Left Ventricular Volume Measurement by Conductance Catheter in Intact Dogs

Parallel Conductance Volume Depends on Left Ventricular Size

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The conductance catheter is a promising new instrument for continuously measuring left ventricular (LV) volume. Absolute LV volume (V(t)) is related to uncorrected conductance volume, B(t), according to the equation: V(t) = (1/α)(B(t) - αVc). The αVc factor represents parallel-conductance volume due to conducting material outside the LV blood pool, and may be estimated by transiently changing blood conductivity using a bolus injection of hypertonic saline. α is the slope in the relation between B(t) and true LV volume. We tested the assumption that αVc and α are constant over a range of hemodynamic conditions. We performed multiple hypertonic saline αVc determinations in seven intact dogs during control conditions and subsequent temporary balloon occlusions of inferior vena cava (IVCO), aorta (AO), and pulmonary artery (PAO). We also compared B(t) with simultaneous biplane angiographic LV volume during similar control and intervention conditions. The saline-derived αVc was 76±2 ml during control and fell significantly by −7±2 ml during IVCO (p<0.001) but not during AO or PAO. According to multiple linear regression analyses, the strongest predictor of saline-derived αVc, was uncorrected end-systolic Bves, with a sensitivity coefficient of 0.60±0.06 ml/ml (p<0.001). Angiographically derived αVc showed a similar dependence on Bves, with a coefficient of 0.77±0.14 ml/ml (p<0.001). Angiographically determined α also showed significant variation with hemodynamic interventions, largely reflecting an underlying dependence on αVc. The variation in αVc and α with LV size may stem from non-linearity in the B(t)-V(t) relation. Although the conductance catheter provides a useful measure of relative LV volume, measurement of absolute LV volume over a wide hemodynamic range using constant αVc and α factors is unrealistic. This result calls into question the current use of this technique for the measurement of the absolute LV volume against electromagnetic flow-probe stroke volume in open-chest dogs,1,2 thermomodulation stroke volume and single-plane angiographic LV volume in humans,2 and balloon LV volume in isolated beating hearts.3 A portion of the total-conductance volume signal is due to electric current that passes outside the LV blood pool; this component has been termed αVc, or parallel-conductance volume. Baan et al2 described a method of estimating αVc using a transient change in blood conductivity.2

Although there are several potential applications for the conductance catheter, there has been particular interest in assessing the end-systolic–pressure-volume relation in animals and humans.4,5 In such studies, the parallel-conductance volume has been assumed constant despite changing conditions of LV preload and afterload. There has been concern, however, that αVc may vary with hemodynamic interventions, such as those that change the right ventricular volume.3,5 To study this problem fur-
ther, we used multiple saline injections to measure \( \alpha V_c \) in closed-chest dogs after hemodynamic interventions that change the relative sizes of the left and right ventricles (balloon occlusions of inferior vena cava [IVCO], aorta [AO], and pulmonary artery [PAO]). As an additional validation test, we compared conductance volume against frame-by-frame biplane angiographic LV volume over a similar set of interventions. Because the conductance catheter is being used in the intact state, even though validations in this setting have been limited, we performed our study in fully intact dogs. We found that the parallel-conductance volume strongly depends on the LV end-systolic-conductance volume itself, with \( \alpha V_c \) increasing as the left ventricle gets bigger. This result calls into question the use of the conductance catheter for measuring the absolute end-systolic-pressure-volume relation.

**Methods**

**Conductance Catheter**

We used the eight-electrode catheter described by Baan et al., with the distal electrode (1) at the LV apex and the proximal electrode (8) just above the aortic valve. This catheter is connected to electronics (Stichting Leycom Sigma-5), which applies a 20-kHz, 0.07-mA RMS current between electrodes 1 and 8, measures conductances between electrode pairs 2–3, 3–4, 4–5, 5–6, and 6–7, and then sums them to obtain the total time-varying conductance, \( G(t) \). Absolute LV volume, \( V(t) \), is computed as

\[
V(t) = (L^2 \rho G(t) - \alpha V_c)
\]

where \( \alpha \) is a unitless constant, \( L \) is interelectrode distance, \( \rho \) is blood resistivity, and \( \alpha V_c \) is volume correction due to parallel conductance, \( G_p \), outside the LV blood pool (\( \alpha V_c = L^2 \rho G_p \)).

In practice, \( L \) and \( \rho \) are set on the Sigma-5 unit, which provides the uncorrected time-varying conductance volume, \( B(t) \). As described by Baan et al., \( \alpha V_c \) may be determined by injecting a bolus of hypertonic saline into the pulmonary artery to produce a transient increase in LV blood conductivity without changing ejection fraction. Accordingly, we regressed multiple consecutive end-systolic \( B_{es} \) (\( B(t) \) minima) against immediately preceding end-diastolic \( B_{ed} \) (peak of electrocardiogram [ECG] R wave) just before and during the ascending limb of saline-induced \( B(t) \) increase according to

\[
B_{es} = m B_{ed} + b
\]

Using these results, we then calculated \( \alpha V_c \) according to

\[
\alpha V_c = b/(1 - m)
\]

\( \alpha \) may be determined from an independent method of LV volume measurements, as discussed under “Angiography.”

**Preparation**

We studied seven adult mongrel dogs weighing 20–25 kg, premedicated with 0.15 ml/kg subcutaneous Innovan-Vet (20 mg droperidol, 0.4 mg fentanyl/ml), and anesthetized with 3 mg/kg i.v. pentobarbital sodium. After the dogs were anesthetized, we placed them supine in a biplane radiographic system. We maintained anesthesia with 40% \( \text{NO}_2 \)-60% \( \text{O}_2 \) by endotracheal tube and Quantiflex VMC ventilator. This regimen avoids reflex tachycardia and myocardial depression. We gave supplemental 1 ml i.m. Innovan-Vet injections as needed.

All catheters were placed percutaneously under fluoroscopic guidance in this closed-chest preparation. Millar PC-471 catheters were placed in the LV and right ventricle (RV) through right femoral artery and vein cutdowns. A balloon-occlusion catheter adapted from a Swan-Ganz catheter was placed in the pulmonary artery by right jugular vein cutdown. This catheter had a separate port just distal to the occlusion balloon to allow injection of hypertonic saline into the pulmonary artery. A similar balloon catheter was placed in the inferior vena cava just proximal to the right atrium by left femoral vein cutdown. The open lumen of this catheter generally was used to obtain blood for \( \rho \) measurements. An aortic balloon catheter adapted from the straight shaft of a pigtail catheter was placed in the descending aorta with the balloon just distal to the left subclavian artery by left femoral artery cutdown. This catheter was filled with dilute Renografin-76 instead of air to help visualize the balloon on x-ray and anchor it when inflated. A 7F Cordis eight-electrode conductance catheter was placed in the LV with the tip at the apex through left carotid artery cutdown. Catheters with 6 or 7 cm total interelectrode distances were used according to LV size, 6–7 electrode-pair segmental-volume signal, and on-line pressure-volume loops. After initial placement of the conductance catheter, its position was not changed during the rest of the protocol.

We killed the dog at the end of the protocol with an intravenous injection of 35–40 ml saturated KCl and then removed the heart and weighed the dissected LV (including the septum) and RV free wall.

**Protocol**

All data were collected with the respirator off at end expiration.

**Saline injections.** We used 3–4 ml bolus injections of hypertonic saline into the pulmonary artery to estimate \( \alpha V_c \) as described above during control conditions and after balloon-occlusion interventions. We inflated the respective balloons to create an IVCO sufficient to decrease LV end-diastolic pressure (LVEDP) by at least 5 mm Hg, an AO sufficient to raise LV systolic pressure approximately 30 mm Hg above baseline, or a PAO sufficient to raise RV systolic pressure 20–30 mm Hg above baseline but without markedly decreasing LV
systolic pressure, and then gave the saline injection after the transient associated with the occlusion had passed. We did not study combinations of balloon occlusions. We volume loaded twice using intravenous infusion of normal saline, and then repeated the initial sequence of data collection after each volume infusion. If ectopy occurred during data collection, we performed more injections in an attempt to obtain at least two acceptable runs. We waited several minutes between each saline injection to allow blood resistivity, \( \rho \), to reequilibrate.

We excluded saline runs from analysis if 1) there was obvious ectopy just before or during the conductivity transient, 2) the coefficient of variation in beat-by-beat heart rate just before and during the conductivity transient exceeded 15%, 3) less than four consecutive cycles meeting these criteria were available for analysis, or 4) the 6–7 electrode-pair segmental-volume waveform suggested that the proximal sensing electrodes had been pushed outside the LV into the aorta.

In each experiment, \( \rho \) started at about 125–150 \( \Omega \) cm, fell steeply with the first few saline injections to about 90–100 \( \Omega \) cm, and then continued to fall linearly with further saline injections to about 70–80 \( \Omega \) cm by the end of the protocol.

**Angiography.** After completing the protocol just described, we conducted the angiographic portion of the study. We recorded pressure and \( B(t) \) data along with 60 frame/sec biplane alternating mode LV angiograms during a control state and after IVCO, AO, and PAO. Just before each LV angiogram and during a similar intervention planned for that angiogram, we performed one or two more saline injections to complement the saline-derived \( \alpha V_c \) data (denoted as \( \text{VOL}_a \) condition below). In experiments 904–907, we also repeated the control angiogram to test for reproducibility before performing the interventions (denoted as \( \text{REPEAT} \)). The Renografin-76 contrast media was premixed with 3–4 ml 23.4% saline to match blood \( \rho \) measured just before each LV angiogram. We injected 30 ml warmed contrast with a power injector at 15 ml/sec.

We used a cine mark that simultaneously produced a pulse on the ECG signal and blanked four frames on the cine film to synchronize the angiographic volume with \( B(t) \). Using the best opacified full cycle, each angiogram was digitized frame-by-frame by hand, and LV volume was computed using a modification of Simpson's rule.\(^6\) Angiographic LV volume, \( A(t) \), was related to \( B(t) \) according to

\[
B(t) = m_a A(t) + b_a
\]  

Comparing Equations 1 and 4 reveals that \( b_a = \alpha V_c \) and \( m_a = \alpha \). Thus, this method provides estimates of \( \alpha V_c \) and \( \alpha \), independent of the hypertonic saline injection method.

We tested the accuracy of angiographic LV volume measurement by performing biplane cine recordings of six clay models of the LV cavity. The models had realistic ellipsoidal LV shapes of decreasing size but with LV outflow and mitral inflow areas of constant size. The displacement volumes of the models were 15–80 ml. Although we did not include trabeulations, we believe the smaller-sized models were reasonable representations of LV shape at end systole. The regression of angiographic volume, \( A \), to actual volume, \( V \), was \( A = 1.07V - 0.3\text{ml} \) \((r = 0.9997, \text{SEE} = 0.7 \text{ml})\).

To assess ventricular geometry and the position of the conductance catheter within the LV, we traced the best opacified end-diastolic and end-systolic LV outlines (i.e., the same cycle used for \( B[t] = A[t] \)-regression analysis) and overlaid them with corresponding tracings of the catheter just before LV opacification. We also computed the distance from the LV apex to the midpoint of the aortic valve\(^6\) using these same frames to test whether total interelectrode lengths of the catheters were appropriate for the ventricles.

**Data Acquisition**

Seven data channels were recorded: 1) LV pressure, 2) RV pressure, 3) electrode-pair 4–5 segmental volume, 4) electrode-pair 5–6 segmental volume, 5) electrode-pair 6–7 segmental volume, 6) total conductance-catheter volume (\( B[t] \)), and 7) ECG. An eighth unrecorded channel was used to multiplex fluid-filled strain gauge LV and RV pressures with LV and RV Millar pressures for in vivo zeroing against a Statham P23BD external strain gauge pressure transducer, zeroed at one-third chest height.\(^7\) All analog signals were recorded on FM magnetic tape (Honeywell 5600C), and the data later digitized with a 200-Hz sampling rate.

We averaged LV and RV peak systolic and end-diastolic pressures and LV dP/dt\(_{\text{max}}\) over the first four beats used to derive \( \alpha V_c \) after a hypertonic saline injection or the four beats just preceding the LV angiogram. We defined the time of end diastole as the peak of ECG R wave and end systole as the time of minimum conductance volume. The values of \( B(t) \) were obtained from one representative beat just before the transient due to the saline injection or simultaneous with the opacified beat analyzed angiographically.

**Statistical Methods**

All hemodynamic data are reported as mean±SD. All regression coefficients are reported with their associated SEs.

To test whether significant changes occurred during the hemodynamic interventions preceding saline injections, we used a multiple linear regression implementation of a repeated-measures analysis of variance, with dummy variables representing the hemodynamic interventions, volume conditions, and dogs.\(^8\) The specific regression model was

\[
y = b_0 + b_1 \text{IVCO} + b_2 \text{AO} + b_3 \text{PAO} + \Sigma b_n \text{VOL}_n + \Sigma b_i \text{D}_i
\]  

\(\text{(5)}\)
where \( y \) is the dependent variable of interest and \( b_0 \) is the mean value over all dogs under the control condition (i.e., before volume expansion using intravenous normal saline infusion). The dummy variable IVCO equals 1 during IVCO and 0 otherwise. The dummy variables AO and PAO are defined similarly. The volume state dummies \( \text{VOL}_2 \) (after the first volume loading), \( \text{VOL}_3 \) (after the second volume loading), and \( \text{VOL}_4 \) (just before the angio-
gram) were also defined according to the (1,0) convention. Using this coding, the coefficients \( b_i \), \( b_A \), \( b_P \), and \( b_{V_N} \) estimate changes from the control state during the corresponding interventions or volume conditions.

The \( n-1 \) dummy variables \( D_i \) account for between-dog differences by allowing the \( n \) dogs to have different mean responses. These dummy variables are defined according to

\[
D_i = \begin{cases} 
1 & \text{if dog } i \leq n-1 \\
-1 & \text{if dog } n \\
0 & \text{otherwise} 
\end{cases}
\]

For example, for the seven dogs in this study, the set of \( D_i \) for experiment 901 are (1 0 0 0 0 0); for 902, (0 1 0 0 0 0); and for 907, (-1 -1 -1 -1 -1 -1). Using this coding scheme, the \( b_i \) represents the deviation from the overall mean value for dog \( i \) (i=901, . . . , 906). The deviation of dog 907 from the overall average is \( b_{907} = -\Sigma b_i, i=901, \ldots, 906 \). This formulation is a standard way of allowing for between-subjects differences in linear-regression analysis.

To assess the change in saline-derived \( \alpha V_c \) with hemodynamics, we used Equation 5, with \( \alpha V_c \) as the dependent variable. In addition, we conducted multiple regressions in which we replaced the experimental condition dummy variables with individual hemodynamic variables. For example,

\[
\alpha V_c = b_0 + b_{\text{LV}} + \sum b_i D_i 
\] (6)

In this case, \( b_{\text{LV}} \) is the change in \( \alpha V_c \) for each 1-ml change in \( \text{LV} \). We computed analogous separate regressions with \( \text{LVEDP}, \text{RVSP}, \text{LVSP}, \text{B}_{ed}, \text{B}_{es} \), and \( \text{B}_{es} \) as single independent variables. We also used stepwise regressions of \( \alpha V_c \) on the combined independent variables \( \text{LVEDP}, \text{LVSP}, \text{RVSP}, \text{B}_{ed}, \) and \( \text{B}_{es} \) to identify the most important independent variables.

To quantify the hemodynamic changes during the interventions used for the angiograms, we performed analysis similar to that in Equation 5, but with the additional dummy REPEAT (1 for repeat control, 0 otherwise), and without volume state dummy variables (control state for this analysis is defined as the first angiogram, performed without balloon occlusion). To quantify hemodynamic dependence, angiographically derived \( \alpha V_c \) was subjected to the same analysis, and this was repeated for \( \alpha \).

Angiographically derived \( \alpha V_c \) and \( \alpha \) were also regressed against single independent hemodynamic variables along with between dog effects, as in Equation 6. Because \( \alpha \) and \( \alpha V_c \) are theoretically and experimentally interrelated, \( \alpha \) was regressed on \( \alpha V_c \), including between-dog effects. We also performed a stepwise linear regression of \( \alpha \) on dog dummies (forced into the regression first), hemodynamic variables, and \( \alpha V_c \), to test the hypothesis that \( \alpha V_c \) is the dominant underlying predictor of \( \alpha \).

We regressed conductance-catheter stroke volume, \( \Delta B = B_{ed} - B_{es} \), on simultaneous angiographic stroke volume, \( \Delta A = A_{ed} - A_{es} \), including between-dog effects, and separately including \( \alpha \) as an additional independent variable.

To test if the catheter lengths matched the LV lengths, we compared conductance-catheter total-interelectrode distance with LV end-diastolic and end-systolic lengths over the various angiographic conditions using a repeated-measures analysis of variance. Ventricular and catheter lengths were compared using the Dunnett’s test, with the catheter length taken as the control measurement.

Just before each angiogram we repeated the saline derivation of \( \alpha V_c \) (during the preangiogram condition previously described, denoted \( \text{VOL}_a \)). We used Student’s paired \( t \) test to compare each such saline-derived \( \alpha V_c \) with the value derived from the angiogram. We used simple linear regression to relate saline- to angiographically derived \( \alpha V_c \)’s (over all the angiograms) and to relate average saline- or angiographically derived \( \alpha V_c \)’s to LV, RV, and total ventricular masses (over all the experiments).

Computations were done with MINITAB Releases 5.1.2 and 6.1 or BMDP1R.9,10

**Results**

**Saline Injections**

Figure 1 shows total-conductance volume, \( B(t) \), and LV- and RV-pressure tracings during IVCO, AO, and PAO and the subsequent saline injections from experiment 901. We chose these particular tracings because we had digitized long-enough segments of the analog data to see the full transients associated with each balloon occlusion. The decrease in \( B(t) \) with IVCO and PAO and the increase with AO before the saline-induced occlusion were appropriate trends for the respective interventions.

We accepted 172 of the total 265 saline runs for analysis (65%) after we determined they had adequate steady state before the saline injection and good catheter position. Saline runs were excluded chiefly because of ectopy; only four were excluded because of changes in the 6-7 electrode-pair segmental \( B(t) \) waveform suggesting movement of that segment outside the LV. The \( 7 \pm 2 \) beats available per saline run to estimate \( \alpha V_c \) yielded excellent linear fits of \( B_{es} \) versus \( B_{ed} \) with correlation coefficients of 0.975 ± 0.025. Figure 2 shows a set of saline
derivations of $\alpha V_c$. The tight linear correlations had an $r$ of 0.939–0.994 for individual saline injections. However, the IVCO $\alpha V_c$ value of 38 ml was quite different from the 70-ml value for AO and PAO. This degree of variation was large compared with that of the overall data, but we show these plots because they are derived from the same saline runs as shown in Figure 1.

Table 1 summarizes the results of analyses using Equation 5. Each dependent variable is shown as a
column heading, with the control value just below, and the changes from control with different interventions further below. For instance, the LVEDP was 11±1 mm Hg during control, fell by −9±1 mm Hg below control during IVCO, rose 6±1 mm Hg above control during AO, and fell by −5±1 mm Hg compared with control during PAO. Note that these effects are superimposed on the different volume-loading states. The ejection fraction FCA was derived by subtracting average saline-derived \( aV_c \) for each experiment from \( B_{ed} \) and \( B_{es} \). The changes in most hemodynamic variables with the different occlusions were statistically significant and appropriate for the interventions. Note that pulmonary artery occlusion only modestly reduced LVSP, despite a doubling of RVSP.

Table 1 also describes \( aV_c \), which had a control value of 76±2 ml, with a between-dog variability \( S_d \) of 10 ml. During IVCO there was a significant shift in \( aV_c \) from control of −7±2 ml (\( p<0.001 \)). The shifts of 1±2 ml for AO and −2±2 ml for PAO were not significant.

\( aV_c \) also was related to individual hemodynamic variables according to Equation 6. As detailed in Table 2, \( aV_c \) showed significant dependence on LVEDP, LVSP, RVEDP, \( B_{ed} \), and \( B_{es} \). \( aV_c \) did not depend on RVSP in Table 2, which is consistent with the lack of a significant fall in \( aV_c \) with PAO in Table 1. To isolate the most important of the interrelated variables affecting \( aV_c \), we conducted a stepwise multiple linear regression analysis of these data with all the hemodynamic variables in Table 2 as potential independent variables, forcing the dummy variables that quantified between-dog differences into the equation first. This analysis revealed that the chief predictor of saline-derived \( aV_c \) was end-systolic conductance volume, \( B_{es} \). \( aV_c \) is quite sensitive to \( B_{es} \) because it increases by 0.60±0.06 ml for every 1-ml increase in \( B_{es} \). The dependencies of \( aV_c \) on the other hemodynamic variables in Table 2 probably reflect colinearity of these variables with \( B_{es} \). Figure 3 illustrates the dependence of \( aV_c \) on \( B_{es} \) for two representative individual dogs (902 and 906). Figure 4 illustrates the results of the pooled analysis relating \( aV_c \) to \( B_{es} \) and the dog dummies according to Equation 6, after subtracting out the deviation of each dog from the average of all dogs (given by \( b_i \) in Equation 6). The graphic equivalent of this analysis is to plot data from individual dogs shifted upward or downward.

![Figure 2](http://circ.ahajournals.org/)

**Figure 2.** Plot of \( aV_c \) estimates from same saline runs shown in Figure 1. Intersection of \( B_{ed},B_{es} \) plot with line of identity yields \( aV_c \). Note that although AO and PAO yield same \( aV_c \) value of 70 ml, IVCO result of 38 ml is much smaller. \( B_{es} \) and \( B_{ed} \) are end-systolic and end-diastolic total-conductance volume; IVCO, AO, and PAO, balloon occlusion of inferior vena cava, aorta, and pulmonary artery, respectively.

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**Table 1.** Control Hemodynamics and Conductance Data, and Changes During Interventions Preceding Saline Injections

<table>
<thead>
<tr>
<th></th>
<th>LVEDP (mm Hg)</th>
<th>LVSP (mm Hg)</th>
<th>dp/dtmax (mm Hg/sec)</th>
<th>RVEDP (mm Hg)</th>
<th>RVSP (mm Hg)</th>
<th>HR (beats/min)</th>
<th>B_{ed} (ml)</th>
<th>B_{es} (ml)</th>
<th>( \Delta B ) (ml)</th>
<th>FCA</th>
<th>( aV_c ) (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>11±1</td>
<td>119±3</td>
<td>3,260±100</td>
<td>6±0.4</td>
<td>30±1</td>
<td>74±5</td>
<td>130±2</td>
<td>99±1</td>
<td>31±1</td>
<td>0.54±0.02</td>
<td>76±2</td>
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<tr>
<td>Changes from control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVCO</td>
<td>−9±9†</td>
<td>−15±3†</td>
<td>−80±110</td>
<td>−6±0.4†</td>
<td>−7±1†</td>
<td>2±5</td>
<td>−19±2†</td>
<td>−13±1†</td>
<td>−6±1†</td>
<td>0.14±0.02</td>
<td>−7±2†</td>
</tr>
<tr>
<td>AO</td>
<td>6±1†</td>
<td>35±3†</td>
<td>−280±110†</td>
<td>2±0.4†</td>
<td>3±1§</td>
<td>−4±5</td>
<td>2±2</td>
<td>6±1†</td>
<td>−5±1†</td>
<td>−0.09±0.02</td>
<td>1±2</td>
</tr>
<tr>
<td>PAO</td>
<td>−5±1†</td>
<td>−9±3‡</td>
<td>−150±110</td>
<td>4±0.4†</td>
<td>28±1†</td>
<td>26±5†</td>
<td>−18±2†</td>
<td>−10±1†</td>
<td>−8±1†</td>
<td>0.04±0.02</td>
<td>−2±2</td>
</tr>
<tr>
<td>VOL2</td>
<td>3±1†</td>
<td>4±3</td>
<td>−70±100</td>
<td>2±0.4†</td>
<td>3±1§</td>
<td>0±4</td>
<td>3±2§</td>
<td>0±1</td>
<td>3±1§</td>
<td>0.03±0.02</td>
<td>−4±2§</td>
</tr>
<tr>
<td>VOL3</td>
<td>1±0.3†</td>
<td>1±1</td>
<td>−130±40†</td>
<td>2±0.1†</td>
<td>2±0.4†</td>
<td>4±2§</td>
<td>2±1†</td>
<td>2±0.4</td>
<td>0±0.4</td>
<td>−0.02±0.01</td>
<td>1±1</td>
</tr>
<tr>
<td>VOL4</td>
<td>1±1</td>
<td>−1±3</td>
<td>−230±120</td>
<td>2±0.5†</td>
<td>5±1†</td>
<td>15±5†</td>
<td>−2±2</td>
<td>2±2</td>
<td>−4±1§</td>
<td>−0.07±0.02</td>
<td>−3±2</td>
</tr>
<tr>
<td>Sd</td>
<td>5</td>
<td>16</td>
<td>570</td>
<td>3</td>
<td>9</td>
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<td>13</td>
<td>8</td>
<td>7</td>
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<td>10</td>
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<tr>
<td>SEE</td>
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<td>14</td>
<td>500</td>
<td>2</td>
<td>6</td>
<td>21</td>
<td>8</td>
<td>6</td>
<td>5</td>
<td>0.10</td>
<td>9</td>
</tr>
</tbody>
</table>

LVEDP and LVSP, LV end-diastolic and peak systolic pressures; dp/dtmax, maximum time derivative of LV pressure; RVEDP and RVSP, RV end-diastolic and peak systolic pressures; HR, heart rate; \( B_{ed} \) and \( B_{es} \), end-diastolic and end-diastolic conductance volumes; \( \Delta B, B_{es} - B_{ed} \); FCA, LV ejection fraction computed using B(t)−<aV_c>, where <aV_c>=averaged value over all saline derivations for a given experiment and \( aV_c=\)parallel conductance volume. IVCO, AO, and PAO are inferior vena cava, aortic, and pulmonary artery occlusions; VOL2 and VOL3, intermediate and high volume conditions; VOL4, preangiographic condition; \( S_d \), between-dogs variability; SEE, standard error of estimation.

*\( n=172 \) for each regression.

†\( p<0.001 \), ‡\( p<0.01 \), §\( p<0.05 \) vs. control.
so that each dog has an intercept equal to the average intercept for all the dogs.

Angiographic Studies

Angiography was performed in all experiments but 902 (because of equipment problems). A total of 28 angiograms were performed, but 2 were excluded from analysis because of unacceptable noise in the simultaneous B(t) signal (PAO in 904, AO in 906).

As with the saline injection data, we used regression analyses to quantify effects of the interventions performed just before the angiography. Table 3 details the results of these analyses. Although reaching lower levels of statistical significance than the analogous changes during the saline runs (because of the lower power associated with the smaller sample size), the trends are similar and appropriate for the interventions.

Figure 5 shows representative plots of B(t) versus simultaneous angiographic LV volume (A[t]) from experiment 907. These plots are typical of the excellent linear relations observed within a single beat between these two methods of volume determination. For the 26 angiograms analyzed, the B(t)-A(t) correlation coefficient averaged 0.91±0.07. As discussed above, the slope of each line is an estimate of α and the intercept is an estimate of αVc. To test whether α and αVc varied significantly with the different experimental interventions, we performed the same regression analysis as used for the other dependent variables listed in Table 3. According to this analysis, the control αVc averaged 91±4 ml. The change in αVc from control during IVCO of −12±6 ml was similar to that found in the saline-derived data (p<0.054). The changes in αVc during AO, PAO, and the repeat control study were not statistically significant.

To explore the determinants of angiographically-derived αVc further, we performed regressions of αVc against single hemodynamic variables using Equation 6. Table 4 summarizes the results of these analyses. Like the saline results, αVc varied significantly with LVEDP, LVSP, RVEDP, Aed, Bes, and Bref; it also varied significantly with ∆A. Although the coefficients were not exactly the same as those in Table 2, the trends were similar. In addition, as with the saline injection data, stepwise regression indicated primary dependence of αVc on Bref with similar coefficients (0.60±0.06 for saline and 0.77±0.14 for angiographically derived αVc). Figure 6 illustrates the dependence of angiographically determined αVc on Bref using the pooled analysis, in analogy with Figure 4.
The variation in $\alpha$ with the hemodynamic interventions was also analyzed. As detailed in Table 3, the control value for $\alpha$ was $0.78 \pm 0.08$. The largest change from control in $\alpha$ of $0.21 \pm 0.11$ occurred during IVCO, but this did not reach statistical significance ($p<0.078$). The smaller changes from control during the other interventions also were not statistically significant.

We also tested for systematic variation in $\alpha$ by regressing it against individual hemodynamic variables, using Equation 6. As detailed in Table 5, $\alpha$ varied significantly with LVEDP, RVEDP, $\Delta A_{es}$, $\Delta A$, and $B_{es}$. We regressed $\alpha$ against $\alpha V_c$ and dog dummies, obtaining the relation

$$\alpha = (-0.014 \pm 0.003)\alpha V_c + (2.12 \pm 0.26) \Sigma b_i D_i$$

with $p<0.001$ for the $\alpha V_c$ coefficient, $R^2=0.83$, SEE=0.14, and $s_a=0.36$. To test that $\alpha$'s dependence on hemodynamic variables is chiefly due to its dependence on $\alpha V_c$ (which also depends on hemodynamics), we performed a stepwise linear regression of $\alpha$ versus dog dummies, $\alpha V_c$, and the significant independent hemodynamic variables in Table 5. We found that, after taking the between-dog effects into account, the independent variable $\alpha V_c$ accounted for most of the remaining explainable variance in $\alpha$ ($\Delta R^2=0.21$ to total $R^2=0.83$). Thus, although $\alpha$ does correlate significantly with hemodynamic variables, this correlation largely reflects the underlying dependence of $\alpha$ on $\alpha V_c$.

**Stroke Volume**

The conductance and angiographic stroke volumes showed only fair correlation (including between-dog effects) according to

$$\Delta B = (0.42 \pm 0.21)\Delta A + (12 \pm 8) ml + \Sigma b_i D_i$$

### Table 3. Control Hemodynamics, Conductance, and Angiographic Data, and Changes During Interventions Preceding Angiograms*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LVEDP (mm Hg)</th>
<th>LVSP (mm Hg)</th>
<th>dP/dt max (mm Hg/sec)</th>
<th>RVEDP (mm Hg)</th>
<th>RVSP (mm Hg)</th>
<th>HR (beats/min)</th>
<th>$B_{es}$ (ml)</th>
<th>$B_{es}$ (ml)</th>
<th>$\Delta A$ (ml)</th>
<th>$\Delta A$ (ml)</th>
<th>$\alpha$ (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>9+2</td>
<td>118+4</td>
<td>2,990+260</td>
<td>61</td>
<td>32+2</td>
<td>81+5</td>
<td>143+5</td>
<td>111+3</td>
<td>33+4</td>
<td>69+4</td>
<td>25+2</td>
</tr>
<tr>
<td>Changes from control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Repeat</td>
<td>-1+2</td>
<td>-5±7</td>
<td>-40±420</td>
<td>0±1</td>
<td>0±3</td>
<td>8±8</td>
<td>-12±8</td>
<td>-6±5</td>
<td>-6±6</td>
<td>-8±6</td>
<td>-1±4</td>
</tr>
<tr>
<td>IVCO</td>
<td>-6±2§</td>
<td>-14±6§</td>
<td>-320±360</td>
<td>-3±1§</td>
<td>-3±3</td>
<td>8±7</td>
<td>-19±7§</td>
<td>-12±4§</td>
<td>-7±5</td>
<td>-18±6§</td>
<td>-4±3</td>
</tr>
<tr>
<td>AO</td>
<td>3±2</td>
<td>19±7§</td>
<td>90±390</td>
<td>3±1§</td>
<td>4±3</td>
<td>-7±7</td>
<td>7±7</td>
<td>13±4±6</td>
<td>-6±5</td>
<td>4±6</td>
<td>10±3±6</td>
</tr>
<tr>
<td>PAO</td>
<td>-3±2</td>
<td>-3±7</td>
<td>95±390</td>
<td>3±1§</td>
<td>24±3§</td>
<td>5±7</td>
<td>11±7</td>
<td>-3±4</td>
<td>-8±5</td>
<td>-15±6§</td>
<td>-4±3</td>
</tr>
</tbody>
</table>

$s_a$ = 2 9 590 2 11 32 16 15 6 15 8 8 18 0.27

$\Delta A_{es}$ and $\Delta A_{es}$, end-diastolic and end-systolic angiographic LV volume; $\Delta A$, $\Delta A_{es}$, $A_{es}$, $B_{es}$, and $B_{es}$, conductance volume simultaneous with $\Delta A$ and $\Delta A_{es}$; LVEDP and RVEDP, LV end-diastolic and peak systolic pressures; dP/dt max, maximum time derivative of LV pressure; RVSP and RVSP, RV end-diastolic and peak systolic pressures; HR, heart rate.

*p=26 for each regression.

fp<0.001, $fp<0.01$, $fp<0.05$, $fp=0.054$. 

![Figure 4. Plots of saline-derived $\alpha V_c$ plotted versus $B_{es}$ over all dogs but with data from individual dogs shifted upward or downward so that each animal has an intercept equal to average intercept over all experiments. Average slope of this relation is 0.60±0.06 ml/ml (p<0.001).](image-url)
where $\Delta B$ and $\Delta A$ are stroke volumes measured by conductance catheter and angiography respectively. $p=0.06$ for the coefficient of $\Delta A$, $R^2=0.49$. SEE=8 ml and $s_d=7$ ml. The correlation of conductance and angiographic stroke volumes improved substantially when $\alpha$ was included as an additional independent variable (to $R^2=0.82$).

Figure 5. Plots of total conductance versus simultaneous angiographic left ventricular volume from five angiograms performed in experiment 907. Vertical axis intercept is an estimate of $\alpha V_e$, whereas the slope is estimate of $\alpha$. Note strong linear correlations between conductance and angiographic volumes, but that slopes and intercepts change for different angiographic conditions. $A$, angiographic left ventricular volume; REPEAT, repeat control condition; $r$, linear correlation coefficient; IVCO, AO, and PAO, balloon occlusion of inferior vena cava, aorta, and pulmonary artery, respectively.

**Geometric Relation of Conductance Catheter and Left Ventricle**

Figure 7 shows end-diastolic and end-systolic LV profiles during control angiograms, along with corresponding conductance-catheter positions. Although the catheter tip generally reached the apex in lateral projections, it sometimes appeared

### Table 4. Dependence of Angiographically Derived $\alpha V_e$ on Various Single Independent Hemodynamic and Volume Variables*

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>LVEDP (mm Hg)</th>
<th>LVSP (mm Hg)</th>
<th>RVEDP (mm Hg)</th>
<th>RVSP (mm Hg)</th>
<th>$B_{ed}$ (ml)</th>
<th>$B_{es}$ (ml)</th>
<th>$\Delta B$ (ml)</th>
<th>$A_{ed}$ (ml)</th>
<th>$A_{es}$ (ml)</th>
<th>$\Delta A$ (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity (ml/column units)</td>
<td>1.45±</td>
<td>0.35±</td>
<td>1.98±</td>
<td>0.13±</td>
<td>0.41±</td>
<td>0.77±</td>
<td>-0.09±</td>
<td>0.43±</td>
<td>0.30±</td>
<td>0.83±</td>
</tr>
<tr>
<td>$s_d$ (ml)</td>
<td>17</td>
<td>18</td>
<td>17</td>
<td>17</td>
<td>15</td>
<td>10</td>
<td>17</td>
<td>21</td>
<td>19</td>
<td>20</td>
</tr>
<tr>
<td>SEE (ml)</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>11</td>
<td>9</td>
<td>7</td>
<td>11</td>
<td>9</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>$R^2$</td>
<td>0.85</td>
<td>0.81</td>
<td>0.82</td>
<td>0.75</td>
<td>0.82</td>
<td>0.90</td>
<td>0.75</td>
<td>0.81</td>
<td>0.76</td>
<td>0.85</td>
</tr>
</tbody>
</table>

LVEDP and LVSP, LV end-diastolic and peak systolic pressures; RVEDP and RVSP, RV end-diastolic and peak systolic pressures; $B_{ed}$ and $B_{es}$, end-diastolic and end-systolic conductance volumes; $\Delta B$, $B_{ed}-B_{es}$; $A_{ed}$ and $A_{es}$, end-diastolic and end systolic angiographic LV volume; $\Delta A$, $A_{ed}-A_{es}$; $B_{ed}$ and $B_{es}$, conductance volume simultaneous with $A_{ed}$ and $A_{es}$; $R^2$, multiple $R$ squared.

* $n=26$ for each regression.

$\dagger p<0.001$, $\ddagger p<0.01$, $\S p<0.05$.  

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proximal to the apex in anteroposterior views (901, 905, and 906). This situation probably was due to our preferential use of the lateral view for conductance catheter positioning because of its superior image quality. In several experiments the catheter tip appeared to extend into trabeculations beyond the LV cavity at end systole (901, 904, 906, and 907). Additionally, in several experiments, portions of the catheter were immediately adjacent to myocardium (903, 904, and 907). However, B(t) generally showed a satisfactory waveform (including plots versus simultaneous LV pressure), suggesting that these deviations from an ideal central catheter position were not technically important. Furthermore, our main finding that $\alpha V_c$ depends on $B_{es}$ was observed in all experiments, independent of these details in catheter positioning.

To assess consistency of catheter position during the intervention angiograms, we made similar overlaid tracings of LV outlines and catheters (Figure 8). While there were no gross changes in catheter position during the angiographic conditions of each experiment, small changes in the relation of catheter to ventricular length were sometimes apparent (Figure 8).

To analyze these length relations over the interventions more formally, we obtained end-diastolic and end-systolic apex to midaortic valve distances, which are calculated automatically as part of the Simpson’s rule volume algorithm used to analyze the angiograms. As detailed in Table 6, the catheter 1–8 interelectrode distances reasonably matched LV lengths at end diastole. The small decrease from the control end-diastolic LV length of $6.9\pm0.4$ cm to $6.6\pm0.5$ cm during IVCO and increase to $7.1\pm0.4$ cm during AO were not statistically significant. However, the end-systolic LV length often was significantly less than the catheter interelectrode length. This result, combined with the observation that the signal from the proximal electrode pair

![Figure 6. Plot of angiographically derived $\alpha V_c$ versus $B_{es}$, with data from individual dogs shifted upward or downward so that intercept for individual animals was equal to average intercept over all experiments. Slope of this relation is $0.77\pm0.14$ (p<0.001).](http://circ.ahajournals.org/)

**Figure 6.** Plot of angiographically derived $\alpha V_c$ versus $B_{es}$, with data from individual dogs shifted upward or downward so that intercept for individual animals was equal to average intercept over all experiments. Slope of this relation is $0.77\pm0.14$ (p<0.001).

---

**Table 5. Dependence of Angiographically Derived $\alpha$ on Various Single Independent Hemodynamic and Volume Variables**

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>LVEDP (mm Hg)</th>
<th>LVSP (mm Hg)</th>
<th>RVEDP (mm Hg)</th>
<th>RVSP (mm Hg)</th>
<th>$B_{ed}$ (ml)</th>
<th>$B_{es}$ (ml)</th>
<th>$\Delta B$ (ml)</th>
<th>$A_{ed}$ (ml)</th>
<th>$A_{es}$ (ml)</th>
<th>$\Delta A$ (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity (l/cm)</td>
<td>$-0.025\pm$</td>
<td>$-0.002\pm$</td>
<td>$-0.035\pm$</td>
<td>$-0.001\pm$</td>
<td>$-0.003\pm$</td>
<td>$-0.010\pm$</td>
<td>$0.006\pm$</td>
<td>$-0.010\pm$</td>
<td>$-0.010\pm$</td>
<td>$-0.017\pm$</td>
</tr>
<tr>
<td>s_d</td>
<td>0.0 0.0</td>
<td>0.0 0.0</td>
<td>0.0 0.0</td>
<td>0.0 0.0</td>
<td>0.0 0.0</td>
<td>0.0 0.0</td>
<td>0.0 0.0</td>
<td>0.0 0.0</td>
<td>0.0 0.0</td>
<td>0.0 0.0</td>
</tr>
<tr>
<td>SEE</td>
<td>0.18</td>
<td>0.21</td>
<td>0.18</td>
<td>0.21</td>
<td>0.18</td>
<td>0.21</td>
<td>0.18</td>
<td>0.21</td>
<td>0.17</td>
<td>0.20</td>
</tr>
<tr>
<td>R^2</td>
<td>0.75</td>
<td>0.64</td>
<td>0.72</td>
<td>0.63</td>
<td>0.65</td>
<td>0.72</td>
<td>0.65</td>
<td>0.65</td>
<td>0.67</td>
<td>0.67</td>
</tr>
</tbody>
</table>

LVEDP and LVSP, LV end-diastolic and peak systolic pressures; RVEDP and RVSP, RV end-diastolic and peak systolic pressures; $B_{ed}$ and $B_{es}$, end-diastolic and end-systolic conductance volumes; $\Delta B$, $B_{ed}-B_{es}$; $R^2$, multiple R squared; $A_{ed}$ and $A_{es}$, end-diastolic and end systolic angiographic LV volume; $\Delta A$, $A_{ed}-A_{es}$; $B_{ed}$ and $B_{es}$, conductance volume simultaneous with $A_{ed}$ and $A_{es}$.

$n=26$ for each regression.

*p<0.001, †p<0.01, ‡p<0.05.
rarely indicated extrusion of that catheter segment into the aorta (this was observed in only 4 of 265 [1.5%] of saline runs), suggests that the catheter bends slightly during systole (Figures 7 and 8) so that it remains properly placed throughout the cardiac cycle.

Comparison of Saline and Angiographic Data

Table 7 summarizes average values of saline-derived $\alpha V_c$, angiographically derived $\alpha V_c$ and $\alpha$, and ventricular mass data for each experiment. The angiograms yielded an overall $\alpha V_c$ of 87±19 ml, which is significantly larger than the 75±15 ml value derived using saline bolus injections ($p<0.001$). To explore this discrepancy further, we regressed angiographically derived $\alpha V_c$ on its saline-derived counterpart over all the angiograms, and obtained the relation

$$\alpha V_{c\text{SALINE}}=0.53 \alpha V_{c\text{ANGIO}}+25 \text{ ml}$$

with $r=0.57$ and SEE=13 ml ($p<0.01$). This poor correlation, as well as the significant difference in mean results, raises questions about the relative accuracy of the two different methods of estimating $\alpha V_c$. Nevertheless, note that for the purpose of studying $\alpha V_c$ variation, saline and angiographic data provide similar results.

Finally, neither saline- nor angiographically derived $\alpha V_c$ correlated significantly with LV, RV, or total ventricular masses. This result suggests that, at least over the range of heart sizes that we studied, the parallel-conductance volume depends on left ventricular cavity size rather than wall mass.

Discussion

The principal finding in this study is that $\alpha V_c$ depends on end-systolic–conductance volume, $B_{es}$. This result contradicts the assumption that the parallel-conductance volume is constant over a wide range of hemodynamic states. $\alpha$ and $\alpha V_c$ are the slope and intercept of the linear-regression relation between conductance volume ($B[t]$) and some other measure of absolute LV volume (compare with Equations 1 and 4). Our data are consistent with the assumption that $\alpha$ and $\alpha V_c$ may be treated as constants during steady-state cardiac cycles. However, both these fitting parameters may change significantly in response to changes in the hemodynamic state in intact dogs. Our findings pose particular problems for conductance-catheter measurement of the absolute end-systolic–pressure-volume relation.5 Because this measurement generally requires interventions that produce a wide range of LV volumes.

The dependence of $\alpha V_c$ and $\alpha$ on LV size suggest a nonlinear relation between the conductance volume ($B[t]$) and true LV volume ($V[t]$). To appreciate the magnitude of this nonlinearity, allow $\alpha$ and $\alpha V_c$ to vary linearly with $B_{es}$ according to

$$\alpha=a_0+a_1 B_{es}$$

and

$$\alpha V_c=b_0+b_1 B_{es}$$

Substituting these expressions into Equation 1 at end systole and rearranging yields

$$B_{es}=(a_0 V_{es}+b_0)/(1-b_1-a_1 V_{es})$$

Figure 9 shows a plot of Equation 9 using average values of $a_0$, $a_1$, $b_0$, and $b_1$ from the angiographic data. Because of the curvature in the $B$-$V$ plot (convex toward the $B$ axis), the intercept ($\alpha V_c$) increases but the slope ($\alpha$) decreases as $V$ increases.
Note that although this nonlinearity is not apparent when analyzing single cardiac cycles (Figure 4), it emerges from analysis over a broad hemodynamic range.

Comparison With Related Literature

The nonlinearity in the B(t)-V(t) relation, which our data suggest, is not necessarily surprising. There were small but significant nonlinearities convex toward the B(t) axis in the theoretical and in vitro results of Mur and Baan11 and of Salo et al.12 Furthermore, because linearity may depend on equipotential surfaces that are planes uniformly spaced and perpendicular to the LV long axis,12 the complex effect of realistic LV geometry on the electric field may amplify the problem of nonlinearity in vivo.13

Baan et al2 found that $\alpha V_c$ estimated by temporarily emptying the LV and RV was essentially the same as that estimated by the saline injection method, when the two results were related over 26 dogs. This is one piece of evidence that $\alpha V_c$ is a constant, independent of LV volume. However, when one examines the data (Figure 7 of reference 2), the strength of the correlation depends on 2 points at the high end of the scale. Indeed, it is surprising that this maneuver worked as well as it did; emptying the LV could result in bizarre ventricular geometry with a high likelihood of catheter extrusion out the aortic valve. Furthermore, if $\alpha V_c$ depends on RV filling as other studies suggest,3,4 then it is also unclear why a near-identity relation between the two estimates was found because the RV was empty in one method but filled in the other.

Baan et al1,2 also found nearly linear relations between conductance and electromagnetic flowprobe stroke volumes over a wide range during IVCO in individual dogs, which is another argument for a linear B(t)-V(t) relation. However, because changes in $\alpha V_c$ may be relatively small during a single beat, stroke volume is less sensitive to variation in $\alpha V_c$ than absolute volume.1,2 The other data presented by Baan et al1,2 showing linearity between B(t) and V(t) within single cardiac cycles do not address the question of $\alpha V_c$ variation over a wide hemodynamic range.

Burkhoff et al3 found a remarkably linear B(t)-V(t) relation over a large volume range using ventricular balloon volume in isolated, ejection dog hearts (with a small shift in the relation when the RV was filled). However, the average $\alpha V_c$ of about 25 ml measured in that study does not fit with the 70–80 ml range observed in open-chest, closed-pericardium dogs4 or fully intact dogs (our data). This difference suggests an insulating effect in their isolated heart preparations. The authors tried to compensate for this problem by using pericardial tissue for the balloon, but this balloon does not

<table>
<thead>
<tr>
<th>TABLE 6. Conductance-Catheter Total Interelectrode Distances and Left Ventricular Lengths (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Exp</strong></td>
</tr>
<tr>
<td>901</td>
</tr>
<tr>
<td>903</td>
</tr>
<tr>
<td>904</td>
</tr>
<tr>
<td>905</td>
</tr>
<tr>
<td>906</td>
</tr>
<tr>
<td>907</td>
</tr>
</tbody>
</table>

Exp, experiment number; C, conductance-catheter total interelectrode distance; ED and ES, end-diastolic and end-systolic LV length; IVCO, AO, and PAO are inferior vena caval, aortic, and pulmonary artery occlusions. *p<0.05 vs. C using Dunnet's test.

<table>
<thead>
<tr>
<th>TABLE 7. Comparison of Saline- and Angiographically Derived $\alpha V_c$, With Corresponding $\alpha$ and Ventricular Masses</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Exp</strong></td>
</tr>
<tr>
<td>901</td>
</tr>
<tr>
<td>902</td>
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<tr>
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<td>905</td>
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<tr>
<td>906</td>
</tr>
<tr>
<td>907</td>
</tr>
<tr>
<td>75±16</td>
</tr>
</tbody>
</table>

$\alpha V_c$, parallel conductance volume.
*Including septum.
†p<0.001 vs. saline $\alpha V_c$. 
ameliorate the insulating effects of the air around the heart. In addition, because Burkhoff et al.\textsuperscript{1,2} incised the mitral valve and suspended the heart from a disc in the mitral orifice, the LV geometry in their preparation was probably much simpler than that occurring in vivo, with potentially important effects on the electric field, and therefore on the B(t)-V(t) relation.\textsuperscript{13}

Kass et al.\textsuperscript{4} used the conductance catheter to measure the end-systolic-pressure-volume relation in open-chest, closed-pericardium dogs and obtained reproducible results that changed appropriately with inotropic interventions.\textsuperscript{4} However, the curve shifted noticeably when PAO was used instead of IVCO. They suggested that alterations in parallel-conductance volume due to variations in RV filling were potentially important, particularly during PAO. In our study, however, $\alpha V_c$ varied significantly with IVCO but not PAO. This difference may stem from milder PAO interventions in our study. Kass et al.\textsuperscript{4} also presented a table of $\alpha V_c$ results over several experimental interventions as evidence that parallel-conductance volume did not vary. We performed similar analysis formally with a much larger data set, and were able to demonstrate significant variation in $\alpha V_c$ with hemodynamic changes.

**Potential Limitations of This Study**

Several animals showed reflex bradycardia during AO (Figure 1B). However, the goal of our study was to quantify variation in $\alpha V_c$ and $\alpha$, and not to measure the end-systolic-pressure-volume relation, per se. Thus, our protocol did not include autonomic blockade. We defined end systole as the point of minimum B(t), again because we were not measuring the end-systolic-pressure-volume relation. We examined the waveform of the 6–7 electrode-pair segmental-conductance volume during each saline and angiographic run. If the 6–7 segment is extruded into the aorta, the waveform shows an increase in conductance volume during systole. Of the 265 saline runs, and 28 angiograms, only four of the saline runs showed waveform changes suggesting significant catheter extrusion, and these runs were excluded from the analysis. Our B(t) waveform sometimes showed slight variation during isovolumic portions of the cardiac cycle (see Figure 11). This has been the general experience with this catheter measurement,\textsuperscript{2,4} and presumably reflects LV shape change or other minor dynamic effects.

Our analysis of the saline data began with a formulation assuming $\alpha$ and $\alpha V_c$ were constant, and then used the results over a range of hemodynamic states to study variation in these parameters. This procedure may seem contradictory. However, the $\alpha$ and $\alpha V_c$ parameters in Equation 1 still may be assumed to be constant during a given steady state, as demonstrated by the linear relations in the B(t)-A(t) data (Figure 4). Thus, the use of steady states allowed us to study variation in $\alpha$ and $\alpha V_c$.

**Assessment of Steady State**

The only theoretical requirement for the saline derivation of $\alpha V_c$ is a constant ejection fraction.\textsuperscript{2} It is possible that non–steady-state conditions, after some interventions, could have resulted in some differences in ejection fraction values from those that would have existed under steady-state conditions. Because it is difficult to measure ejection

![Figure 9](http://circ.ahajournals.org/)

**Figure 9.** Theoretical plot of end-systolic conductance volume versus true end-systolic left ventricular volume, accounting for linear dependencies of $\alpha V_c$ and $\alpha$ on B\textsubscript{es}. Because of nonlinearity in relationship, which is convex toward B axis, y axis intercept ($\alpha V_c$) increases but slope ($\alpha$) decreases as V increases.
fraction continuously in an intact animal (or patient), as a practical matter, one requires that the animal (or patient) be in hemodynamic steady state during the saline injection. Like most investigators, we assessed steady state during the experiments by visually examining the on-line pressure and conductance tracings after applying the occlusion, and then performed the saline injection when these signals had stabilized. Because we sought to validate the conductance catheter in an intact preparation to obtain data directly comparable with that obtained in clinical investigations, we had less control than is possible in open-chest or isolated heart preparations previously used for validation studies of the conductance catheter. For the conductance catheter to be a useful clinical tool, it must perform accurately under these conditions and over a wide range of hemodynamic states.

To ensure that modest deviations from steady state that may not have been detected during the experiment were not affecting our conclusions, we subjected our data to an extremely strict criteria of "steadiness," then checked whether our results changed. We tested for the presence of steady state in the originally accepted saline runs in the following way (see Figure 10): We used beat-to-beat values of $B_{es}$, LVEDP, LVSP, $dP/dt_{max}$, RVEDP, and RVSP for several beats before the saline injection and during the beats used to estimate $\alpha V_c$ after the injection, then fit these values with the regression equation

$$y = c_0 + c_1b + c_2bS$$

where $y$ is the hemodynamic variable of interest, $b$ is the beat number, defined to be zero for the beat just preceding the saline-induced transient in conductance volume, and $S$ is a dummy variable defined as 0 before the saline transient ($b<0$) and as 1 during the saline transient ($b\geq0$). According to this analysis, $c_0$ is the value of $y$ on beat zero, $c_1$ is the change in $y$ per beat before the saline transient, and $c_2$ is additional change in $y$ per beat after the onset of the saline transient. If $y$ is in steady state before the saline injection, $c_1$ will be 0, and if the saline injection does not affect the hemodynamic variable, $c_2$ will be 0. (We did not consider $c_2$ for $B_{es}$ or $B_{es}$, because the saline injection is designed to change these signals.) We can test formally whether each of these coefficients is significantly different from 0.

Because of the statistical power of this method, in many cases we detected a statistically significant trend, even though the absolute changes in the hemodynamic variables were very small, often less than a 1% change or small fraction of a millimeter of mercury per beat.

We applied this analysis to each of the 172 saline injections and rejected an injection if any one of the hemodynamic variables was associated with a value of $c_1$ or $c_2$ significantly different from 0, no matter how small the effect. (The departures from strict steady state in Figure 1 are somewhat larger than what we observed in many of the 172 saline runs analyzed, and that run was rejected according to this criteria; therefore, Figure 1 provides a conservative presentation of "typical" data.) Only 26 saline injections met these extremely strict criteria.

We used these 26 saline injections to again test the dependence of $\alpha V_c$ on $B_{es}$ using Equation 6 and obtained $b_{hes}$ equal to $0.534\pm0.162$ ($p<0.01$), which is not significantly different from the value of $0.598\pm0.059$, based on the full data set of 172 saline injections. The dependence of $\alpha V_c$ on end-

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**Figure 10. Definition of model used for steady-state analysis.**

$\text{Analysis of Steady State}$

$y = c_0 + c_1b + c_2bS$

$\text{Slope} = c_1$

$\text{Intercept} = c_0$

$\text{Slope change} = c_2$

$\text{Dependent variable, } y$

$\text{Beat number, } b$
systolic–conductance volume remains constant (within sampling variability) and statistically significant, despite the loss of statistical power associated with reducing the sample size from 172 to 26. This consistency provides convincing evidence that the conclusion that \( aV \) varies with \( B es \) is reliable and is not somehow an artifact of small deviations from steady state in our intact dogs. The results of the analysis also suggest that the small hemodynamic variations that were present in some of the saline runs did not have a systematic impact on the \( aVc \) determinations.

### Multiple Saline Injections

In planning the saline portion of the protocol, we anticipated giving multiple injections to obtain sufficient data to study variation in \( aVc \) under a variety of hemodynamic conditions. We, therefore, anticipated that blood conductivity would increase, so that a small injection of saturated saline would have a decreasingly measurable effect on the conductance signal. For this reason, we chose to inject 3–4 ml saturated saline throughout the protocol, instead of the usual 1–1.5 ml. There might have been imperfect mixing of this much saline within the LV blood pool, but we did not have enough channels to analyze all the segmental \( aVc \)’s for proper mixing. However, it is unlikely that a mixing problem would have led to the systemic trends we observed.

We found almost no evidence that the saline injections caused a hemodynamic disturbance. There were 48 saline runs during control conditions out of the total 172 runs analyzed. When these episodes were submitted to the steady-state analysis detailed above, only two of 48 showed a statistically significant \( c2 \) coefficient for LVEDP or RVEDP, which should be sensitive indicators of a volume loading effect.

The large total salt load did cause \( \rho \) to fall and, therefore, \( Gp \) to rise, during the course of the protocol, and the possibility that this confounded the \( aVc \) determinations is an appropriate concern. To investigate this issue, we regressed \( aVc \) versus \( \rho \) and the dog dummy variables, and found no significant dependence on \( \rho \). Thus, \( Gp \) goes up as \( \rho \) goes down, but these two effects cancel out such that \( aVc = \rho L^2 Gp \) shows no net dependence on \( \rho \). This fact allowed us to analyze hemodynamic dependence of \( aVc \), despite variation in \( \rho \) and \( Gp \) during data acquisition. Furthermore, variation in \( \rho \) in no way accounted for the dependence of \( aVc \) on \( B es \). The preparation probably deteriorated because of the salt loading during the course of the protocol. However, our goal was assessment of \( aVc \) and not contractile performance, and the lack of dependence of \( aVc \) on \( \rho \) implies that deterioration of the preparation did not confound this analysis. In addition, because \( aVc \) showed no significant dependence on \( \rho \) over the entire protocol, it is unlikely that salt loading and myocardial edema accounted for the lack of correlation between control \( aVc \) and postmortem LV wall mass.

### Data Analysis

There may be a concern that because both \( aVc \) and \( B es \) depend on animal size, our pooled analysis of different-sized dogs led to an artifactual dependence of \( aVc \) on \( B es \). However, our use of dummy variables for individual dogs is a standard way of allowing for between-subjects differences in linear regression. As illustrated in Figures 3 and 5, this analysis is graphically equivalent to plotting \( aVc \)
versus $B_{es}$ but with $\alpha V_{c}$ data from individual subjects shifted upward or downward so the line for each dog has an intercept equal to the average intercept for all dogs.

**Angiography**

Angiography, although not perfect, is an established modality that continues to have an important role in the study of ventricular function.\textsuperscript{16} Baan et al\textsuperscript{3} believed angiography was dependable enough to include in their validation studies. Our biplane Simpson’s rule LV volume computation showed excellent correlation with displacement volumes of realistic ventricular models. However, the actual angiograms often had less than ideal opacification, especially in the anteroposterior projection. Mild hysteresis in the $B(t)$-$A(t)$ plot was present in nine of the 26 angiograms performed but not consistently during any one intervention (Figure 5). This hysteresis may have reflected a technical problem due to less LV opacification during the second half of the cardiac cycle. Despite the limitations of angiography, however, it is unlikely that random errors in the angiographic data would have lead to the systematic trends that we observed.

We took care to match the resistivity of the angiographic material to that of blood just before each angiogram. This is an important technical detail in comparing simultaneous conductance and angiographic volumes, which was neglected in the study of Baan et al.\textsuperscript{2} We do not interpret the conductance catheter sometimes projecting beyond the opacified LV chamber as a measure of angiographic error (Figures 7 and 8). We believe this observation represents the catheter tip being extruded beyond the true LV blood pool, that is, between trabeculations compressed together during cardiac contraction. Indeed, angiography permitted us to check actual catheter placement. The fact that the actual LV geometry and catheter placement are often different from theoretic assumptions may require more realistic accounts of the electric field and $B(t)$-$V(t)$ relation.\textsuperscript{13}

Because the angiographic and saline injection methods are independent ways to estimate $\alpha V_{c}$, the consistent dependence on $B_{es}$ lends credence to our conclusion regarding volume dependence of $\alpha V_{c}$. In addition, Applegate et al\textsuperscript{17} recently reported similar findings when comparing conductance volume to sonomicrometer LV volume. Furthermore, preliminary analyses of conductance volume versus fast computerized tomographic data show similar results (J. Baan et al, unpublished observations). Although single modalities may be questioned, the consistent dependence of $\alpha V_{c}$ on LV size over four independent modalities is persuasive.

**Right Ventricular Effects**

It may be argued that most of the $\alpha V_{c}$ variation in our data was due to changes in RV filling. Measurement of RV volume would have been desirable, but this was not feasible in our closed-chest preparation. Nevertheless, there is little doubt that PAO sufficient to cause a decrease in LVSP causes a substantial increase in RV volume. If RV volume were the only factor causing variation in $\alpha V_{c}$, then $\alpha V_{c}$ should have increased significantly during PAO; it did not (see Table 3). To explore this question further, we performed stepwise regression of saline-derived $\alpha V_{c}$ against $B_{es}$, the PAO dummy variable, and the dog dummy variables. $B_{es}$ again explained most of the variance in $\alpha V_{c}$ ($\Delta R^2=0.21$ to total $R^2=0.66$), with an additional upward increase of 4.5 ml during PAO (further, $\Delta R^2=0.02$ to total $R^2=0.68$). Thus, during PAO, there is an increase in $\alpha V_{c}$, presumably due to RV dilation, which is sufficient to obscure the effect of concomitant decrease in $B_{es}$. However, this probable RV-filling effect was not strong enough to cause a significant net increase in $\alpha V_{c}$.

**Potential Applications of the Conductance Catheter**

All studies to date, including the current one, show a linear relation between $B(t)$ and $V(t)$ over single steady-state cardiac cycles.\textsuperscript{2,3,17} Even when limited to single cardiac cycles, however, there are practical difficulties with measurement of absolute LV volume because estimation of $\alpha V_{c}$ and $\alpha$ are required. The saline method of estimating $\alpha V_{c}$ showed significant variability. For instance, after accounting for all effects associated with the interventions and the between-dog differences, the standard deviation of the residuals (SEE) in $\alpha V_{c}$ was 9 ml (Table 1, Figure 4). This result is not surprising because the saline method is essentially an indicator-dilution washout method of estimating $\alpha V_{c}$, and such washout methods are subject to variability of the order we observed. Moreover, because saline estimation of $\alpha V_{c}$ derives from the intersection of the $B_{es}$-$B_{ed}$ regression with the line of identity, small errors in the slope of that regression may cause large errors in the $\alpha V_{c}$ intercept (Figure 2). As with other dilution methods, our experience suggests that multiple (i.e., 3–5) saline runs should be performed to obtain a representative average $\alpha V_{c}$ in a given steady state. This many saline injections may alter the state under study or may not be tolerated clinically. Although this inherent uncertainty in the parallel conductance volume is only about 10–15% of the parallel-conductance volume (which is actually quite precise for a washout method), the absolute uncertainty can be significant compared with the LV volume, which is approximately 50 ml in a dog.

On the other hand, in applications where absolute measurement is not required, the conductance catheter remains a promising technique for potentially high time-resolution measurement of changes in LV volume over single cardiac cycles.

The significant underestimation of $\alpha V_{c}$ by saline injection compared with that by angiography in the current study also raises questions about the ulti-
mate accuracy of the saline method. Baan et al. found a similar discrepancy in several of their patients studied angiographically. In contrast, Burkhoff et al. found that the saline method almost exactly predicted the value of $\alpha V_c$ obtained by comparison with balloon-ventricular volume. However, the saline was injected into a closed system with a rigorously controlled ejection fraction, which is an idealized model of what actually happens in an intact circulation. Kass et al. assumed $\alpha$ to be equal to unity in different dogs. Our angiographic results contradict this assumption (Table 7), and emphasize that $\alpha$ should be estimated in individual experiments or patients, if the goal is absolute volume measurement or between-subject comparison.

Because $\alpha V_c$ cancels out in the calculation, conductance-catheter measurement of stroke volume (and by inference, stroke filling) is not hampered by variation in $\alpha V_c$, and appears relatively accurate. However, our angiographic data suggest that $\alpha$ (which does not cancel out) may vary enough to limit the accuracy of conductance stroke-volume measurement when multiple hemodynamic states are studied. In contrast, Baan et al. validated conductance stroke volume against electromagnetic flow probe over a similarly broad hemodynamic range and provided more positive results. Baan et al. performed multiple conductance and electromagnetic flow-probe stroke-volume comparison in individual dogs, whereas we only obtained 4–5 comparisons per animal. By combining the stroke-volume data from all the dogs, where the $\alpha$ for individual animals varied from 0.60 to 1.18, our analysis exaggerated the importance of $\alpha$ variation. Furthermore, electromagnetic flow-probe data are superior in accuracy to our angiographic measurements of stroke volume.

The major attraction of the conductance-catheter technique has been the possibility of continuous absolute LV volume measurement over a broad range of hemodynamic states. Unfortunately, our results suggest that this application will remain elusive until variations in $\alpha$ and $\alpha V_c$ somehow are taken into account. Our data do not, however, exclude the possibility that the conductance catheter gives a useful measurement of relative LV volume over a range of hemodynamic states. If $\alpha$ and $\alpha V_c$ vary chiefly in relation to LV size, as our data suggest, then uncorrected $B(t)$ would still have a monotonic (albeit nonlinear) dependence on LV volume. Assuming that the $\alpha$ and $\alpha V_c$ dependencies are fairly constant in an individual subject, this would explain why end-systolic–pressure–conductance volume studies show appropriate within-subject behavior during pharmacologic interventions. However, as illustrated in Figure 10, variations in $\alpha$ and $\alpha V_c$ with LV size would affect estimation of the true slope and intercept in the absolute end-systolic–pressure-volume relation, as also recently reported by Applegate et al. In addition, our findings suggest that the conductance catheter is not an ideal modality for assessing nonlinearity of the absolute end-systolic–pressure-volume relation, itself.

**Conclusion**

The parallel component of the conductance-catheter volume signal is not constant over a broad range of hemodynamic states; it increases as LV size increases. The variations in $\alpha V_c$ and in $\alpha$ presumably reflect nonlinearity in the B(t)-V(t) relation. Although it provides a useful measurement of relative LV volume, the conductance-catheter technique cannot provide accurate absolute-volume measurement over a broad hemodynamic range if $\alpha$ and $\alpha V_c$ are treated as constants. This result calls into question the current use of the conductance catheter to measure the absolute end-systolic–pressure-volume relation in experimental or clinical studies.

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