{DCC}s of ≈0, 25, 50, and 100 mm Hg are illustrated in Figure 3a. Peak LV and RV pressures increased linearly as P_{DCC} was increased, with the relationship between P_{DCC} and change in peak pressure being statistically indistinguishable from the line of identity. These findings were confirmed in the 4 animals in which these measurements were made systematically, as shown in Figure 4 ($y=x$, $r^2=0.999$, P=NS compared with line of identity).

Figure 3b and 3c illustrates representative pressure-time waveforms for the LV, RV, and device obtained with different compression onset times (ranging between 0 and 150 ms from the QRS spike) and with different compression durations (ranging between 20% and 60% of the cardiac cycle). Although peak pressures did not vary significantly for either ventricle with the different compression onset times or durations, there was consistent influence on the shape of the pressure waves.

Effect of DCC on Hemodynamics During Ejection

The effects of DCC on hemodynamic parameters during ejecting conditions are summarized in Figure 5. As summarized in the figure, for both the LV and RV, ESPs increased significantly, whereas EDPs decreased (Figure 5a and 5c). In contrast to the isovolumic data, the increase in peak ventric-

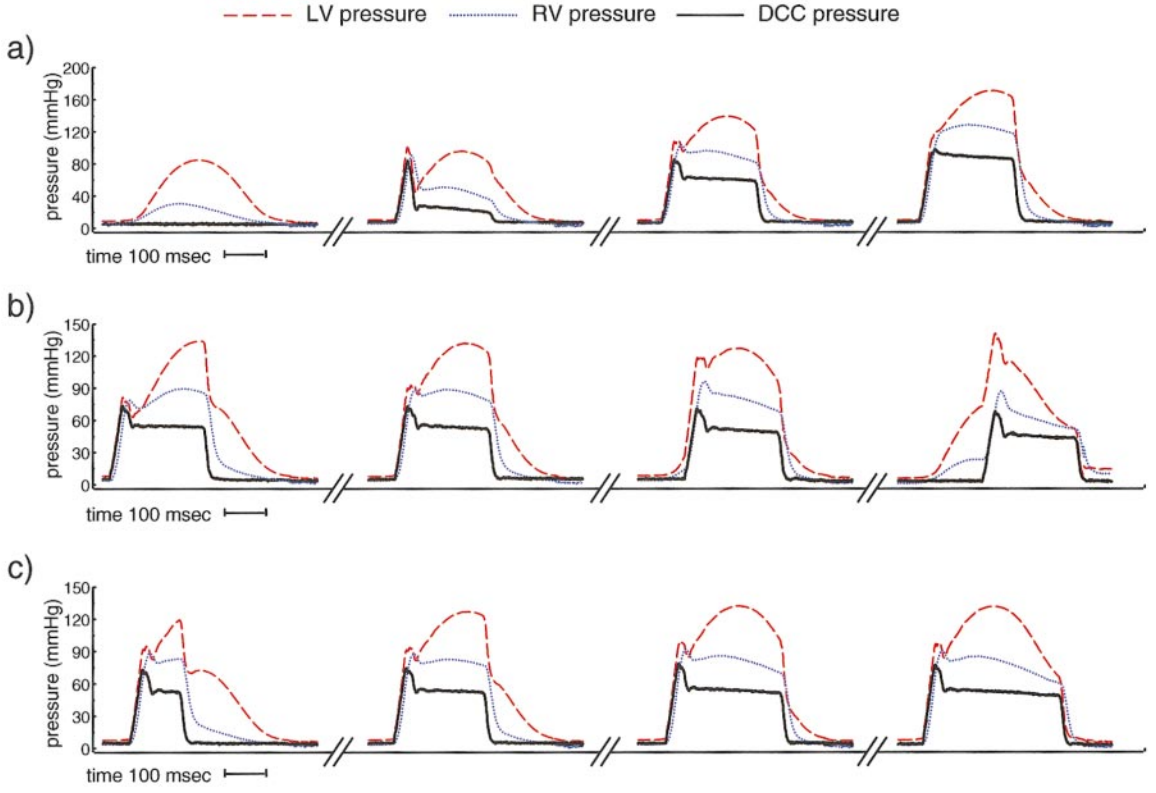

Figure 3. Representative pressure waveforms for LV, RV, and compression chamber tested over a series of (a) P_{DCC}s, (b) compression onset times, and (c) compression durations.

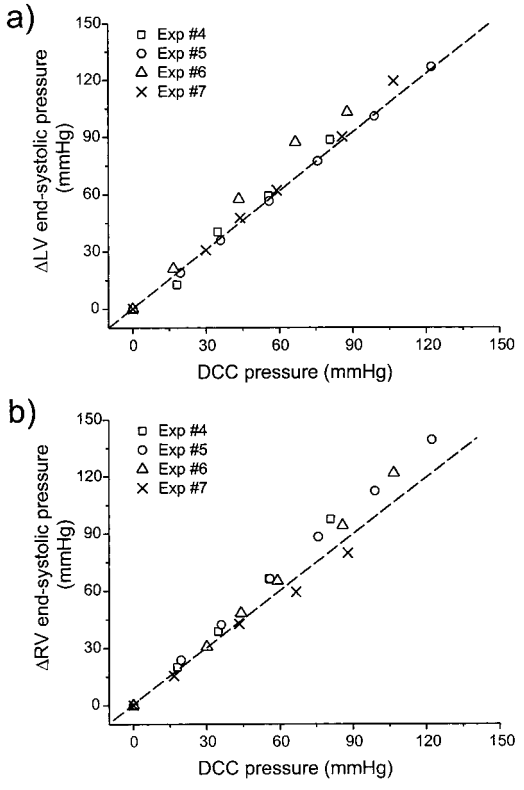

Figure 4. Change in ventricular ESP contributed by DCC is plotted against chamber P_{DCC} for (a) LV and (b) RV. Dashed line is line of identity ($y=x$).

ular pressures were substantially less than the P_{DCC}. As will be detailed below (see Discussion), this is because DCC also created significant reductions in LV and RV ESVs (Figure 5b and 5d). Although EDVs were also decreased, there was a significant ≈60% increase in SV (Figure 5b).

Effect of DCC on ESPVR and EDPVR During Ejection

The effects of DCC on ESPVR and EDPVR during ejecting conditions are shown in the representative results of Figure 6. Similar to the findings with isovolumic conditions, the ESPVRs of both the LV and RV were shifted upward in a parallel manner by an amount approximately equal to the P_{DCC}.

Discussion

Several non–blood-contact devices that assist the heart by directly compressing the external surface are currently under development. The methods for achieving DCC use a pneumatic driver to provide an equally distributed pressure over the epicardial surface of the LV and RV. Unlike cardiac compression with a skeletal muscle wrap (cardiomyoplasty), in which the compression forces vary with ventricular volume,[1,7] cardiac compression with the present pneumatic system is independent of such factors, and we therefore refer to it as a constant-pressure DCC device. The isolated canine heart preparation offers a unique opportunity to study the effects of constant-pressure DCC under a variety of hemodynamic loading conditions while being able to characterize

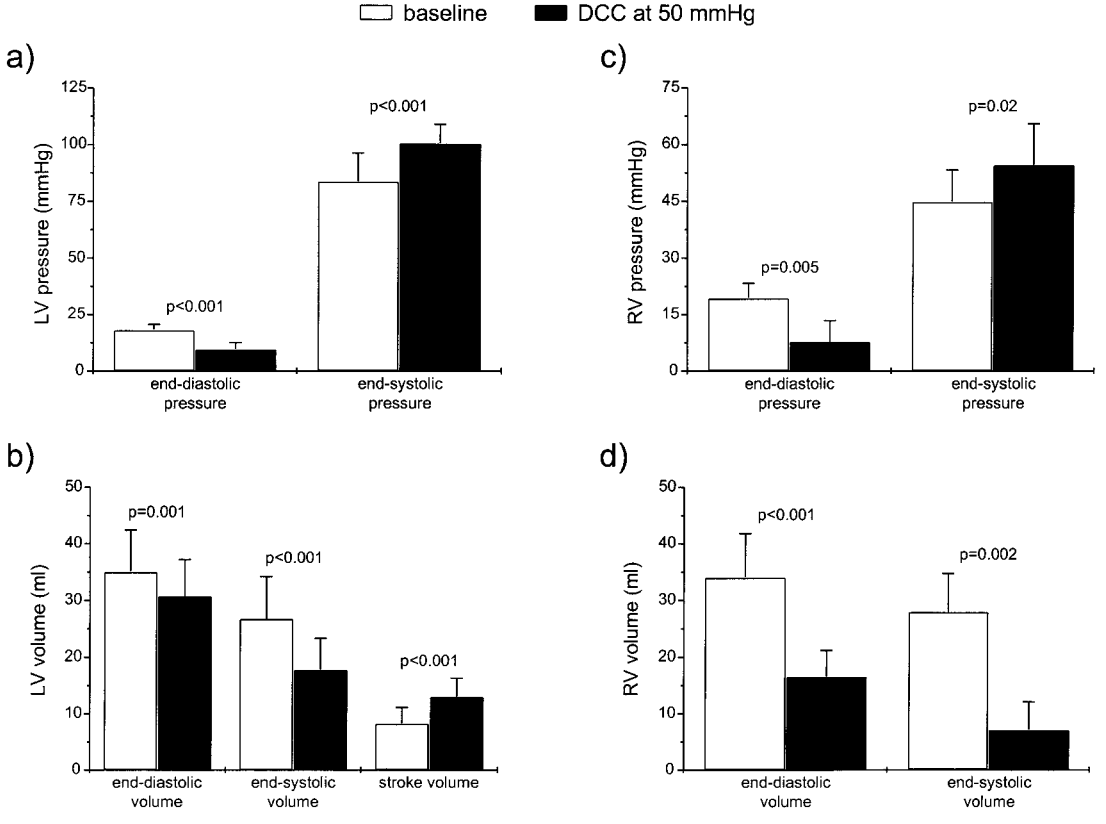

Figure 5. Hemodynamic effects of DCC on (a and b) LV and (c and d) RV under physiological ejecting conditions.

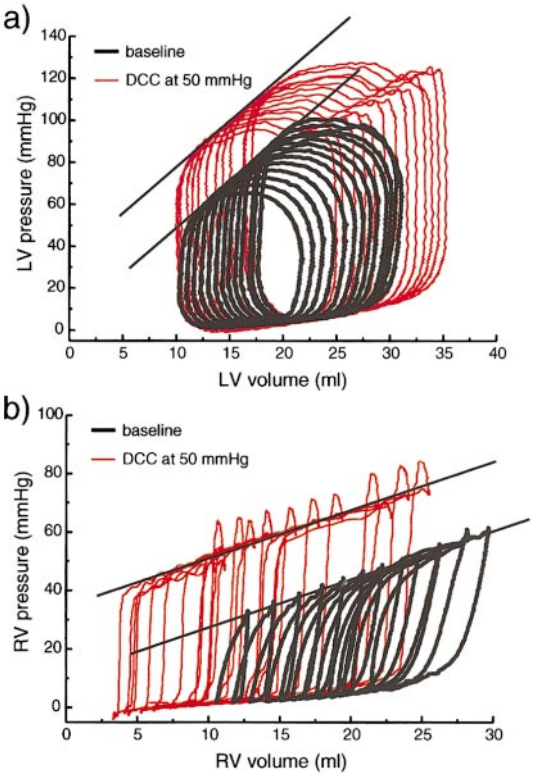

Figure 6. Pressure-volume tracings from representative experiment showing effects of DCC on ESPVR and EDPVR for both (a) LV and (b) RV under physiological ejecting conditions.

ventricular effects with accurate measurements of ventricular volume.

Under isovolumic conditions, the total pressure measured inside the LV cavity equals the sum of the pressure generated because of systolic and diastolic myocardial properties (normally referred to as the transmural pressure) plus the pressure applied by the device to the heart surface. Accordingly, the isovolumic ESPVR was shifted upward by an amount approximately equal to the P_{DCC} for both ventricles. In other words, there was no change in the E_{es} but a substantial decrease in the V_o. The reduction in V_o was predictably related to the P_{DCC} and the baseline value of E_{es} ($\Delta V_o = -P_{DCC}/E_{es}$), with the extrapolated V_o values typically assuming negative values. Negative extrapolated V_o values have been observed previously in the setting of increased contractility, where ESPVRs are curvilinear.[14] Fitting a linear equation to these curvilinear relations frequently resulted in negative values of extrapolated V_o. However, the negative V_o values observed with DCC reflect the extrapolations from the upwardly shifted ESPVRs rather than erroneous linear extrapolations of nonlinear relationships. In summary, despite the constancy of E_{es}, DCC results in an increased overall pump strength by an amount related to P_{DCC}.

Importantly, the benefits for systolic function are achieved with no apparent effect on ventricular diastolic function or on intrinsic myocardial properties. The EDPVRs were not affected for either ventricle: α and β did not change. In addition, the increase in overall pump strength is achieved without added metabolic cost to the myocardium. The slope changes of the $M\dot{V}O_2$-PVA relationship observed with DCC in the present study do not reflect effects on myocardial properties, but rather the enhanced net pressure-generating capacity in the absence of an increase in oxygen consumption.

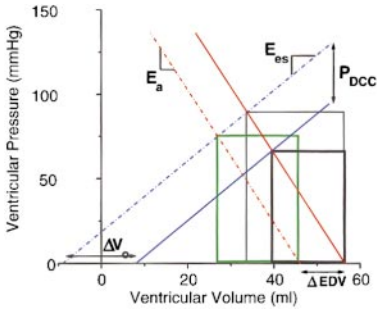

Figure 7. Effect of DCC on steady-state pressure-volume relations that occur under physiological ejecting conditions is shown schematically (see Discussion for details).

The effects of DCC on hemodynamic performance under ejecting conditions are more complicated. As under isovolumic conditions, the ESPVRs of both ventricles were shifted upward, with the change in V_o being related to E_{es} and P_{DCC} as described above for isovolumic conditions (Figure 2 versus Figure 6). Unlike isovolumic conditions, however, peak ventricular pressure during DCC was not simply the sum of P_{DCC} and unassisted peak LV pressure. This is because application of DCC under ejecting conditions influences ESV and EDV, as shown in Figure 5. Importantly, the shift in EDV is not related to an effect on diastolic properties (demonstrated by an absence of effect on the EDPVRs, shown in Figures 2 and 6); rather, it reflects changes due to the increased ventricular pumping capacity (demonstrated by a decrease in ESV). In other words, preload decreases when pump strength increases.

These effects are explainable within the context of current theories of ventricular-vascular coupling,[15] in which ventricular contractile state is quantified by E_{es} and V_o, afterload by the effective arterial elastance (E_a), and preload by EDV. E_a is proportional to total peripheral resistance (TPR) and inversely proportional to the cardiac cycle duration (T): $E_a \propto TPR/T$. The E_a line is a line drawn on the pressure-volume plane starting on the volume axis at the EDV whose slope equals $-E_a$. The E_a line therefore provides a means of graphically depicting afterload on the same axes as the ventricular pressure-volume relations and loops. The intersection of the E_a line and the ESPVR provides an estimate of the end-systolic pressure-volume point for the specified E_{es}, V_o, EDV, and E_a. As illustrated in Figure 7, if baseline ESPVR is shown by the solid blue line and baseline E_a and EDV are shown by the solid red line, then the baseline pressure-volume loop would be approximated by the thick solid black line. If DCC is applied, the ESPVR would be shifted upward by an amount equal to P_{DCC} (dashed-dotted blue line). Under conditions in which neither preload volume nor afterload resistance would change, the new pressure-volume loop would be approximated by the thin solid black line. Peak pressure of

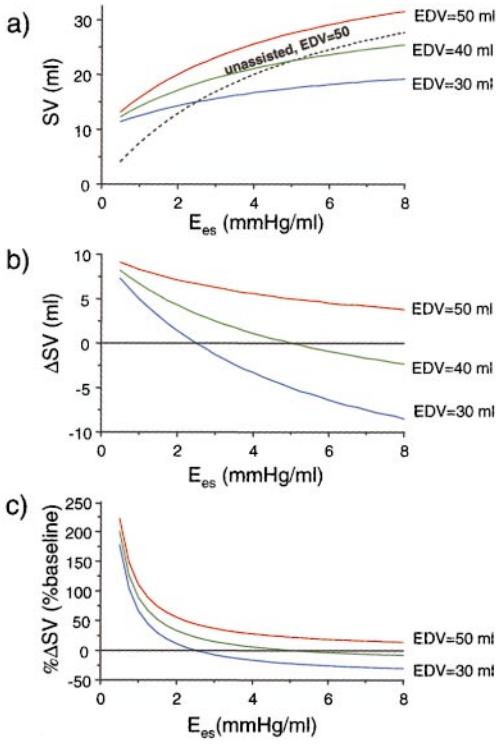

Figure 8. Effect of DCC on relationship between SV and ventricular contractility (E_{es}) for 3 different preloads (EDV of 30, 40, and 50 mL): (a) SV vs E_{es}, (b) change in SV ($\Delta SV = SV_{DCC} - SV_{base}$) vs E_{es}, and (c) percent increase in SV $\{\%\Delta SV = [(SV_{DCC} - SV_{base})/SV_{base}] \times 100\}$ vs E_{es}. SV_{DCC} is SV with DCC and SV_{base} is baseline SV.

this loop is increased compared with baseline by only ≈50% of P_{DCC}; SV is increased by ≈40%. In practice, however, preload is also reduced during DCC, so the E_a line shifts leftward (dashed-dotted red line), which has the effect of diminishing both the pressure- and SV-augmenting effects of DCC, as shown by the green pressure-volume loop. Thus, the amount of pressure and SV augmentation will be dependent on the baseline contractile state, the baseline afterload resistance, and the amount of EDV shift caused by DCC.

These interrelationships are further summarized in Figure 8. The dashed line in panel a shows how SV varies as a function of contractile state at a fixed EDV (50 mL) and a fixed afterload (E_a=5 mm Hg/mL). The solid line at the top depicts how DCC with a P_{DCC} of 50 mm Hg would affect this relationship, assuming that there were no change in EDV. As EDV decreases, however, this curve shifts downward, as shown by the middle and lower solid lines. Graphs depicting the amount of SV augmentation (expressed in absolute and relative terms, panels b and c, respectively) formally illustrate 2 fundamental aspects of the physiology of constant-pressure DCC. First, the amount of augmentation is a function of baseline contractile state. Substantial SV augmentation is achieved only in a weak heart (E_{es}<3 mm Hg/mL, which is ≈40% of normal E_{es} of a 20-kg dog). Second, the reduction in EDV will blunt SV augmentations and can even result in a diminution at higher baseline levels of contractile state.

A full explanation of the effects of DCC, however, is more complicated. DCC affects both ventricles, and only a single-ventricle analysis has been presented above. Because the intrinsic contractile strength, measured in terms of E_{es}, of the RV is much less than that of the LV, the effects of DCC on the RV are significantly greater under every condition. As Figure 5 shows, reductions in RV EDV are substantially greater than in the LV, with the RV being nearly emptied during active DCC. The amount of preload shifts and ultimate degree of pressure and flow augmentation will therefore depend on the complex effects of the unequally altered pumping capacity of the LV and RV. Although there is no analytical solution to this problem, numerical solutions could be used to understand the relationship between baseline cardiovascular parameter values, shifts of LV and RV EDVs, and pressure and flow augmentation by DCC.

Effects of DCC have been studied previously in isolated hearts.[6–8] In those studies, however, ESPVRs and EDPVRs were not directly investigated, single-ventricle preparations were used, and predetermined LV volume changes were imposed on the LV. With regard to the last point, EDVs, ESVs, and SVs were specified in the previous studies, and effects of DCC on LV pressure generation were measured. In contrast, in our physiological afterloading system, volumes were allowed to shift in response to changes in effective LV and RV pumping strengths as they would in vivo. Although different volume settings were studied in the previous investigations, V_o values were assumed to be constant, and changes in performance were interpreted as reflecting changes in E_{es}. In our study, ESPVRs were directly measured to reveal that with a device that delivers a constant P_{DCC}, E_{es} does not shift, but rather V_o is decreased. Accordingly, insights into the in vivo effects of DCC could be obtained.

With the increased use of mechanical assist devices and the complications associated with a blood/device interface, there has been a renewed interest in supporting the failing but still beating heart with external mechanical compression. The present study in isolated hearts demonstrates the feasibility of mechanical DCC as an alternative form of ventricular assist and provides the foundation for understanding the physiological effects of such a device in vivo.

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