LINEAR END-SYSTOLIC PRESSURE-VOLUME RELATIONSHIP DURING PULSATILE LEFT VENTRICULAR BYPASS REPRESENTS NATIVE HEART FUNCTION

This study assessed whether the end-systolic pressure-volume relationship obtained without any interventions during pulsatile left ventricular bypass adequately represents native heart function. In 11 anesthetized Holstein calves, left ventricular pressure was measured with a micromanometer while left ventricular volume was simultaneously calculated from orthogonal left ventricular diameters measured with ultrasonic dimension transducers. End-systolic pressure and volume data were subjected to linear regression analysis to achieve an end-systolic pressure-volume relationship. Data from both caval occlusions and aortic occlusion were used for the control end-systolic pressure-volume relationship (median $r = 0.941$, slope = 7.4 ± 0.8 mm Hg per milliliter per 100 gm left ventricular weight; mean $\pm$ standard error of the mean). During left atrial-aortic bypass with a Pierce-Donachy pneumatic assist pump in the asynchronous mode, the end-systolic pressure-volume relationships were obtained without interventions to change ventricular loading conditions. During maximal ventricular unloading during full to empty pumping, termed 100%, the resulting narrow range of pressure and volume data did not yield highly linear end-systolic pressure-volume relationships (median $r = 0.669$, slope = 4.9 ± 0.9 mm Hg per milliliter per 100 gm left ventricular weight). However, at reduced rates of pumping, the end-systolic pressure-volume relationships were considerably linear (80%, median $r = 0.819$; 60%, median $r = 0.868$; 40%, median $r = 0.899$). Slopes did not significantly differ from control values (80%, 6.9 ± 1.1 ; 60%, 8.2 ± 1.1 ; 40%, 7.8 ± 1.1). The end-systolic pressure-volume relationship obtained without exogenous load changes during asynchronous, pulsatile left ventricular bypass represents native left ventricular systolic function. (*J THORAC CARDIOVASC SURG* 1995;109:780-6)

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Left ventricular (LV) bypass has become an accepted therapy for patients who cannot be weaned from cardiopulmonary bypass. Approximately 45% of the patients with postcardiotomy cardiogenic shock who are treated with mechanical LV assistance are weaned from the devices, and nearly 50% of these ultimately survive.¹⁻³

An important consideration for appropriate timing of weaning from LV bypass in patients with postcardiotomy cardiogenic shock involves determi-

nation of recovery of native heart function sufficient for maintaining the systemic circulation. Mean aortic pressure, pulmonary arterial pressure, left atrial pressure, ejection fraction, and cardiac index, with and without LV bypass, have been used to assess native heart function.⁴⁻⁷ However, because LV bypass affects ventricular loading conditions, most of the conventional, load-dependent hemodynamic parameters are not necessarily appropriate in assessing native heart recovery. Therefore, it has been difficult to accurately determine suitable myocardial recovery without weaning trials.

The linear end-systolic pressure-volume relationship (ESPVR), described by its slope (E_{es}) and volume intercept (V_0), has been found to be a load-independent index of ventricular contractile state.^{8,9} For the ESPVR to be extrapolated, interventions that change ventricular loading conditions (preload or afterload) are generally necessary.¹⁰⁻¹² During asynchronous pulsatile LV bypass, though, LV loading conditions change with variation of the pumping rate and with each pumping cycle. There-

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fore the ESPVR can be generated during asynchronous LV bypass without any other invasive manipulations to alter ventricular loading conditions. The purpose of this study was to evaluate whether the ESPVR generated during asynchronous LV bypass is a good index of native LV contractility.

Materials and methods

Experimental preparation. A total of 11 Holstein calves weighing from 86 to 112 kg (average 95 ± 8 kg) was studied. All animals involved in this study received humane care in compliance with the "Principles of Laboratory Animal Care" formulated by the National Society for Medical Research and the "Guide for the Care and Use of Laboratory Animals" prepared by the Institute of Laboratory Animal Research and published by the National Institutes of Health (NIH Publication No. 86-23, revised 1985).

With the animal under halothane anesthesia, endotracheal intubation was performed and ventilation maintained by a volume respirator with 100% oxygen. After median sternotomy, the left internal thoracic artery was cannulated to monitor aortic pressure. The azygos and hemiazygos veins were ligated. Reversible occluders were placed around the superior and inferior venae cavae.

As illustrated in Fig. 1, pulse-transit ultrasonic dimension crystals (4 mm diameter), which were made of 5 MHz piezoelectric crystals (LTZ-2, Transducer Products, Goshen, Conn.) and coated with epoxy in our laboratory, were placed in the endocardium across the anteroposterior minor axis, septal-free wall minor axis, and base-apex major axis of the LV. The septal transducer was placed into the ventricular septum just to the right of the left anterior descending coronary artery and positioned as near as possible to the LV endocardial surface midway between the anterior and posterior transducers. The base transducer was positioned in the groove between the left sinus of Valsalva and the left atrium overlying the fibrous continuity between the aortic and mitral valves.

A micromanometer-tipped catheter (model SPC-350, Millar Instruments, Inc., Houston, Tex.) was inserted into the LV through the LV free wall to measure LV pressure. A fluid-filled polyethylene catheter was inserted into the LV in the same manner. The electronic micromanometer in the LV was connected to a pressure transducer control unit (model TCB-500, Millar Instruments, Inc.) and calibrated and balanced at 37°C with a mercury manometer before each experiment. Catheter signal drift was rechecked *in vivo* by comparison with the LV pressure signal obtained simultaneously from the fluid-filled catheter.

Anticoagulation was achieved with an intravenous heparin injection (300 units/kg). The assist pump outflow cannula was sutured to the ascending aorta, and the 51F cannula for assist pump inflow was inserted through a pursestring suture in the left atrial appendage. These cannulas were connected to the inlet and outlet ports of a Pierce-Donachy pneumatic assist pump (100 ml stroke volume) built in our laboratory and LV bypass was initiated.

Fig. 1. Schematic diagram of the heart preparation. Three pairs of piezoelectric crystals are implanted endocardially. *AO*, Aorta; *Inlet*, inlet cannula of LV assist device from left atrium; *IVC*, inferior vena cava; *LA*, left atrium; *LVAD*, left ventricular assist device; *LVP-Millar*, catheter-tipped electronic LV pressure monitor; *LVP-Fluid*, fluid-filled LV pressure monitor; *Outlet*, outlet cannula of LV assist device to ascending aorta; *PA*, pulmonary artery; *RA*, right atrium; *SVC*, superior vena cava.

Digoxin (0.25 mg, intravenously) and lidocaine (2.5 mg/min, intravenously) were administered to prevent arrhythmia during the preparation. If needed, a constant infusion of epinephrine (0.4 to 2.5 $\mu\text{g/kg}$ per minute, intravenously), phenylephrine (0.3 to 1.0 $\mu\text{g/kg}$ per minute, intravenously), isoproterenol (0.002 to 0.01 $\mu\text{g/kg}$ per minute, intravenously), or a combination thereof, was used in some of the preparations to prevent systemic hypotension or pulmonary hypertension. In all cases, these catecholamines were successfully withdrawn before data collection began. To maintain appropriate ventricular filling throughout the experimental protocol, we made minor adjustments of intravascular blood volume by infusion of whole blood.

Experimental protocol. After the preparation had reached a steady state, baseline pressure and volume measurements were taken by changing preload or afterload during transient occlusions of the venae cavae and then the ascending aorta (5 to 8 seconds for each); these data yielded a control ESPVR (control run) from a wide range of pressure and volume data. Asynchronous pulsatile LV bypass was then brought to a maximal rate, termed 100%, as determined by the pump filling in the full to empty mode, and data were obtained without applying aortic or caval occlusions (LV bypass run). Further LV

Table I. Hemodynamic changes before and during left atrial-aortic bypass

	LV bypass: Pump rate (beats/min)/% rate				Control
	71 ± 9/100%	57 ± 7/80%	43 ± 6/60%	28 ± 4/40%	NA
HR (beats/min)	100 ± 4	102 ± 4	101 ± 4	100 ± 4	99 ± 4
EDV (ml)	90.3 ± 10.1*	101.5 ± 10.3*	104.4 ± 10.7*	109.2 ± 11.7	118.9 ± 12.1
EDP (mm Hg)	6.9 ± 1.1*	8.9 ± 1.1*	10.1 ± 1.1*	11.6 ± 1.2	14.0 ± 1.4
ESV (ml)	75.9 ± 8.5*	85.1 ± 8.6	86.2 ± 8.6	87 ± 8.8	92.2 ± 9.8
ESP (mm Hg)	46 ± 4*	60 ± 4	64 ± 4	64 ± 4	68 ± 4
CVP (mm Hg)	6.7 ± 1.0	6.4 ± 0.8	6.4 ± 0.8	6.6 ± 0.7	6.8 ± 0.6
mAoP (mm Hg)	58 ± 4	61 ± 4	59 ± 3	58 ± 3	57 ± 4
CO (L/min)	6.7 ± 0.7	7.0 ± 0.6	7.4 ± 1.0	7.0 ± 0.7	6.8 ± 0.5
+dP/dt (mm Hg/sec)	339 ± 31*	464 ± 30*	472 ± 34*	514 ± 41	577 ± 41

HR, Heart rate; EDV, end-diastolic volume; EDP, end-diastolic pressure; ESV, end-systolic volume; ESP, end-systolic pressure; CVP, central venous pressure; mAoP, mean aortic pressure; CO, cardiac output; +dP/dt, maximal rate of ventricular pressure rise. Mean ± standard error of the mean is indicated.

* $p < 0.05$ compared with control value.

bypass data collections were conducted with the pumping: 80%, 60%, and 40% of the maximal pumping rate. Steady-state equilibrium of the preparation was assured before acquisition of each data set by inspection of real-time pressure-volume loops and E_{es} . The measurements were repeated at an interval of 1 to 2 minutes under the same steady-state conditions to confirm reproducibility of the data.

At the conclusion of the experimental protocol, the animal was put to death. The heart was excised to verify proper positioning of the transducers, and the LV was weighed.

Data analysis. Ultrasonic signals were continuously monitored with a four-channel ultrasonic dimension system (system 6 chassis, Triton Technology, San Diego, Calif.) at a sampling rate of 1302 Hz and a practical frequency response of 0 to 64 Hz. Minimal resolution was 1 mm. The instantaneous distance between each pair of crystals was calculated according to the velocity of sound in blood (1.58×10^5 cm/sec). These dimension signals and the LV pressure signals were sampled at 7 msec intervals for 13 seconds and stored on a floppy disk by a custom-made, on-line data acquisition system. Data were also recorded on a multichannel thermal-pen recorder (Gould 3000 series thermal chart recorder, Gould Inc., Cleveland, Ohio).

Data were analyzed with interactive computer software developed in our laboratory. LV volume was calculated from a modified ellipsoidal shell model:

$$LV \text{ volume} = \pi/6 \cdot D_{AP} \cdot D_{SL} \cdot D_L$$

where D_L is the endocardial base-apex major axis, D_{AP} is the anteroposterior minor axis, and D_{SL} is the septal-free wall minor axis orthogonal diameter of the LV.¹³⁻¹⁶ The contractile state of the LV was assessed by ventricular end-systolic elastance, E_{es} .^{8,9} The ESPVR was generated with linear regression analysis through simultaneous end-systolic pressure and volume data.¹⁰⁻¹⁴ E_{es} was defined as the slope of the ESPVR, and LV unloaded volume (V_0) was determined as the volume intercept of the ESPVR. We determined provisional end-systole at the timing of minimal LV compliance and then used repetitive linear regressions in which the linear estimation of V_0 was used

to determine end-systole as the maximal pressure/(LV volume - V_0) ratio in each cardiac cycle for a subsequent linear regression.¹⁷ We defined end-diastole from electrocardiography. Iteration was continued until E_{es} and V_0 converged to their respective values. All E_{es} values were normalized for 100 gm LV weight. We also measured maximal rate of pressure rise (max dP/dt) as one of the traditional measures of LV contractility.

Statistics. Comparisons of variables among the groups were tested by two-way analysis of variance. When analysis of variance showed statistical significance by F test, mean values were compared by the least significant difference method. Probability values smaller than 0.05 were considered statistically significant. Data are presented as mean plus or minus standard error of the mean unless otherwise indicated.

Results

Table I shows hemodynamic parameters with and without LV bypass. LV bypass did not affect heart rate or cardiac output at any rate of pumping. End-diastolic volume and pressure significantly decreased with increases in pumping rate. Central venous pressure and mean aortic pressure remained unchanged. Inasmuch as the maximal rate of pressure rise (max dP/dt), considered one index of ventricular contractility, is dependent on end-diastolic volume, it decreased as pumping rate increased.

Fig. 2 shows representative pressure and volume tracings and pressure-volume loops from one animal during LV bypass. Pumping rate was fixed at 80 beats/min. LV pressure and volume tracings varied beat by beat as the asynchrony of timing between native heart ejection and ejection from LV bypass altered preload and/or afterload. From these pressure-volume loops, an ESPVR could be generated by linear regression without any other interventions to alter LV loading conditions.

Fig. 2. A, Representative time tracings of LV pressure and volume signals and electrocardiogram. B, Pressure-volume loops of the control (□) and left ventricular bypass (○).

Fig. 3 shows the end-systolic pressure-volume data points and regression line during both control and LV bypass runs for the same heart shown in Fig. 2. As shown in Fig. 3, A, a highly linear, control ESPVR was found by altering ventricular loading conditions with vena caval and aortic occlusions. In each varied setting of pumping rate, linearity was evident, and the E_{es} and V_0 of the ESPVRs were consistent with the E_{es} and V_0 of the other ESPVRs shown in Fig. 3, B to E. This fact is further demonstrated in Fig. 3, F, in which all end-systolic pressure-volume data points are superimposed.

Table II averages the results of linear regression analysis for end-systolic pressure-volume data points from all 11 experiments. During maximal pumping (100%), highly linear ESPVRs were not generally obtained from the relatively narrow ranges of data. V_0 during maximal pumping was significantly lower than V_0 values obtained during the other pumping rates or control runs. However, this difference is understandable because of the need to extrapolate V_0 from 100% pumping rate data that had a relatively poor linear fit (median $r = 0.669$). In contrast, correlation of a linear ESPVR was high during other pumping rates (median $r > 0.8$); in these runs there were no significant differences from control E_{es} and V_0 .

Discussion

Complications such as infection, embolus, and renal failure are associated with mechanical LV bypass. Therefore, attempts are made to wean pa-

tients from the LV bypass as soon as possible. On the other hand, because use of LV bypass as a bridge to heart transplantation has achieved excellent results, continuation of LV bypass until subsequent heart transplantation would be another option for the patient with postcardiotomy cardiogenic shock who is dependent on the device and does not have contraindications to transplantation. Therefore, it is important to assess not only whether the patient can be weaned from LV bypass but also whether he can survive without LV bypass. Assessing the propriety of weaning requires an accurate determination of ventricular performance. Because most of the traditional hemodynamic parameters are load dependent, as shown in maximal rate of pressure rise (max dp/dt), hemodynamics have been assessed during transient discontinuance of LV bypass pumping. Despite such a maneuver, a single hemodynamic parameter does not consistently reflect native heart function, and thus combinations of parameters are needed.⁵⁻⁷ Additionally, abrupt cessation of LV assistance can conceivably overload a recovering ventricle and further impair its function.

The slope of the ESPVR, E_{es} , which we quantified in this study, has been recognized as a load-independent measurement of ventricular performance in both the experimental and clinical settings.^{14, 15} A wide range of LV pressure and volume data is generally necessary to determine the linear ESPVR,^{14, 15} and usually interventions that explicitly change ventricular loading conditions are used to provide this range. Unfortunately, techniques for altering ventricular

Fig. 3. ESPVRs in the control and during indicated pumping rates of LV bypass. % Rate, Percent pumping rate; E_{es} , slope of end-systolic pressure-volume relationship; r , correlation coefficient. Linear regression lines are indicated in each panel.

Table II. Results of linear regression of end-systolic pressure and volume

	LV bypass: % Rate				Control
	100%	80%	60%	40%	NA
Median r	0.669	0.819	0.868	0.899	0.941
E_{es} (mm Hg/ml/100 gm LV)	4.9 ± 0.9	6.9 ± 1.1	8.2 ± 1.1	7.8 ± 1.1	7.4 ± 0.8
V_0 (ml)	$32.7 \pm 8.6^*$	50.0 ± 8.4	55.5 ± 8.4	53.9 ± 8.7	56.7 ± 6.4

NA, Not applied; median r , median of correlation coefficient; % rate, percentage of maximal pumping rate. Mean $\pm$ standard error of the mean is indicated.

* $p < 0.05$ compared with control value.

loading conditions, such as balloon occlusion of the descending aorta or venae cavae, make the measurement of E_{es} complicated.¹⁰⁻¹⁴

When LV bypass is operated in an asynchronous, full-to-empty mode, loading conditions of the native ventricle change beat-to-beat because of competition for preload and changing afterload between LV bypass and the native heart. In theory, therefore, determination of the native heart's ESPVR during asynchronous LV bypass could be made without any

interventions to alter ventricular loading conditions. As revealed in Table II, neither a good, linear fit for the ESPVR nor an accurate representation of E_{es} was generally obtained during 100% pumping; therefore this slope of the ESPVR may not adequately represent native heart contractility. At lower rates, though, a broader range of pressure-volume data and linearity of the ESPVR were preserved. E_{es} and V_0 values were consistent with the control values at the lower rates. As demonstrated by com-

parison of panels *A* and *F* in Fig. 3, pooled pressure-volume data from different pumping rates essentially duplicated E_{es} and V_0 obtained in the traditional (control) manner. Thus the LV load-independent contractility index, E_{es} , can be faithfully estimated during LV bypass without the risk of myocardial injury precipitated by abruptly stopping the pump.

If the native heart cannot yield systemic pressure and cardiac output sufficient for coronary circulation, then the coronary blood supply essentially depends on the output of the LV bypass. Below a critical level, coronary perfusion pressure adversely affects LV contractility.¹⁸ In such a situation, the E_{es} of the native heart estimated during LV bypass might not be the same as the E_{es} derived with the pump turned off, because deterioration in the coronary pressure and flow after weaning from LV bypass would depress the native heart function. The presence of this degree of ventricular dysfunction could be detected by decreases in E_{es} as pumping rate is gradually lowered, because our method enables us to evaluate E_{es} at each pumping rate. We did not specifically investigate this possibility in this study, and further experiments are needed to address diagnostic information potentially made available by pump rate changes.

Because we did not change native heart contractility, we cannot estimate the sensitivity of the measured E_{es} in reflecting acute changes in LV contractility during LV bypass. Previous experimental and clinical experience has shown that E_{es} can reasonably characterize acute changes in LV contractility,¹⁷ and we suspect that E_{es} derived in this new manner would behave similarly. Additional study of E_{es} during LV bypass at increased and reduced contractilities, however, is needed to clarify this problem. In addition, we did not induce heart failure in this study. Validity of this method in the failing heart is needed in the experimental and clinical settings.

The analysis of ventricular function by the pressure-volume relationship provides a load-independent measure of LV contractility. However, volume measurement of the ventricle is important to achieve a reasonable ESPVR. We used ultrasonic crystals to calculate ventricular volume in this study. Implantation of the crystals is complicated, however, and not practical in a clinical setting. Although further development of transesophageal echocardiography would provide an LV volume measurement, the technique has not been established yet.

The recently developed conductance catheter enables on-line measurement of continuous pressure-volume data.¹⁹ At present the conductance catheter is the only option for instantaneous volume measurement in the clinical setting. We will have to determine the best techniques for obtaining pressure-volume data when we apply our method to an LV assist patient.

In conclusion, the LV contractility index, E_{es} , obtained without applying loading interventions during asynchronous LV bypass faithfully estimates native heart contractility.

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