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Determination of left ventricular end-systolic pressure-volume relationships by the conductance (volume) catheter technique

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ABSTRACT Using a multielectrode conductance catheter to estimate continuous left ventricular volume we determined the end-systolic pressure-volume relationship (ESPVR) in situ in open-chest anesthetized dogs. Dogs (n = 8) were studied in the control state and after pharmacologic sympathectomy (hexamethonium) and surgical vagotomy both before and after the administration of dobutamine. ESPVR was measured during brief (5 to 6 sec) preload reduction by balloon occlusion of the inferior vena cava (IVCBO). The relationship was highly reproducible. The slope (E_{es}) and volume intercept (V_o) (mean ± SD) in the control series were 5.8 ± 3.6 mm Hg/ml and 6.5 ± 12.5 ml, respectively. Upon release of the IVCBO (preload recovery), E_{es} was 7.7 ± 3.6 mm Hg/ml and V_o was 12.4 ± 9.6 ml ($p < .01$). Autonomic blockade produced a 50% reduction in E_{es} and a concomitant decrease in V_o ($p < .01$), and eliminated the difference between ESPVR generated by preload reduction (IVCBO) and preload recovery (IVCBO release). Subsequent dobutamine infusion increased E_{es} to 6.1 ± 3.5 mm Hg/ml and V_o to 4.1 ± 6.9 ml, consistent with reported changes of the ESPVR with positive inotropic intervention. A small artifact of right ventricular filling was observed in the left ventricular volume catheter signal, but this did not appreciably alter the ESPVR. These results demonstrate the feasibility of the determination of ESPVR in situ by the conductance catheter and brief IVCBO and underline the importance of the use of rapid load changes to minimize reflex activation during the measurements.
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SINCE THE initial description of the end-systolic pressure-volume relationship (ESPVR) in isolated canine ventricles,[1, 2] investigators have confronted several obstacles in an attempt to measure and characterize this relationship in intact hearts.[3–5] While the ESPVR is generally accepted as an index of ventricular contractile state insensitive to load,[5] the major impediment to its widespread clinical use has been the lack of practical means to make the necessary measurements.

Assessments of ESPVR in situ have relied extensively on echocardiographic, radiographic, or sonomicrometric dimension measurements. The relationship has often been expressed in terms of a dimension or volume estimated with the use of geometric modeling assumptions.[6–12] Such volume estimates have been successfully compared with flow and stroke volume data,[13–15] but they are by nature somewhat sensitive to changes in ventricular shape and orientation, they do not provide an instantaneous volume signal since off-line numerical processing is required, and in the case of sonomicrometry, they are not well suited to general clinical investigation. Alterations in loading necessary to determine ESPVR have often been achieved with vasoconstrictors and dilators.[6–8, 10] Pharmacologic manipulation of loading conditions, which requires at least several minutes for stabilization of a load change, makes repeated determinations of ESPVR difficult, and might provoke cardiovascular reflexes altering the pressure-volume relationship. Generation of a rapid loading change such as by transient inferior vena caval occlusion (IVCBO) is much less likely to cause fully activated reflex alterations in ventricular contractility. This technique has been used in several recent studies[13, 14] and enabled the determination of ESPVR in conscious dogs.

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Determination of ESPVR would ideally utilize easy and rapid methods to accurately measure left ventricular pressure and volume and a technique of altering load without evoking a reflex alteration in contractility. While high-fidelity semiconductor transducers have provided pressure measurements, a similar means to record instantaneous volume has not been previously available. Recently, a multielectrode catheter has been developed by Baan et al.[15] that continuously measures instantaneous left ventricular conductance, from which left ventricular volume can be estimated. Studies in which this volume signal was compared with absolute volume in an isolated beating heart,[16] or with cardiac output measured independently,[17] have indicated a strong linear correlation between them. The catheter requires careful calibration since the total signal combines left ventricular cavity conductance with conductance of the ventricular wall and other structures outside the ventricle. Yet the unique advantage of providing continuous instantaneous volume information, when combined with left ventricular pressure micromanometry, enables an easy and rapid determination of ESPVR.

In the present study we investigated the ESPVR in eight left ventricles in situ using the volume catheter and IVCBO in anesthetized open-chest dogs. Specifically we sought to clarify (1) the capability and limitations of the volume catheter technique in measuring ESPVR in situ, (2) the response of ESPVR in situ to alterations in inotropic state, (3) evidence for reflex activation during IVCBO and the time span over which reflexes are not likely influential, and (4) the reproducibility of such rapidly determined ESPVRs.

Methods

Eight healthy adult mongrel dogs (20 to 25 kg) were anesthetized with intravenous thiopental (20 mg/kg), subcutaneous chlorolose (80 mg/kg), and urethane (800 mg/kg). Morphine sulfate (1 mg/kg iv) was administered if the resting heart rate exceeded 150 beats/min after induction of anesthesia.

Volume catheter technique. A full description of the principles and technique of the Baan volume catheter method has appeared elsewhere.[15–17] Briefly, we used specially designed No. 8F woven Dacron catheters that had eight equally spaced platinum ring electrodes at the distal end (Webster Labs). These electrodes had a width of 1 mm and were spaced 1 cm apart on one catheter and 0.87 cm apart on another to accommodate ventricles of different size. When positioned in the left ventricle, the catheter lay parallel to the long axis, with the most distal electrode placed at the apex and the most proximal electrode just cephalad to the aortic valve (figure 1, *insert*). An alternating current (0.07 mA root-mean-square at 20 kHz) passed through the distal and proximal electrodes. Five successive pairs of the intervening electrodes (second through seventh) measured voltages that were assumed to delineate five intraventricular cylindrical segments with an equal height L. These voltages were proportional to conductances and the sum of the five segment conductances [G(t)] was considered related to left ventricular volume by the expression

$$V(t) = (1/\alpha) \cdot (L^2/\sigma) \cdot G(t) - V_p \qquad (1)$$

In this expression σ represents the conductivity of blood surrounding the catheter in the ventricular cavity. V_p is a volume signal error due to conduction of the alternating current through the left ventricular wall and other tissues, and α is an empirical slope coefficient for the $V(t) - G(t)$ correlationship, which tends to vary among hearts within a range from 0.8 to 1.1.[16, 17] Sigma can be directly measured and V_p and α can be estimated by calibration procedures described in the Appendix. An analog computer/stimulator (Sigma 5, Leycom, Holland) provided the

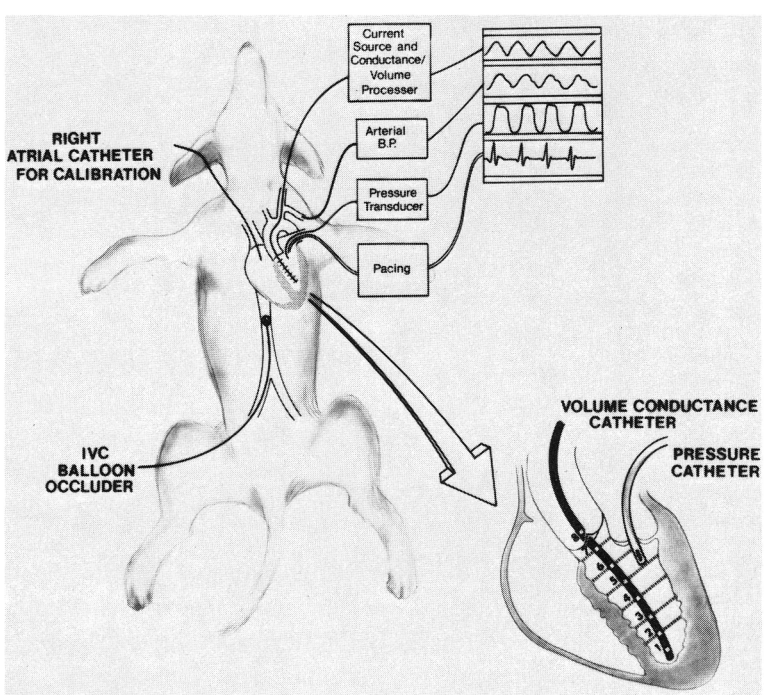

FIGURE 1. Experimental preparation (see text for full description). The *insert* shows the position of the volume-conductance catheter in the left ventricle. The dashed lines indicate the successive volume segments. Electrodes are numbered. Current is passed between electrodes 1 and 8, and conductance is measured with electrodes 2 to 7. A cone segment is automatically added to the lowest measured segment (2–3) to approximate apical volume.

current source and processed the segment conductances, producing a continuous instantaneous analog volume signal.

Preparation. After anesthesia, dogs were intubated and ventilated by a fixed-volume positive-pressure respirator (Harvard Apparatus). Animals were instrumented with a central venous cannula, a No. 8F introducer sheath (Cordis) in the left carotid artery, a latex balloon occluder catheter placed in the inferior vena cava through the right femoral vein, and a central arterial pressure cannula positioned in the left brachial artery (figure 1). The volume catheter was advanced under fluoroscopic guidance into the introducer sheath and passed retrograde through the aortic valve until the distal electrode lay at the left ventricular apex. The inferior vena caval balloon was positioned above the diaphragm and just below the inferior vena caval–right atrial junction.

The chest was opened through a left lateral thoracotomy. A small incision was made in the pericardium and left atrial appendage through which a transducer-tip pressure catheter (Millar) was advanced into the left ventricular chamber. The pressure transducer was calibrated at the start and conclusion of each experiment (drift <3 mm Hg). Atrial pacing wires were attached and the heart was returned to a normal resting position, with the pericardium essentially intact. Atrial pacing (Grass SD9) maintained a constant heart rate during the measurement of ESPVR. Control paced heart rates ranged between 140 and 160 beats/min due to sympathetic stimulation of the preparation. This rate fell to 120 to 140 after autonomic blockade. ESPVR in isolated supported hearts has not been found to significantly vary due to chronotropic effects within this range of heart rates.[18] Continuous recordings of left ventricular pressure, arterial blood pressure, the electrocardiogram, and left ventricular volume were made on a eight-channel analog recorder (Gould, Model 480). Arterial blood gases were periodically analyzed and ventilatory adjustments were made to maintain P_{O_2} above 70 mm Hg and P_{CO_2} at about 30 mm Hg.

For measurement of ESPVR, the inferior vena cava was transiently occluded by inflating the intraluminal balloon with 10 to 15 ml of air. The pressure-volume signals during a 10 sec IVCBO and the subsequent 5 to 6 sec recovery period after balloon deflation were continuously recorded. Ventilation was held at end-expiration during the measurements. Three IVCBO runs were performed under each experimental condition. A recovery period of 3 to 5 min was provided between runs. Data were digitized at 200 Hz (PDP 11/23) and stored on magnetic tape for future processing.

Protocol. Dogs were first studied under the control condition and with reflexes intact. Determinations of the volume offset error V_p (figure 1) were made (see Appendix) after the control runs as well as after each subsequent intervention. After the control study, hexamethonium chloride (35 mg/kg) was infused intravenously and bilateral cervical vagotomy was performed to block autonomic reflexes. Arterial systolic pressure was maintained at a level of at least 80% of control by volume loading with 10% dextran and normal saline. IVCBO runs were then performed as in the control series. Positive inotropic stimulation was then provided by intravenous dobutamine at 2 to 3 μg/kg min. This rate was adjusted to produce a near 100% increase in maximum dP/dt at a similar end-diastolic volume. Heart rate increased slightly after dobutamine and sometimes exceeded the selected pacing rate. The order of the above interventions was not randomized due to their irreversibility.

To examine the influence of shifts in right ventricular volume on the left ventricular ESPVR as measured with the volume catheter, five of the eight animals were further instrumented. A large-bore cannula with multiple side holes was placed in the right or left atrium and connected through a roller pump to a volume reservoir. Thorough mixing of blood and a heparinized saline-dextran solution was achieved within the reservoir before the study. A snare was placed around the pulmonary artery to permit transient pulmonary arterial occlusion. Reductions in left ventricular preload and concomitant measurements of ESPVR were then made by randomly inducing IVCBOs, right atrial hemorrhage, left atrial hemorrhage, and pulmonary arterial occlusion.

At the conclusion of each experiment, animals were killed with KCl arrest of the heart, and the position of each catheter was confirmed.

Data analysis. Data were analyzed off-line by computer. Values for dP/dt were calculated digitally. Digitized pressure and volume values were smoothed with a three-point moving average before calculation of instantaneous elastance, $P(t)/(V(t)-V_o)$ or dP/dt calculations. The end-systolic pressure-volume point of each cycle was selected as the data point with the maximum pressure/volume ratio. ESPVR was generated by subsequent linear regression of these chosen points. After IVCBO, 6 or 7 beats were usually required before left ventricular pressure decreased. The data used to construct each ESPVR were taken after an initial 3 to 4 mm Hg decrease in end-systolic left ventricular pressure had occurred. An average of 13 subsequent cycles were used, representing a mean data collection period of 5.5 ± 0.4 sec. After balloon deflation, several beats were again required before left ventricular pressure began to rise. The ESPVR upon IVCBO release was then determined over the next 3 sec. Linear regression of end-systolic pressure on end-systolic volume analysis was performed for each run individually. The calculated slopes and volume intercepts were compared by a two-way analysis of variance and the Newman-Keuls method for multiple comparisons between means. Differences reported as significant were at the $p < .05$ level. Statistical analysis was performed by computer (MV8000, Data General) using the SAS statistical package.[19]

Results

Control mean resting values for peak left ventricular pressure and maximum dP/dt were 105 ± 10 and 2769 ± 700 mm Hg/sec, respectively. Mean end-diastolic and end systolic volumes were 53.7 ± 14.2 and 32.4 ± 14.1 ml, respectively, with a stroke volume of 21 ± 4 ml and estimated cardiac output of 2.6 ± 0.4 liters/min, at a mean heart rate of 156 ± 20 min^{-1}. These values are in agreement with previously reported baseline measurements in anesthetized dogs.[20] The somewhat reduced ejection fraction (38%) was likely associated with the anesthetized conditions.

An example of the experimental record during an IVCBO run is shown in figure 2. Maximum reduction in left ventricular volume after IVCBO generally occurred within 14 to 16 successive cycles (or 6 sec). The ESPVRs were well described by a linear relationship ($r^2 = .98$, SEE = 4.0 mm Hg).

Studies with intact autonomic reflexes. Figure 3, *A* shows an example of the pressure-volume loops during an IVCBO in the control (reflexes intact) state. The initial few cycles demonstrated a 3 to 4 ml reduction in volume without a concomitant change in end-systolic pressure. After this, a linear relationship between declining end-systolic pressure and volume were ob-

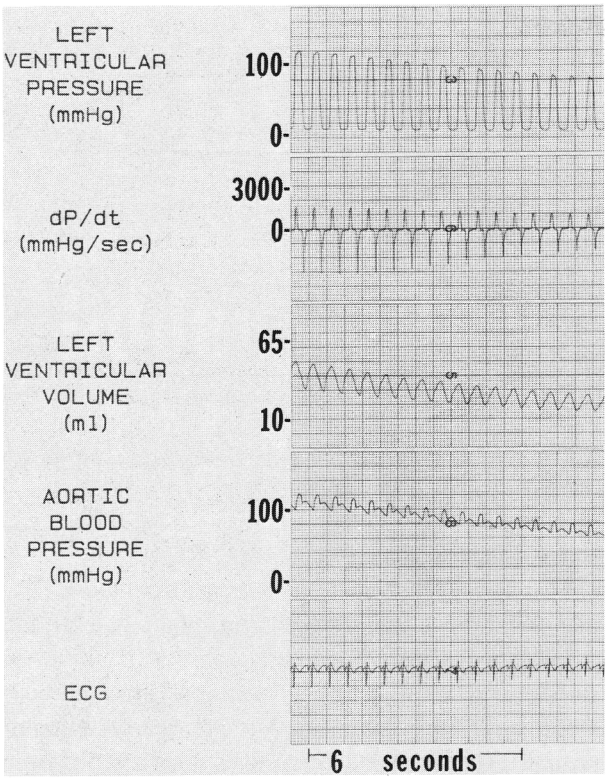

FIGURE 2. Example of data recorded from an animal during IVCBO. After an initial reduction in peak left ventricular pressure, ESPVR was determined during the subsequent 5 to 6 sec of IVCBO.

served. The slope, volume intercept, and r^2 are indicated in the figure. On release of the balloon occluder (figure 3, *B*), left ventricular volume was restored. The resultant ESPVR also showed a significant shift toward increasing slope and volume intercept as compared with that determined during preload reduction. This response did not seem to be a result of the open-chest preparation since we have observed similar results in several closed-chest anesthetized animals (n = 4). In these animals, the ESPVR during IVCBO (5.95 ± 2.4) also increased significantly by 48.7% when redetermined during subsequent IVCBO release in the control (unblocked) state.

Table 1 provides the mean data from all eight ventricles. Equal numbers of separate runs for each animal were entered into the mean and subjected to two-way analysis of variance. Data are presented as mean ± SD. Mean slope determined during preload recovery after balloon deflation (control (R) in table 1) increased by 33% over that measured during IVCBO. Concomitantly, mean volume intercept increased 6 ml.

Effect of autonomic blockade. Hexamethonium chloride and cervical vagotomy blocked sympathetic and parasympathetic innervation, reducing baseline inotropic stimulation and peripheral arterial and venous tone. Intravenous fluid was provided such that the mean end-diastolic volume both before and after administration of hexamethonium was not significantly altered (mean 54 vs 56 ml). The net effect of this combined change in afterload and contractility was no significant change in ejection fraction, with a fall in mean peak left ventricular pressure of 21 ± 22 mm Hg. The ESPVRs after autonomic blockade were substantially altered from control, with a 43 ± 16% reduction in slope and decrease in volume intercept by a mean of 11 ± 2 ml (figure 4). The marked extent of this reduction likely reflected the initial heightened baseline sympathetic tone associated with the open-chest anesthetized preparation. In further contrast to control, the ESPVRs determined during IVCBO (figure 4, *B*) and following its release (figure 4, *C*) no

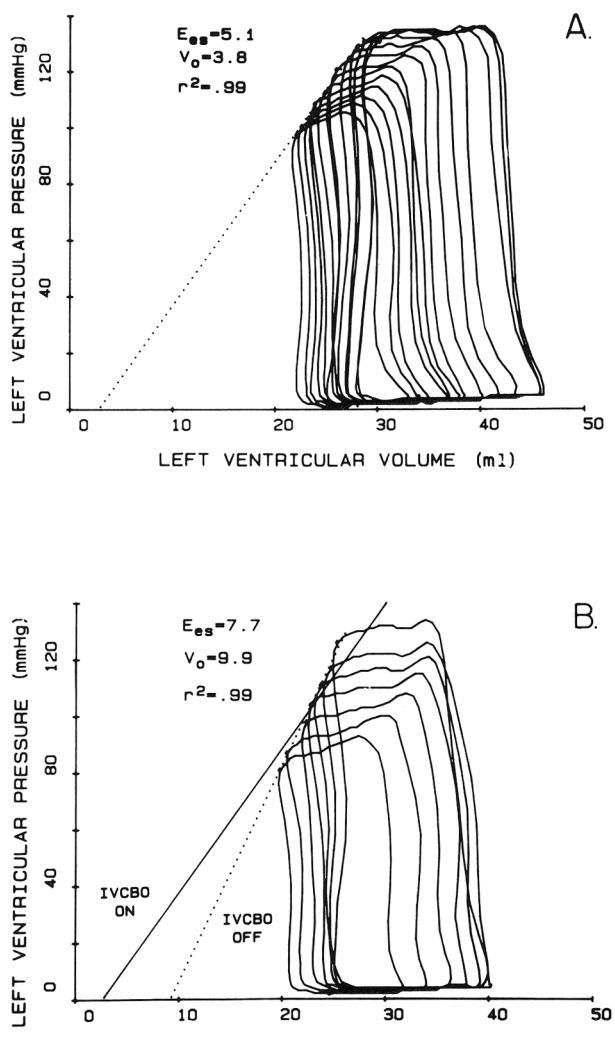

FIGURE 3. *A*, Representative pressure-volume data and ESPVR from a ventricle under control (reflex intact) conditions. Slope (E_{es}), volume intercept (V_o), and r^2 are shown. *B*, ESPVR generated during preload recovery after deflation of the inferior vena caval balloon occluder. A shift in both slope and volume intercept is seen. The ESPVR determined with preload reduction (solid line) is provided for comparison.

TABLE 1
ESPVR and hemodynamic data for control and post–autonomic (A) blockade conditions (n = 8)

	Control	Control (R)	A blockade	A blockade (R)	Dobutamine	Dobutamine (R)
Heart rate (min^{-1})	152±20	156±21	134±15	134±15	149±11	150±11
Slope (mm Hg/ml)	5.8±3.6	7.7±3.6[B]	2.8±1.3[B]	3.4±1.8[B]	6.1±3.5	6.1±3.1
Volume intercept (ml)	6.5±12.6	12.4±9.6[B]	−1.1±8.3[B]	5.2±9.2	5.1±5.2	7.5±4.1
r^2	0.97±0.006	0.95±0.009	0.97±0.006	0.96±0.008	0.96±0.005	0.92±0.04
End-diastolic volume (ml)[A]	54±14		52±15		49±19	
Ejection fraction (%)[A]	38±8		36±9		42±8	
Maximum dP/dt (mm Hg/sec)[A]	2769±700		1703±239[B]		3148±611	

Dobutamine was administered after achieving autonomic blockade (see text).
Values are mean ± SD.
(R) = data determined immediately after IVCBO release (restoration of venous return).
[A]Measured before IVCBO.
[B]$p < .05$ compared with control values.

longer displayed significant differences (for comparison see figure 3).

Effect of dobutamine on ESPVR. Dobutamine was infused after achieving autonomic blockade to enhance left ventricular contractility to near-control levels. This produced a small mean increase in peak left ventricular pressure (16 mm Hg), and a rise in maximum dP/dt of 85% at a similar end-diastolic volume. The resulting ESPVR displayed both an increase in slope to control levels, and a small increase in volume intercept (figure 5). The hysteresis in ESPVR with IVCBO and IVCBO release remained absent despite the return of catecholaminergic drive.

Reproducibility of ESPVR within the same heart. The overall variability between repeated ESPVR determinations in the same animal under the same condition was small. Figure 6 displays the data from two examples for three successive runs under the control and post–autonomic blockade conditions. Variabilities in slope are provided. Despite these variabilities, the end-systolic pressure-volume points are nearly superimposable. The slope and intercept estimates varied from run to run despite little real physiologic difference in the measured data, most probably due to the sensitivity of the regression parameters to small shifts in individual ESPVR points and to the inability to measure the relationship over the entire loading range. Table 2 provides mean data for all eight ventricles and lists absolute change and percentage change normalized to the initial reference values. With normalization, the influence of intra-animal variability was reduced. Under control conditions slope demonstrated a 16 ± 13% mean increase ($p < .05$) after repeated measures. After

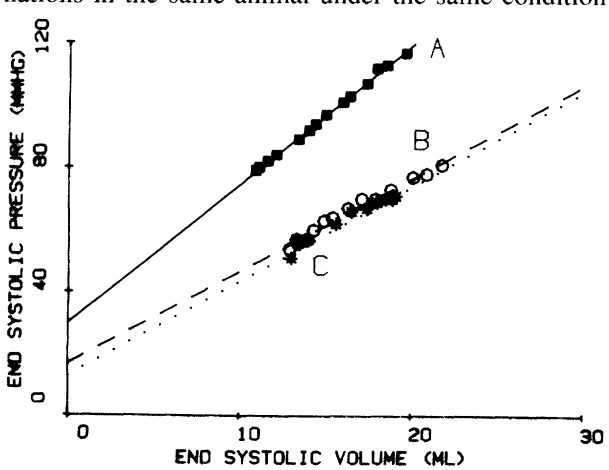

FIGURE 4. ESPVR from a representative animal before and after autonomic blockade. Control data (*A*) are shown during IVCBO. A reduction in slope was seen after blockade. These data are displayed both during IVCBO (*B*), and during subsequent preload recovery (IVCBO release, *C*). In contrast to control, no increase in E_{es} was observed when it was measured during preload recovery as compared with during IVCBO.

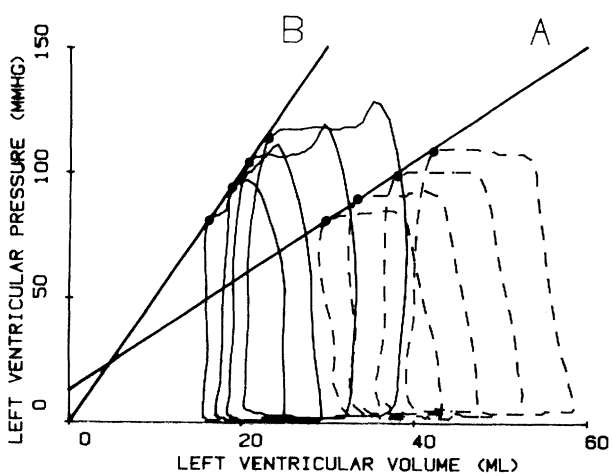

FIGURE 5. Representative pressure-volume data and ESPVR from an animal after autonomic blockade, before (dash lines) and after (solid lines) the administration of dobutamine. Dobutamine produced a marked increase in slope, and a small rightward shift in volume intercept.

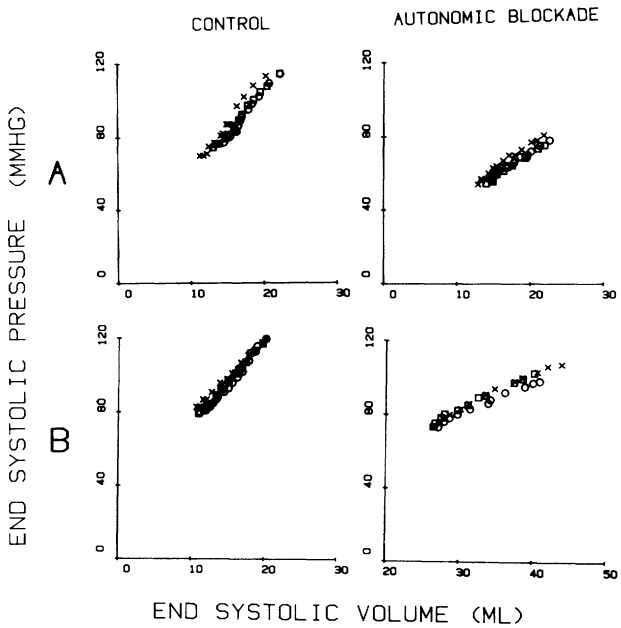

FIGURE 6. Reproducibility of ESPVR determinations in the same ventricle. Data are shown for three successive determinations in two animal examples under control conditions and after the administration of hexamethonium and cervical vagotomy. Each determination was separated in time by 3 to 5 min. Slope variability in example *A* was 6.3%, and it was 10.3% in example *B*.

autonomic blockade, no significant change was seen ($-2 \pm 6\%$). Due to the small initial volume intercept values and the occurrence of negative estimates, changes in volume intercept could not be normalized. To provide a more valid comparison between the placement of the individual ESPVRs along the volume axis, V_{mean} was used. The mean end-systolic pressure for the measured data was determined, and the corresponding end-systolic volume (V_{mean}) for each ESPVR was calculated at this pressure value. When changes in V_{mean} were normalized to the reference run, volume shift was less than $5 \pm 5\%$ for both control and post-blockade data. As shown in table 2, this represented a real volume change of less than 2 ml.

Influence of right ventricular volume on the measured ESPVR. At the onset of each IVCBO, a small reduction in volume without a concomitant fall in left ventricular pressure was observed. This observation led us to suspect potential artifacts in the volume catheter signal. Since IVCBO lowered right ventricular volume before affecting left ventricular filling, this right ventricular volume change might influence the catheter signal several cycles before and possibly during the determination of ESPVR. To assess this potential influence, we compared the ESPVR determined with the use of four different modes of reducing left ventricular preload: IVCBO as previously described, right or left atrial hemorrhage, and pulmonary arterial occlusion. Studies were performed after autonomic blockade. The results are summarized in table 3. The initial shallow portion of ESPVR representing the first 5 to 6 beats after IVCBO was not observed when left ventricular preload was reduced either by direct volume removal from the left atrium or by pulmonary arterial occlusion (figure 7). No significant change was observed between the ESPVR determined after IVCBO and that after right atrial hemorrhage. Direct removal of blood volume from the left heart resulted in a slope and intercept only slightly larger than those during IVCBO. In contrast, when the pulmonary artery was constricted, a sharp rise in both the slope and volume intercept was seen ($p < .05$).

Discussion

Our study demonstrated that, with the use of the conductance catheter technique for left ventricular volume determination[15–17] and transient IVCBO, ESPVR could be determined reproducibly in open-chest anesthetized dogs. Comparison of ESPVRs during preload reduction (IVCBO) and preload restoration (IVCB deflation) revealed substantial differences when reflexes were intact. This hysteresis was essentially eliminated after autonomic blockade while both the slope and volume intercept of ESPVR were significantly re-

TABLE 2
Reproducibility of ESPVR — absolute and normalized changes in slope and V_{mean} relative to an initial reference run

	Control		After blockade	
	E_{es}	V_{mean}	E_{es}	V_{mean}
Reference values	5.4±3.4	26.6±11.2	3.1±1.4	29.6±8.7
Repeat 1 (% Δ)	10±19	1.5±5.0	−3±8	5±7
Absolute Δ	0.51±0.87	0.17±1.0	−0.06±0.26	1.6±2.1
Repeat 2 (% Δ)	16±13	0.6±5.0	−4±11	6±7
Absolute Δ	0.86±0.97^A	−0.1±1.0	−0.1±0.27	1.9±2.4

E_{es} = slope; V_{mean} = mean end-systolic volume (of ESPVR) over the measured data range.
^A$p < .05$.

TABLE 3
Comparison between ESPVR slope (E_{es}) and volume intercept (V_0) determined during IVCBO and after three different methods of left ventricular preload reduction

	IVCBO	Right atrial hemorrhage	IVCBO	Left atrial hemorrhage	IVCBO	Pulmonary artery occlusion
E_{es} (mm Hg/ml)	2.8±0.4	2.8±0.5	3.0±1.0	3.2±0.8	3.1±0.6	8.5±2.1
V_0 (ml)	10.1±4.5	9.3±4.6	3.2±9.2	5.3±10.8	5.3±1.5	22.6±5.3

duced. Inotropic enhancement with dobutamine increased both parameters toward control, yet the hysteresis remained absent. We also found that influences of right ventricular volume change on the catheter volume signal during IVCBO led to only minimal errors in determination of ESPVR.

As shown in figure 4 and table 1, we found substantial and consistent increases in slope and volume intercept of the ESPVR determined after release of IVCBO compared with those values obtained during IVCBO. One explanation is that the fall in systolic pressure produced by the preload reduction stimulated baroreceptor reflexes, inducing an increase in myocardial contractility.[21–23] The hysteresis was essentially eliminated after autonomic blockade, and this remained so even after contractility had been restored to control levels by dobutamine. Since any mechanical effects of the inferior vena caval balloon or possible influences of right ventricular volume reduction on the volume catheter signal during IVCBO would have been similar both before and after autonomic blockade, they could not explain the hysteresis. Since we maintained heart rate constant, the contribution of chronotropic change to contractility was absent.

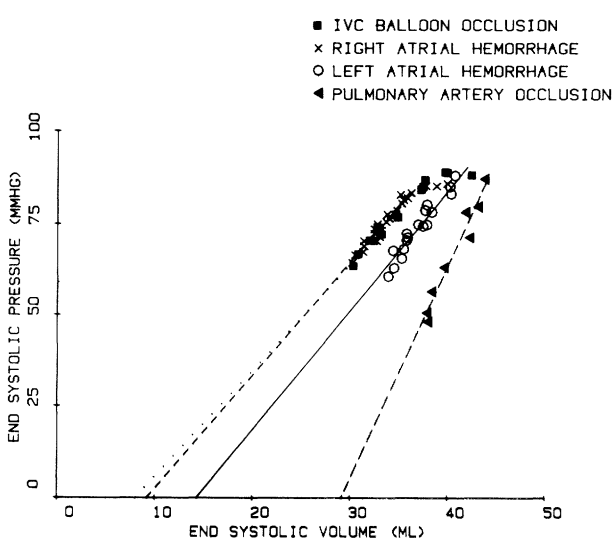

FIGURE 7. ESPVR determined by four different methods of lowering left ventricular filling volume. The various methods are identified on the figure.

It is possible that decreases in coronary perfusion pressure lead to changes in the ESPVR with acute preload reduction. At peak left ventricular pressures of around 70 mm Hg, autoregulation of coronary flow becomes compromised,[24] and the ventricle is made vulnerable to ischemia. In an isolated heart study, Sunagawa et al.[25] demonstrated that if coronary perfusion pressure was permitted to decrease simultaneously with left ventricular pressure during the measurement of ESPVR, then the ESPVR was nonlinear in a pressure-volume range below a critical pressure of 60 mm Hg, and the slope in this low range was seemingly greater than control. Arterial diastolic pressure and hence coronary perfusion pressure was reduced in our studies during IVCBO; thus the rise in slope seen after balloon deflation might have only been an apparant increase due to some degree of global ischemia. However, in several animals the increase in slope was observed at pressures well above 70 mm Hg. Most importantly, the lack of a similar increase in slope after autonomic blockade when left ventricular pressure was lower to start with and the potential influences of myocardial ischemia should have been greater makes it highly unlikely that reduced coronary perfusion played a major role in the hysteretic change in slope.

Despite evidence of development of autonomic reflex influences after 10 sec of sustained preload reduction, the ESPVR determined during the initial 4 to 6 sec of IVCBO likely represented a reliable measurement of left ventricular function. Because autonomic blockade was associated with a reduction in inotropic state, direct comparisons of ESPVR with control values could not be made. It is unlikely that substantial reflex inotropic stimulation occurred within the first few seconds of preload reduction, but the data cannot truly rule out this possibility. We believe our data emphasize the importance of rapid loading changes in attempting to minimize reflex contributions to the measured pressure-volume relationships. Future studies, using surgically isolated carotid and aortic barore-

ceptor circuits with controlled receptor area pressures, may precisely elucidate their influences on ESPVR measurement.

Effects of altered inotropic state. Changes in inotropic state and those in the slope of the ESPVR were found to be directly related. This finding was consistent with responses of slope reported in studies of excised canine ventricles,[1, 2] hearts in situ,[13] and in humans.[6, 10] In general, we found a small but consistent change in the extrapolated volume intercept as well. When a large variation in slope occurred, it was usually accompanied by a shift in the intercept in the same direction. Several previous investigators have noted similar changes.[10, 13] However, the large extent of the extrapolation makes it difficult to interpret the changes in intercept. This extrapolation, the use of linear modeling of possibly curvilinear data, and possible errors in the estimate of offset correction factor V_p of the volume catheter likely contributed to the large variation in estimates of intercept, including the negative values occasionally observed.

Hexamethonium produced a combined reduction in preload and afterload. Although hexamethonium does not have a direct negative inotropic effect,[26] by markedly reducing baseline sympathetic tone to the heart it is known to reduce cardiac performance indexes such as stroke work or maximum dP/dt.[27] In an earlier study,[21] slope was found to decrease from control by 31% after cerebral infarction, with total loss of sympathetic drive. In our anesthetized open-chest preparation, the fall in slope was likely enhanced.

Because of the markedly altered load associated with ganglionic blockade, ejection fraction reflected cardiac contractile function very poorly. Average response of maximum dP/dt for the eight animals showed a mean decrease of 33 ± 27%; however, individual responses were variable. In contrast, slope fell significantly in every animal studied, with an average decrease of 43 ± 16%. When positive inotropic stimulation was provided with dobutamine, slope increased as did mean maximum dP/dT, while ejection fraction showed only a small and insignificant rise. Thus, as in isolated ventricles, the slope of the ESPVR provided a superior index of ventricular performance over isovolumetric and ejection phase indexes when substantial loading changes were present that counteracted and thus hid a contractility change.

Evaluation of the ESPVR under differing conditions of left ventricular unloading. Studies using the Baan volume conductance catheter have generally demonstrated a small but measurable influence of maximal variations in the filling volume of the right ventricle on the left ventricular volume signal on the order of 10%.* We noted that upon IVCBO, the first several pressure-volume loops were nearly always characterized by a horizontal shift to the left (equivalent to a decrease of 5 to 7 ml in end-diastolic volume and end-systolic volume), unaccompanied by any fall in left ventricular pressure or stroke volume. Possible explanations of this effect included right ventricular–left ventricular interaction mediated through septal unloading,[28, 29] or an artifact of the catheter signal registering the acute right ventricular volume decrease before preload reduction reached the left heart.

In order for right ventricular–left ventricular interaction to explain the very flat initial portion of the ESPVR, we would have to postulate that this altered geometry and regional loading immediately increased the end-systolic pressure-volume relationship beat by beat until a stable plateau level was reached. In a previous study in isolated perfused canine hearts[30] changes in right ventricular volume loading only minimally altered the ESPVR and produced only a slight rightward shift with decreasing right ventricular volume. Thus, it seems unlikely that septal unloading can explain the initial leftward shift of the ESPVR on IVCBO.

Artifactural effects on the left ventricular volume signal due to changes in right ventricular volume seem likely. No difference was observed in ESPVR determined with IVCBO or right atrial hemorrhage; thus direct influences of balloon distension were not significant. If right ventricular volume contributed some percentage to the left ventricular signal, then increases in right ventricular volume after pulmonary arterial occlusion would lead to an overestimation of end-systolic left ventricular volume during the simultaneous left ventricular preload reduction, and the slope and intercept of the ESPVR would appear greater than their true values. A similar artifact but in the opposite direction could then be postulated during IVCBO. The slope of the measured ESPVR would be smaller than that of the true ESPVR due to a gradual fall in right ventricular volume and a decreasing offset contribution. When we compared ESPVR derived with IVCBO to that obtained with left atrial and left ventricular hemorrhage only a very slight slope difference was observed. Thus, despite a potential error in the ESPVR determined during IVCBO occlusion, this error appeared to minimally alter the measurements as compared with the large offset when right ventricular volume was markedly increased. These observations suggest potential limita-

*Baan J: Personal communication.

tions of the present technique in assessing right ventricular–left ventricular interaction, particularly if large increases in right ventricular loading are produced.

Some additional error in estimating the absolute volume is expected to result from the lack of ability to actually measure the slope coefficient α (see equation 1). Since α has been found to vary from heart to heart, probably due to geometric and extracardiac conduction effects, this variability would contribute primarily to interanimal variation. Comparisons of data from the same animal, such as those after the various pharmacologic and surgical interventions used in the present study, would not be significantly affected by this factor. Geometric changes within the same heart, such as those associated with ejection at different filling volumes, have not been found to significantly alter the accuracy of the volume catheter estimate.[16]

To a large extent, efforts to determine ESPVR in situ have evolved along with improved techniques for measuring left ventricular dimensions and volume. Early studies used contrast radiography,[6, 10] which was limited by the physiologic effects of the contrast media itself as well as by the geometric assumptions needed to convert ventricular silhouette into volume.[11, 12] Nuclear ventriculography[7] requires minutes for image acquisition, thus preventing its use with rapid loading changes. While the sonomicrometer[9, 13, 14] provides excellent regional dimension signals, they are not readily applicable to human investigations. The use of echocardiography[7, 8] has often been limited by image quality as well as geometric assumptions. Despite their shortcomings, much of the data obtained with these techniques have yielded relationships of end-systolic pressure to volume (or dimension) that provide useful information about ventricular contractile state. The volume catheter used in the present study provides three important advantages over these techniques. First, it generates an instantaneous signal providing immediate information on ventricular performance, allowing rapid loading changes to be used, and enabling examination of quick-response phenomena such as postextrasystolic potentiation. Second, it is essentially free from pure shape change influences, as we have previously demonstrated.[16] Finally, while it requires invasive techniques routine to cardiac catheterization, it has been used in man.[17, 31]

Combining the conductance catheter with brief IVCBO, we have shown that ESPVR can be easily and reproducibly determined in situ. The data suggest that rapid load alterations (<8 sec) are important for avoiding reflex activation. The ESPVR measured by the present method showed a good degree of short-term reproducibility within a given subject, which has not been a uniform finding in previous studies. We believe this relates to the rapid and reversible load alteration and improved accuracy of the volume signal used in the present study. The anesthetized preparation used in the study may have also contributed to a greater reproducibility than might be present in conscious animals. A small increase in slope was seen after repeated IVCBOs in the presence of intact reflexes, and some caution must be exercised when responses to several interventions are compared serially. Finally, small influences of right ventricular volume on the left ventricular catheter signal did not appear to significantly alter the measured ESPVR, although this effect can be greater in settings of marked right ventricular enlargement. We expect that use of a similar system and technique in man will enable measurement of ESPVR and provide more reliable information about contractile state of the ventricle and its systolic and diastolic performance than possible with other volume estimation methods.

Appendix

Blood conductivity is determined by passing alternating current through a separate four-electrode chamber of known volume. The voltage measured between the inner electrode pair is inversely related to specific conductivity. Once measured, this value is entered into the analog computer-stimulator and used for the signal processing.

Alpha, an empirical slope coefficient, has been determined with an isolated heart preparation,[17] in comparison with thermodilution and flow outputs,[18] and found to vary between 0.85 and 1.1. Measurements obtained with the use of thermodilution cardiac output in several closed-chest dogs yielded a mean value of 1.0. Since the thermodilution measurement is subject to $\pm$ 10% to 15% error, we did not determine the slope coefficient in each animal, and instead used the mean value of 1.0 for all the hearts.

Determination of the volume correction factor V_p was by a saline calibration technique previously described and validated. V_p was determined after placement of the catheter in the left ventricle. Five to seven milliliters of 6N saline was rapidly infused into the right heart. One to two seconds after infusion, the output volume signal gradually increased due to enhanced conductivity of the blood-saline mixture. By equation 1, conductances measured at end-systole, $G_{es}(\sigma)$, and at end-diastole, $G_{ed}(\sigma)$, of each cycle were related by the expression

$$G_{es}(\sigma) = G_{ed}(\sigma) - \sigma \times SV/L^2 \quad (2)$$

where SV is stroke volume.

Assuming that SV was not significantly altered during the saline injection, G_{es} is related to G_{ed} as a linear function of σ. With the use of the multiple values of end-systolic and diastolic volumes measured by the catheter during the injection, a regression line was generated. When this line was extrapolated to the point where $\sigma = 0$, represented by the identity line, then the apparent $V_{es} = V_{ed} = V_p$ (or $G_{es} = G_p$). This derived value represents the parallel conductance for the alternating current

TABLE 4
Values of V_p (ml) for the parallel conductance shown in equation 1

Animal No.	Control	Hex	Vag	Dobutamine
1	81	63	71	65
2	62	77	74	64
3	58	58	57	66
4	66	66	78	70
5	110	102	95	106
6	112	85	68	68
7	63	86	66	66
8	76	78	77	64

Hex = hexamethonium chloride; Vag = bilateral cervical vagotomy.

through the left ventricular wall and surrounding structures, and hence the volume correction to be subtracted from the volume signal. The results of two or three separate saline injections were averaged to determine a V_p. This was performed after each intervention throughout the experiment. The determination of V_p was made after the experiment was completed. The overall average value of the volume correction from eight experiments under different conditions was 70 ± 11 ml.

Use of V_p to estimate absolute volume assumed that the parallel conductance was constant. Small variations in the volume signal were associated with lung inflation (even after cardiac arrest), and therefore all data were collected at end-expiration. The effect of changes in blood content of left ventricular wall, wall edema, and right ventricular volume was assessed by measuring V_p after each intervention. No consistent change in the correction factor was found under the various conditions (table 4).

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