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Assessment of Left Ventricular End-Systolic Pressure-Volume Relations With an Impedance Catheter and Transient Inferior Vena Cava Occlusion: Use of This System in the Evaluation of the Cardiotonic Effects of Dobutamine, Milrinone, Posicor and Epinephrine

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The end-systolic pressure-volume relation has been postulated as a load-independent measure of cardiac contractility, but has been difficult to measure because of technical problems associated with the serial measurement of intracardiac volume over a physiologic range of ventricular loading conditions. Utilizing a multielectrode impedance catheter to assess continuous, on-line left ventricular relative volume during transient inferior vena cava occlusion, a method is described for determining the end-systolic pressure-volume relation and for assessing changes in this relation secondary to inotropic modulation. In particular, using this method, the relative inotropic properties were determined of four drugs: dobutamine, milrinone, epinephrine and an experimental cardiotonic agent (Ro 13-6438, Posicor).

Left ventricular micromanometer pressure and impedance catheter volume were measured continuously in 10 open chest, anesthetized dogs and 14 pigs. Arterial pressure was altered over a range of 20 to 60 mm Hg by brief inferior vena cava constriction. A linear end-systolic pressure-volume relation was observed in pressure-volume diagrams constructed from on-line pressure and impedance catheter recordings. Administration of dobutamine, milrinone and epinephrine resulted in a leftward shift and an increase in the slope of the end-systolic pressure-volume relation as compared with baseline; Posicor did not alter the slope over a range of doses, despite an increase in the cardiac output secondary to arterial vasodilation. Volume changes as measured by the impedance method closely paralleled simultaneous changes in the ultrasonic crystal-determined segment length, and the impedance end-systolic pressure-volume relation slope was reproducible with repeated load-altering manuevers.

It is concluded that the end-systolic pressure-impedance volume relation can be determined on a beat to beat basis during acute decreases in ventricular preload induced by transient inferior vena cava occlusion. This method of determining relative changes in the end-systolic pressure-volume relation may be useful in the assessment of relative inotropic effects of experimental cardiotonic drugs.

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The end-systolic pressure-volume relation has been proposed as a load-independent indicator of cardiac contractility which is sensitive to inotropic modulation (1–4). Determination of end-systolic contractile indexes in the intact organism, however, has been difficult. This is primarily due to technical limitations of current techniques to measure ventricular volumes over a range of physiologic loading conditions, while still maintaining constant contractility. As

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a result, there has been interest both in assessment of new methods of chamber volume measurement and in new techniques to alter ventricular loading conditions in an attempt to facilitate end-systolic pressure-volume analysis.

One area of potential utility of end-systolic contractile indexes is the assessment of the mechanism of action of new cardiotonic drugs. An experimental cardiotonic agent may improve ventricular performance by acting as an inotrope or by favorably changing ventricular loading conditions, or by having both effects. Routinely used ejection phase contractile indexes often are unable to distinguish between these two mechanisms because these measurements are primarily load dependent. End-systolic contractile indexes, however, are insensitive to loading conditions and, at least theoretically, are able to distinguish between an inotrope and a vasodilator.

The continuous on-line recording of intraventricular electrical impedance has been documented previously as an accurate method for instantaneously monitoring left ventricular relative chamber volumes (5–10). Preliminary studies have also shown the utility of the impedance method for measuring the left ventricular end-systolic pressure-volume relation over a range of ventricular loading conditions (9,10), but there has been no report on the use of this technique to assess changes in the end-systolic pressure-volume relation secondary to inotropic modulation. Utilizing a multielectrode impedance catheter with a 1.3 kHz measuring current of 4 μA in combination with transient inferior cava occlusion, we describe a method for determining a baseline left ventricular end-systolic pressure-volume relation in open chest anesthetized animals and for assessing relative inotropic changes with the administration of cardiotonic drugs. This technique was successfully applied in both dogs and pigs.

Methods

Study design. Left ventricular high fidelity micromanometer pressure and impedance volume signals were recorded continuously over a range of ventricular loading conditions induced by inferior vena cava occlusion in a total of 24 anesthetized open chest animals, including 10 dogs initially and 14 pigs subsequently. (During the course of the study, dogs became extremely difficult to obtain and our laboratory has switched, almost entirely, to the use of farm-bred pigs.) Left ventricular pressure tracings and impedance volume signals were subsequently digitized to produce pressure-volume diagrams and to determine a baseline end-systolic pressure-volume relation. Changes in this relation were assessed after intravenous infusion of four cardiotonic drugs, including dobutamine, milrinone, epinephrine and Ro 13-6438 (Posicor) (11). Changes in the end-systolic pressure-volume relation were confirmed in all animals by determining simultaneous changes in the end-systolic pressure-dimension relation using ultrasonic crystals.

This study was performed in two parts: in part 1, the end-systolic pressure-volume relation was assessed during the steady state infusion of dobutamine and before and after the administration of an intravenous bolus of milrinone in dogs. In part 2, a more complete hemodynamic study was carried out in pigs and the end-systolic pressure-volume relation was assessed during administration of graded intravenous doses of Posicor and after the steady state infusion of intravenous epinephrine.

Surgical preparation. *Part 1.* In the first portion of the study, 10 mongrel or retired racing greyhound dogs were premedicated with ketamine intravenously (10 mg/ml) and anesthesia was induced with chloralose (100 mg/kg). Respiration was supported mechanically using room air after placement of an oral endotracheal tube. Periodic injections of 100 mg chloralose were given intravenously as required to maintain adequate anesthesia. A left lateral thoracotomy was performed, and the pericardium was incised to support the heart. The inferior vena cava was isolated and a length of umbilical tape was passed around it and passed through a short length of tubing to create a snare, thereby allowing the rapid and reversible partial interruption of venous return. Left ventricular pressure was monitored with a micromanometer-tipped catheter (Millar Instruments) passed retrograde from the carotid artery. A 7F thermodilution Swan-Ganz catheter was inserted into the internal jugular vein and advanced to the pulmonary artery to monitor thermodilution cardiac output. The impedance catheter (Cardiac Pacemakers Inc.) was also placed in the left ventricle after passing retrograde from the carotid artery, and driving and sensing electrodes were selected to span the left ventricular cavity (see later). Catheter position was not changed after initial placement.

Part 2. In the second portion of the study, 14 farm-raised young pigs (31 to 48 kg) were premedicated with ketamine before induction of anesthesia with thiamylal (10 mg/kg) intravenously. Bolus injections of chloralose (100 mg/kg) were given as necessary to maintain anesthesia. Respirations were maintained with mechanical ventilation and supplemental oxygen at 4 liters/min by way of an endotracheal tube placed through a tracheostomy. Adequacy of ventilation was ascertained by periodic determinations of arterial and pulmonary artery blood oxygenation; arterial oxygen saturation was maintained above 95% in all experiments. A median sternotomy and pericardial incision were performed to expose and support the heart, and the inferior vena cava was isolated and a snare was placed. The animals were anticoagulated with heparin, 4,000 U intravenous bolus, followed by 1,000 U/h bolus injections. A left ventricular micromanometer-tipped catheter and a thermodilution Swan-Ganz catheter were placed in the left ventricle and pulmonary artery, respectively, as described in part 1 of the study. In part 2 of the study the rate of rise of left ventricular pressure (dP/dt), as derived electronically from the high

fidelity pressure recording, was acquired as well. The impedance catheter used in this part of the study was identical to that used in part 1. In these animals, the impedance catheter was inserted into the left ventricular cavity through an apical stab incision and the tip of the catheter was passed out the aortic valve, and remained in that position for the duration of the study. All pressure and impedance data were recorded on a Honeywell Electronics for Medicine model VR-16 or a Gould ES 1000 recorder.

Impedance measurements. The impedance catheter system used in this study has been described previously (9). Briefly, it consists of a 9F catheter that tapers to an 8F endhole distal shaft with 12 platinum ring electrodes spaced at 1 cm intervals along the distal end of the catheter. Once the catheter was positioned in the left ventricular cavity, a 1.3 kHz alternating driving current of 4 μA was applied to the electrode pair spanning the ventricular cavity. Impedance volume signals were recorded subsequently from a pair of sensing electrodes located between the driving electrodes within the left ventricular cavity. Impedance measurements throughout the experiment utilized the same driving and sensing electrode pairs as at baseline.

The theoretical basis of volume determination from impedance has been described previously (5–10). As a first approximation, the volume of blood that is measured between any two sensing electrodes can be considered to be a cylinder with boundaries defined by the endothelial surfaces of the cardiac walls and by the equipotential surfaces through the electrodes. The change in impedance sensed during atrial contraction in any one of these cylinders is caused by a change in resistance between the two sensing electrodes as a result of a change in the cross-sectional area of the cylinder. The relation between resistance and cross-sectional area is given by

$$R = \rho L/A, \quad (1)$$

where R = resistance, ρ = resistivity of blood, L = distance between sensing electrodes and A = cross-sectional area. For a cylindrical volume where volume (V) is equal to cross-sectional area times length (A × L), equation 2 may be substituted for resistance.

$$R = \rho L^2/V \quad (2)$$

Resistance at end-diastole and end-systole can now be defined as

$$R_{ed} = \rho L^2/V_{ed} \quad (3)$$

and

$$R_{es} = \rho L^2/V_{es}, \quad (4)$$

where ed = end-diastole and es = end-systole. By combining these two equations and subtracting we get

$$V_{ed} - V_{es} = \rho L^2 (R_{es} - R_{ed})/(R_{ed})(R_{es}). \quad (5)$$

Thus, for a given cylinder of blood between any two sensing electrodes, the change in volume that occurs with ventricular contraction can be determined from the difference in impedance between end-systole and end-diastole.

No attempt was made to calibrate impedance volume signals to determine absolute ventricular volumes. Instead, the initial end-diastole impedance volume was designated as V_I and the initial end-systolic volume was determined by measuring the forward stroke volume (thermodilution cardiac output/heart rate) and subtracting it from V_I. Volume changes during inferior vena cava occlusion and drug administration were subsequently measured relative to the initial end-diastolic and end-systolic volumes.

Ultrasonic crystal dimension. In all animals, ultrasonic crystals were implanted in the left ventricular subendocardium approximately 1 cm apart in an equatorial plane in the midventricle. These were activated by a commercially available sonomicrometer (Triton Technologies Inc.). The crystal separation was electronically calibrated and the crystal positioning confirmed at the end of each experiment at necroscopic examination.

Hemodynamic, impedance volume and dimension data. Following placement of the right heart thermodilution catheter and the left ventricular micromanometer and impedance catheters and ultrasonic crystals, baseline recordings of heart rate, hemodynamic data, impedance volume and ultrasonic crystal dimension were made. Next, inferior vena cava occlusion, with respirations suspended, was applied in all animals to interrupt venous return with a subsequent fall in left ventricular systolic pressure. Continuous on-line recordings of left ventricular pressure, volume and dimension were made on a beat by beat basis over a 20 to 60 mm Hg fall in systolic pressure. Pressure declined smoothly over 10 to 20 beats until the constriction was released at a peak systolic pressure of approximately 55 mm Hg. Inferior vena cava occlusion was then discontinued with a subsequent return of heart rate, pressure, volume and dimension to baseline. For all animals hemodynamic data recorded at baseline included mean and phasic pulmonary artery, pulmonary wedge and aortic pressures. Thermodilution cardiac output was determined in triplicate with 10 ml bolus injections of ice-cold saline solution with an Edwards model cardiac output computer. Heart rate was determined from recordings of the electrocardiogram over at least a 10 second interval.

In part 2 of the study (Posicor and epinephrine), mean right atrial pressure was also recorded and the following indexes were derived: stroke volume (ml) was calculated from the formula stroke volume = cardiac output/heart rate; systemic vascular resistance (dynes·s·cm^{-5}) from systemic vascular resistance = (mean aortic pressure − mean right atrial pressure) (80)/cardiac output; and pulmonary vascular resistance (dynes·s·cm^{-5}) from pulmonary vascular resistance = (mean pulmonary artery pressure − mean pul-

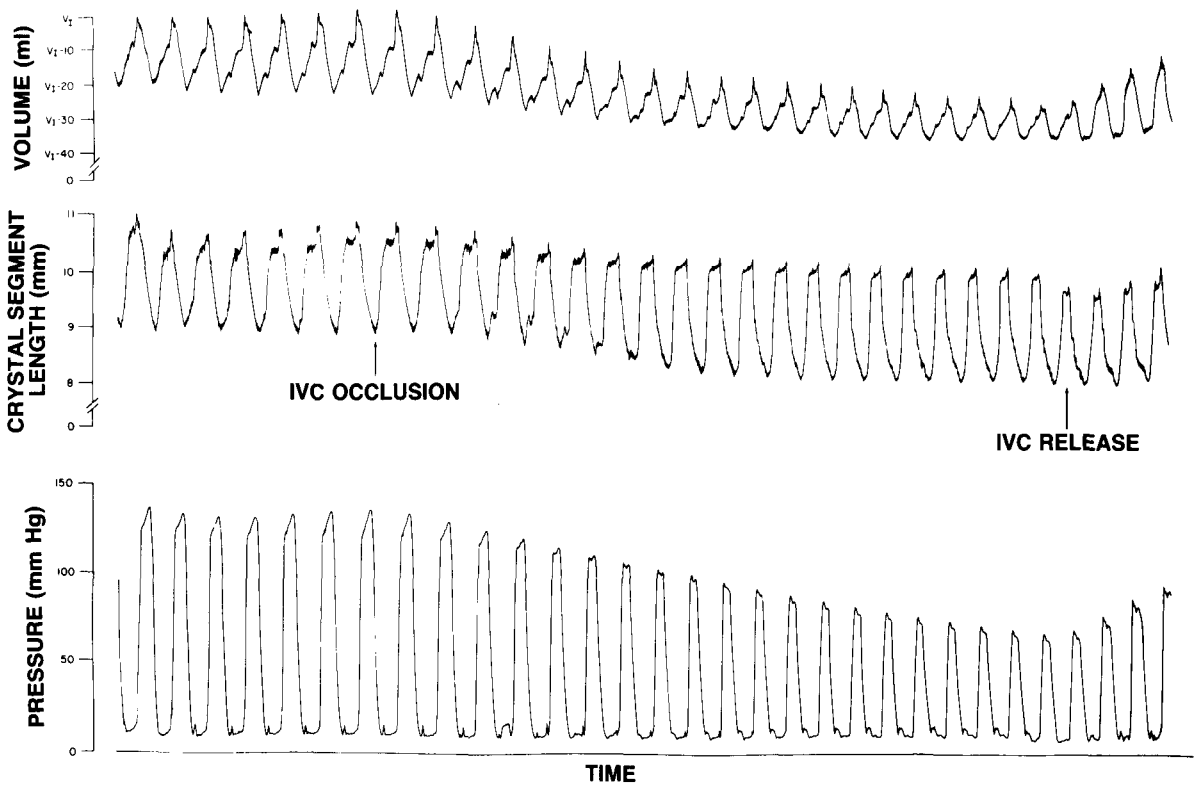


Figure 1. Continuous on-line recordings of left ventricular pressure, impedance volume and ultrasonic crystal dimension during inferior vena cava (IVC) occlusion. **Arrows** mark onset and release of occlusion. Impedance volume and crystal dimension closely parallel each other. Impedance volume is expressed relative to initial end-diastolic volume (V_I).

monary wedge pressure) (80)/cardiac output. The maximal rate of rise in left ventricular pressure (peak positive dP/dt) (mm Hg/s) was determined from the electronically calibrated signal.

Administration of cardiotonic drugs. After the recording of data at baseline and during inferior vena cava occlusion, and a subsequent return of pressure, volume and dimension to baseline with the release of inferior vena cava occlusion, cardiotonic drugs were administered to all animals.

Part 1. In five dogs a steady state infusion of dobutamine at 10 μg/kg per min was begun. In five additional dogs a bolus injection of milrinone of 10 μg/kg was given. Five minutes after drug administration, after the establishment of a new steady state, heart rate, thermodilution cardiac output, left ventricular pressure, impedance volume and ultrasonic crystal dimension were again recorded at baseline and during inferior vena cava occlusion.

Part 2. In 14 pigs progressive doses of Posicor were administered as described later. The Posicor was stored at −20°C as a lyophilized powder, and reconstituted by dis-

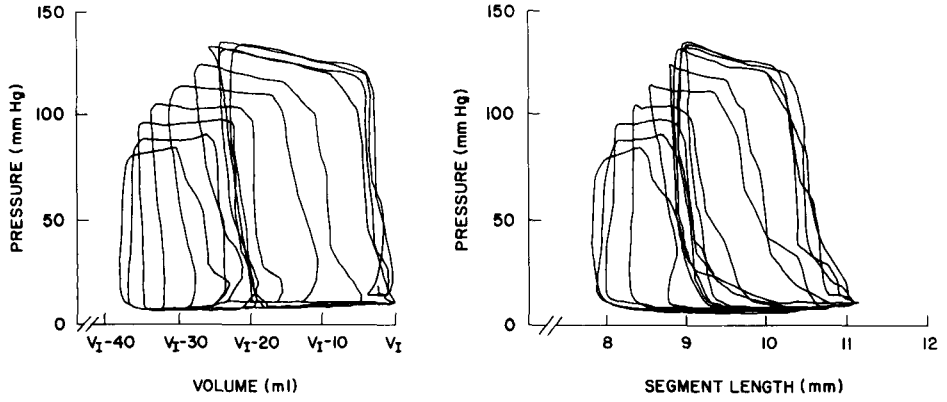


Figure 2. Pressure-volume (**left**) and pressure-dimension (**right**) diagrams obtained from digitization of data in Figure 1. End-systolic pressure-volume and pressure-dimension points both show a progressive leftward and downward displacement during inferior vena cava occlusion. V_I = initial end-diastolic impedance volume; V_I-10 to V_I-40 = V_I − forward stroke volume (end-systolic impedance volume).

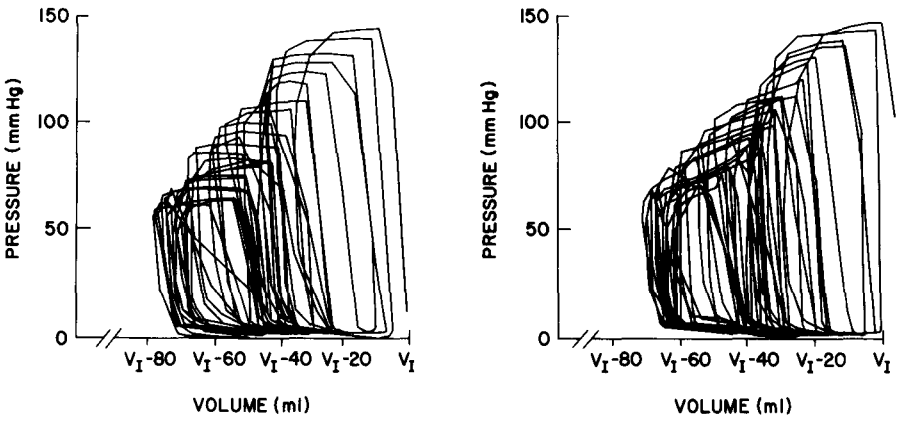


Figure 3. Left ventricular pressure-volume diagrams obtained from two sequential inferior vena cava occlusions in the same animal. The end-systolic slope is 1.6 mm Hg/ml in both examples. Again, left ventricular volume is represented relative to initial end-diastolic volume (V_I).

solving in a solution of 50% distilled water, 25% polypropylene glycol and 25% ethanol at a concentration of 1 mg/ml. This solution was made fresh at room temperature with each experiment. Posicor was administered as an intravenous bolus over 30 seconds at a dose of 30 μg/kg. At 5 and 25 minutes after the administration of the first dose, complete hemodynamic data acquisition and a repeat recording of left ventricular pressure and impedance volume during inferior vena cava constriction were performed. At 30 minutes after the administration of the first dose, a second dose of 100 μg/kg was given and the data were recorded similarly. This dose was followed at 30 minutes by the final bolus administration of 300 μg/kg, and the data were again recorded at 5 and 25 minutes after administration.

In seven pigs, this protocol was followed by the administration of epinephrine at a steady state rate of 2 μg/min. Hemodynamic information and left ventricular pressure and impedance volume during inferior vena cava constriction were recorded after the animal had been in a steady state for at least 10 minutes after the start of the infusion.

Data analysis. Micromanometer pressure and impedance catheter volume were digitized off-line from the recorded data using a Tektronix 4052 computer interfaced with a Tektronix 4956 graphics tablet, and pressure-volume loops were constructed from the digitized data. Ectopic ventricular beats, postextrasystolic beats and beats with a peak systolic pressure of less than 60 mm Hg were excluded from analysis. The end-systolic pressure-volume point for each cardiac cycle was defined as the maximal ratio of pressure to impedance volume. E_{max} was defined as the slope of the end-systolic pressure-volume relation (1) and was determined by fitting a line to these points by linear regression. Only pressure-volume loops in which there had been less than a 5% change in heart rate during inferior vena cava occlusion were used in the derivation of the slope of the end-systolic pressure-volume relation.

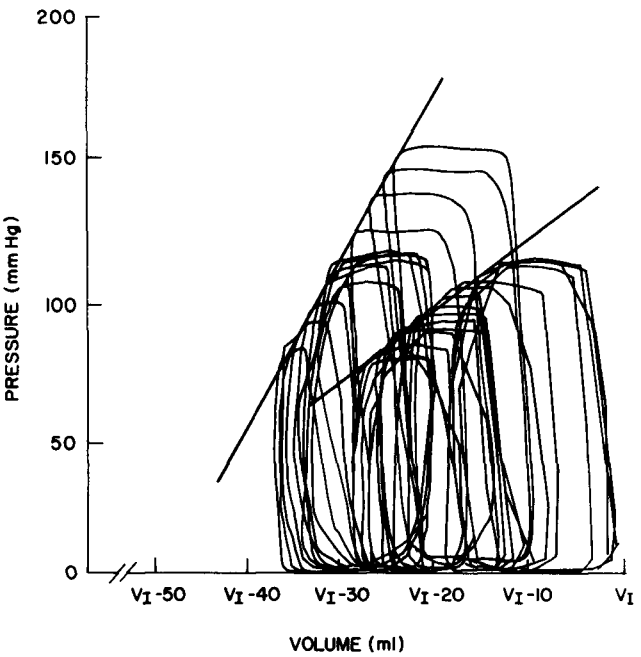
The hemodynamic data for Posicor and epinephrine administration were analyzed using analysis of variance. A probability level of less than 0.05 was considered significant.

Results

Baseline Impedance Catheter Measurements

The impedance catheter generates a signal that can be displayed and recorded on standard laboratory recording equipment. Typical analog tracings obtained during an acute change in loading conditions induced by inferior vena cava constriction are shown in Figure 1. Also illustrated is the signal obtained from the ultrasonic crystals implanted in the left ventricular wall. Of note, impedance volume signals and crystal dimensions parallel each other. Similar findings were noted in all animals during inferior vena cava occlusion and the administration of cardiotonic drugs. Pressure-vol-

Figure 4. Pressure-volume diagrams obtained before (**right**) and after (**left**) dobutamine administration in a representative experiment. Pressure-volume diagrams are shifted leftward with an increased slope. End-systolic slope before dobutamine administration is 2.6 mm Hg/ml and after dobutamine is 5.8 mm Hg/ml.



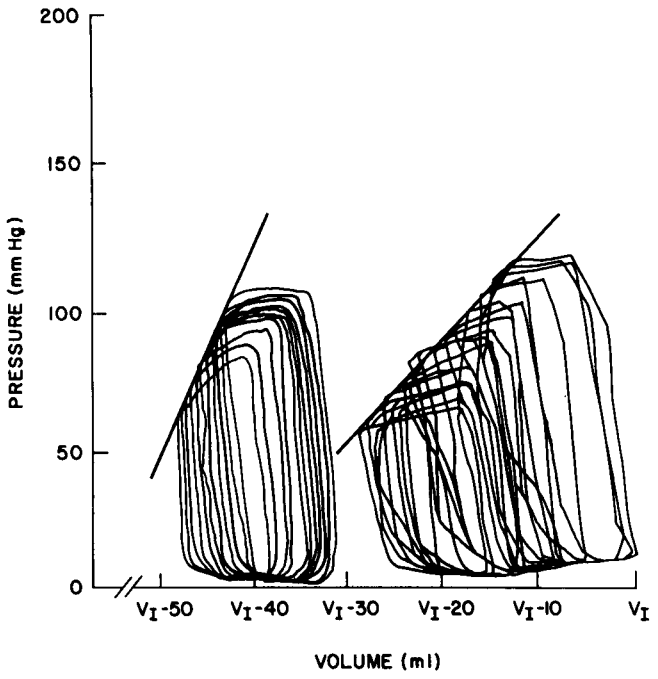


Figure 5. Pressure-volume diagrams obtained before (**right**) and after (**left**) administration of milrinone in a representative experiment. The diagrams are shifted to the left with an increase in slope of the end-systolic pressure-volume relation after milrinone. End-systolic slope before milrinone is 3.3 mm Hg/ml and after milrinone is 6.6 mm Hg/ml.

ume diagrams and pressure-dimension diagrams obtained during the inferior vena cava occlusion in Figure 1 are shown in Figure 2. Of note, both the end-systolic pressure-volume and pressure-dimension relation appear linear.

Figure 3 shows pressure-volume diagrams obtained during two sequential inferior vena cava occlusions. The end-systolic pressure-volume relation appears similar in both cases. Similar results were found in all animals, suggesting a high degree of reproducibility of the technique.

Effect of Inferior Vena Cava Occlusion

Inferior vena cava occlusion successfully decreased preload in all animals, resulting in as much as a 60 mm Hg fall in left ventricular systolic pressure over 10 to 15 seconds. There were no significant heart rate changes during a decrease in systolic pressure from 15 to 20 mm Hg. With larger decreases in systolic pressure due to more prolonged vena cava occlusion, there was a variable increase in heart rate by as much as 30% (range 0 to 30%).

Part 1. Effects of milrinone and dobutamine. The administration of dobutamine resulted in a mild increase in heart rate (90 ± 6 to 98 ± 7 beats/min, $p < 0.05$), an increase in cardiac output (2.1 ± 0.6 to 2.4 ± 0.8 liters/min, $p < 0.05$) and an increase in left ventricular pressure (120 ± 20/8 ± 4 to 148 ± 30/10 ± 4 mm Hg, $p < 0.01$). Milrinone similarly produced an increase in heart rate (100 ± 10 to 110 ± 7 beats/min, $p < 0.05$) and cardiac output (2.2 ± 0.3 to 2.5 ± 0.8 liters/min, $p < 0.05$), but resulted in mild fall in left ventricular pressure (115 ± 12/8 ± 4 to 105 ± 10/6 ± 4 mm Hg, $p < 0.05$). Figures 4 and 5 show representative examples of pressure-volume loops obtained before and after the administration of dobutamine and milrinone, respectively. Both drugs resulted in a leftward shift of the end-systolic pressure-volume relation with an increased slope suggesting an increase in inotropic state. In dogs that received dobutamine, the slope of the end-systolic pressure-volume relation increased from 3.0 ±

Table 1. Hemodynamic Data on Posicor and Epinephrine Administration in 14 Pigs

		Posicor			Epinephrine
	Baseline	Dose 1 (30 μg/kg)	Dose 2 (100 μg/kg)	Dose 3 (300 μg/kg)	Infusion (2 μg/min)
HR	95 ± 6	101 ± 8	110 ± 10	126 ± 6*	112 ± 9
LVSP	101 ± 8	105 ± 10	98 ± 8	93 ± 7*	125 ± 11†
LVEDP	8 ± 4	7 ± 3	7 ± 4	7 ± 2	8 ± 4
RAP	6 ± 2	6 ± 2	6 ± 3	5 ± 3	7 ± 2
PAP	30 ± 12	28 ± 10	29 ± 9	29 ± 8	24 ± 7
PCWP	8 ± 2	7 ± 3	8 ± 5	8 ± 1	9 ± 3
CO	2.0 ± 0.9	2.1 ± 1.1	2.1 ± 1.2	2.4 ± 1.1*	3.5 ± 1.6†
SVR	3,873 ± 314	4,030 ± 386	3,665 ± 424	3,021 ± 444*	3,068 ± 679*
PVR	810 ± 94	780 ± 96	767 ± 104	677 ± 111	399 ± 100
+dP/dt	1,615 ± 116	1,584 ± 131	1,612 ± 164	1,813 ± 145	2,902 ± 123*
E_{max}	2.6 ± 0.9	2.4 ± 0.8	2.6 ± 0.9	2.0 ± 0.4	4.9 ± 2.3†

*$p < 0.05$; †$p < 0.01$. CO = cardiac output (liters/min); +dP/dt = peak positive dP/dt (mm Hg/s); HR = heart rate (beats/min); LVEDP = left ventricular end-diastolic pressure (mm Hg); LVSP = left ventricular systolic pressure (mm Hg); PAP = mean pulmonary artery pressure (mm Hg); PCWP = pulmonary capillary wedge pressure (mm Hg); PVR = pulmonary vascular resistance (dyne·s·cm^{-5}); RAP = right atrial pressure (mm Hg); SVR = systemic vascular resistance (dyne·s·cm^{-5}); E_{max} = slope of the end-systolic pressure-volume line (mm Hg/ml).

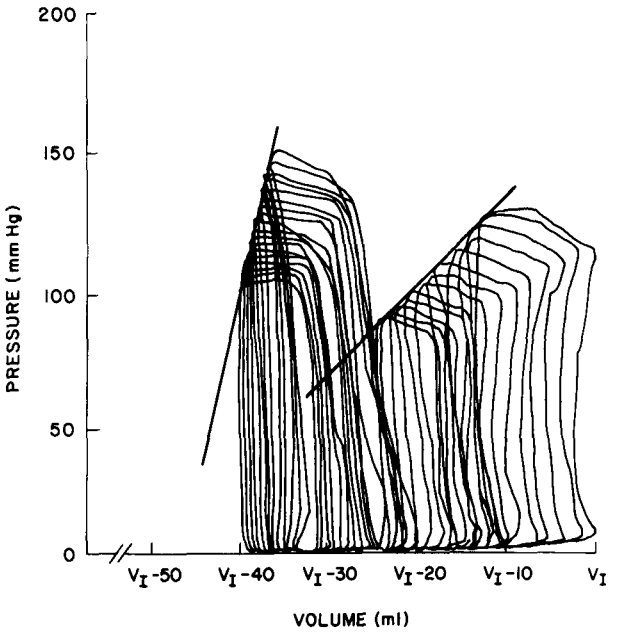


Figure 6. Pressure-volume diagrams obtained before (**right**) and after (**left**) administration of epinephrine. End-systolic slope has increased from 3.3 to 12.1 mm Hg/ml.

1.4 to 5.6 ± 1.5 mm Hg/ml ($p < 0.01$). In dogs that received milrinone, this slope increased from 3.5 ± 1.0 to 5.9 ± 1.6 mm Hg/ml ($p < 0.01$).

Part 2. Effects of epinephrine and posicor. Table 1 summarizes complete hemodynamic data obtained for the administration of these drugs. Figures 6 and 7 show pressure-volume loops obtained in pigs before and after the administration of epinephrine and Posicor, respectively. Epinephrine resulted in a leftward shift of the end-systolic pressure-volume relation with an increase in slope as well as in dP/dt and cardiac output. Posicor resulted in no significant change in the end-systolic pressure-volume relation with no change in dP/dt, although there was a mild fall in systemic vascular resistance with a subsequent increase in cardiac output. The data suggest little or no significant inotropic change with Posicor but a mild vasodilatory effect.

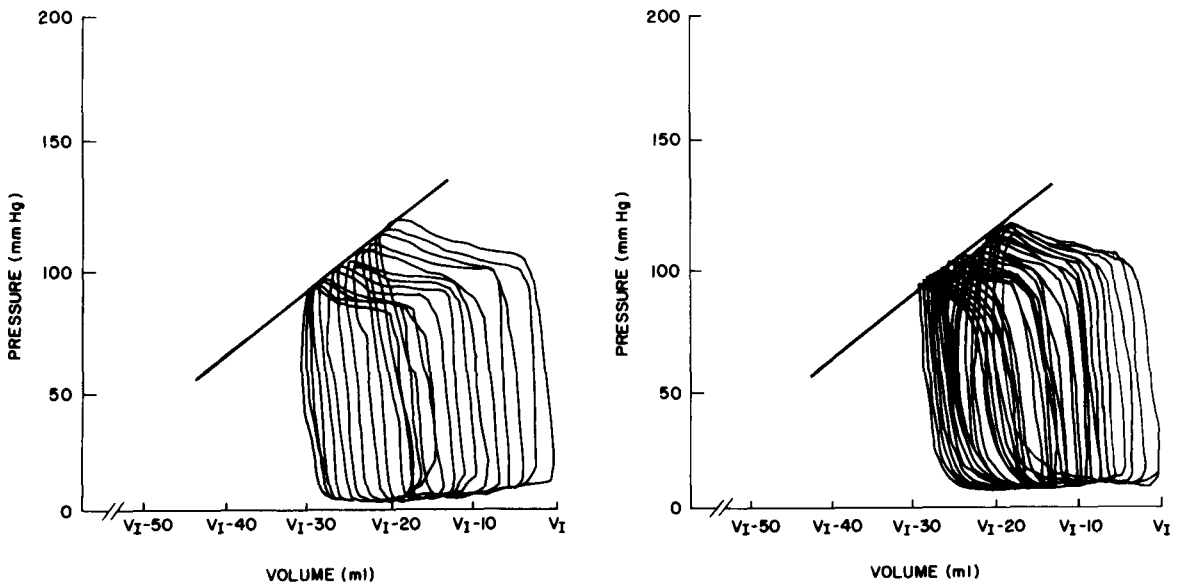
Discussion

In the present study, we examined the utility of a new method (measurement of impedance volume during transient inferior vena cava occlusion) for determining the relative inotropic properties of several drugs. This method of determining left ventricular volume has the advantage of allowing for the determination of dynamic pressure-volume relations during acute alterations in left ventricular loading conditions. We utilized this property in the determination of the end-systolic pressure-volume relation of the left ventricle, a known measure of the contractile state of the heart that is largely independent of loading conditions. Our data suggest that dobutamine, milrinone and epinephrine all have a positive inotropic effect, while Posicor appears to alter hemodynamics only by acting as a vasodilator.

Potential Utility of the Impedance Catheter for Measuring End-Systolic Contractile Indexes

Rationale. The theoretic appeal of end-systolic pressure-volume contractile indexes lies in their load independence

Figure 7. Pressure-volume diagrams obtained before (**right**) and after (**left**) administration of Posicor. No significant change was noted in the end-systolic pressure-volume relation. End-systolic slope before Posicor is 2.7 mm Hg/ml and after Posicor is 2.8 mm Hg/ml.



so that they can presumably be used to assess basal contractility and inotropic modulation. Use of these indexes could potentially improve our assessment of left ventricular pump function in a wide variety of pathophysiologic states. Until recently, however, derivation of these indexes in humans has been difficult. Angiographic methods are hindered by the limited number of cardiac cycles that can be analyzed, a high incidence of ventricular arrhythmias, the presence of regional wall motion abnormalities that make geometric assumptions for volume calculations inaccurate, the effect of iodinated contrast medium on ventricular function, and the risk to the patient from multiple contrast injections. Similarly, echocardiographic methods are limited by difficulties of echo visualization in many patients and regional wall motion abnormalities that adversely affect geometric volume calculations.

In view of the technical limitations associated with current methods of serial volume analysis over a physiologic range of ventricular loading conditions, there has been interest in new methods of cardiac chamber volume measurement in an attempt to facilitate end-systolic pressure-volume analysis. Theoretically, impedance volume measurement could improve end-systolic pressure-volume analyses by being able to produce an unlimited number of beat to beat pressure-volume diagrams over a wide range of loading conditions. Results from this study and others (10) in both animals and humans suggest that impedance measurements can be used to determine baseline end-systolic indexes and to assess changes in the end-systolic pressure-volume relation secondary to changes in inotropic state. The applicability and utility of impedance-catheter determined volume measurements for ascertaining the end-systolic pressure-volume relation in humans deserves further investigation. In this regard, our laboratory is currently studying the use of a left ventricular impedance catheter in patients in combination with transient balloon occlusion of the inferior vena cava to determine end-systolic contractile indexes.

Application. As addressed by this study, one area in which impedance end-systolic measurement might be applicable is the assessment of the mechanism of action of experimental cardiotonic drugs. The mechanism of action of some of the newer cardiotonic agents may be difficult to discern from traditional hemodynamic variables, because the vasodilating and positive inotropic properties (that essentially all of these agents possess) may produce similar changes in the measured variables (12). It is only with careful attention to the preload and afterload status of the heart that the most reliable isovolumic phase indexes (that is, peak positive dP/dt, dP/dt_{P40}, and so on) can be applied. Because the determination of the slope of the end-systolic pressure-volume relation incorporates afterload and is independent of preload (1,2), the validity of this index of contractility might find wide application in the evaluation of new cardiac drugs if a simple and reliable method of determining the pressure-volume relation over a wide range of arterial pressures were available. The present study suggests that impedance volume measurements are uniquely suited for this type of analysis and thus may serve as a suitable technique for drug testing in the future.

Limitations. This study examined only relative volume changes in a determination of baseline end-systolic pressure and volume and after inotropic modulation. Once the surgical preparation was completed, impedance catheter position and sensing characteristics were not altered and the baseline impedance volume detected through the course of a single study remained constant. All volume changes secondary to inferior vena cava occlusion and drug administration were measured relative to the initial end-diastolic impedance volume (V_I) and the initial end-systolic impedance volume (V_I − forward stroke volume). Thus each animal served as its own control, and inotropic changes in the end-systolic pressure-volume relation were assessed relative to baseline. Utilizing this method, we were able to determine an absolute end-systolic pressure-volume slope, termed "E_{max}" by Suga and Sagawa (1), but not an absolute volume intercept of the end-systolic pressure-volume relation.

Difficulties in determining absolute impedance volumes had been previously reported (9), although Baan et al. (10) were recently successful in measuring accurate absolute impedance volumes. Perhaps the major problem in the calibration of impedance volume is the issue of parallel conductance, that is, the leakage of driving current through nonblood tissues of the myocardium and surrounding structures. We do not consider this to be a problem in the present study. The frequency of the alternating current used in the impedance catheter device is such that the electrical impedance of the myocardium is approximately 100-fold greater than that of the blood, tending to contain the current and to render changes in myocardial impedance relatively insignificant in comparison with changes in blood volume (9). Additionally, we were able to show a good correlation between the left ventricular dimension as determined by ultrasonic crystals and the impedance catheter-derived ventricular volume.

Additional limitations of this study need to be emphasized. Because the impedance catheter is measuring volume changes from a pair of sensing electrodes located within the left ventricular cavity, the end-systolic indexes generated in this study represent *regional* contractility measurements. It is possible that these indexes do not represent global contractile performance, particularly in animals with marked regional contractile variations. This is, of course, a criticism of the present study and not of the impedance catheter technique in general, because the sensing electrodes that are used to measure ventricular volume can be chosen to span the entire ventricular cavity.

A final limitation of the present study includes the use of thermodilution cardiac output to determine left ventricular

stroke volume and thereby calibrate relative volume changes measured with the impedance catheter. Thermodilution measurements may vary as much as 10 to 15% and, as a result, our determination of end-systolic slopes would be expected to vary in a similar fashion. Much more important than the determination of an individual slope, however, are the gross pressure-volume diagram changes that were observed (Fig. 4 through 7). Even without knowledge of calculated individual end-systolic slopes, by visual inspection it is clear which agents cause positive inotropic changes (for example, dobutamine, milrinone, epinephrine) and which produce no change in contractile state (for example, Posicor).

Use of Transient Inferior Vena Cava Occlusion to Alter Loading Conditions

Any method that attempts to determine end-systolic contractile indexes must by definition include a technique for altering ventricular preload or afterload, or both, without changing contractile state. Previous attempts to do this in the intact animal have primarily involved the use of pharmacologic agents (for example, nitroprusside, nitroglycerin, phenylephrine) to change filling pressures and systolic blood pressure. Sympathetic reflex changes in response to load alteration, as indicated by changes in heart rate, have been a consistent problem with this technique. As a result, use of pharmacologic agents to alter load has also necessitated the administration of atropine or beta-adrenergic blocking agents, or both, in the organism to blunt the effect of reflex contractile changes. The administration of either atropine or beta-blockers, however, presumably changes baseline contractility. As an alternative, transient inferior vena cava occlusion offers a potentially new technique for changing loading conditions without inducing major sympathetic reflexes. As can be seen from Figure 1, decreasing an animal's blood pressure by as much as 50 mm Hg with inferior vena cava occlusion does result in a mild increase in heart rate, indicating at least a mild sympathetic discharge. However, no change in heart rate is noted over a smaller decrease in blood pressure (for example, 15 to 20 mm Hg), suggesting a constancy of contractile state. Further support for the use of transient inferior vena cava occlusion as a suitable load-altering technique was recently cited by Bashore et al. (13), who utilized transient vena caval balloon occlusion in 12 patients to acutely decrease preload. Their study showed that with a mean change of left ventricular systolic pressure from 120 ± 29 to 104 ± 23 mm Hg, there was no change in heart rate. Further studies on the use of this technique to acutely change preload while minimizing cardiovascular reflexes are thus indicated.

Posicor: inotrope or vasodilator? We cannot exclude species differences or the effect of surgical preparation and anesthesia as the reason for the apparent lack of positive inotropy of Posicor. Also, the dose at which an increase in contractility of the myocardium of the pig might occur is not known. Moreover, our animals did not have an induced state of cardiac failure and must be considered normal animals from a cardiovascular standpoint. Still another consideration with the acute intravenous administration of Posicor is the potential effect of the diluent on cardiac function. Although the diluent's hemodynamic effects were transient, ethanol and polyethylene glycol are known to be negative inotropic agents and may have counteracted potential positive inotropic effects of Posicor. In spite of the lack of a major inotropic effect of Posicor, the drug did produce an improvement in cardiac output. This can be accounted for by the decrease in systemic vascular resistance or the increase in heart rate, or both, at similar right and left heart filling pressures. We conclude from these data that the mechanism of beneficial effect noted with Posicor is primarily a result of vasodilator rather than positive inotropic properties.

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