Determinants of End-Systolic Pressure-Volume Relations During Acute Regional Ischemia In Situ

David A. Kass, MD, Paolo Marino, MD,
W. Lowell Maughan, MD, and Kiichi Sagawa, MD†

The influence of extent and location of regional ischemia, baseline left ventricular systolic function, and autonomic reflexes on in situ left ventricular end-systolic pressure-volume relations (ESPVRs) during coronary occlusion were studied in 13 open-chest dogs. Circumflex or left anterior descending arteries were randomly occluded (at proximal or distal sites) for 3 minutes in reflex-blocked (n=6, hexamethonium/vagotomy) and unblocked (n=7) animals. Pressure-volume data were obtained by the conductance-catheter technique, with ESPVRs determined by transient inferior vena caval occlusion. Ischemic zone size was estimated for each occlusion by radiolabeled microspheres. The relative influence of each variable on ESPVR change with ischemia was determined by multiple regression analysis. As in previous studies, regional ischemia displaced ESPVRs to the right by an amount that varied directly with ischemic bed size (y=+0.48x, r=0.76, p<0.001). However, in contrast to previous data, coronary occlusion also reduced the ESPVR slope (end-systolic elastance, Ees) in the majority of cases. The extent of slope change was primarily dependent on the baseline elastance (Eesbase), such that the higher the initial elastance, the larger its subsequent reduction for any amount of ischemia (ΔEes=−0.78Eesbase, r=0.94, p<0.001). Active reflexes added an offset constant to this relation (+3.15 mm Hg/ml, p<0.001). In addition, Ees fell slightly more with larger ischemic regions. Thus, although previous studies have reported primarily rightward parallel shifts in ESPVR with regional ischemia, the present data also demonstrate that the slope of the relation is often reduced. Greater baseline elastances typical of in situ, as opposed to isolated, ventricles probably explain the differences in apparent responses. (Circulation 1989;80:1783–1794)

Regional ischemia leads to complex changes in the end-systolic pressure volume relation (ESPVR) due to heterogeneity of myocardial function. In isolated canine ventricles, acute regional ischemia results in ESPVR curvilinearity (convex to the volume axis), such that at sufficiently high end-systolic pressures, the local slope is similar to baseline, but the relation is shifted rightward by a volume amount that varies directly with ischemic zone size (Figure 1). The only previous study of in vivo ESPVR during regional ischemia also demonstrated a rightward shift of the relation with little change in slope (Ees), similar to isolated heart data. Ischemic zone size, however, was not determined in this study; thus, a relation between ischemia extent and ESPVR shift could not be quantified.

Although these two previous experimental studies found negligible Ees change during regional ischemia, several theoretical models1-3 have suggested that Ees reduction might well occur. Other factors in addition to ischemic extent could play important roles in determining the net ESPVR response to regional ischemia. For example, baseline systolic function, autonomic reflex activation,4,5 or the site of ischemic insult6,7 (anterior versus posterolateral wall) might modify any responses. A quantitative assessment of the relative contribution of each of these factors would be useful, not only towards interpreting in vivo animal data, but also in assessing data obtained in humans during acute ischemia, after reperfusion, or both, and in patients undergoing coronary balloon angioplasty.8,9

The purpose of the present study was to identify those factors that principally determine the nature

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From the Department of Internal Medicine, Division of Cardiology, and the Department of Biomedical Engineering, Johns Hopkins Medical Institutions, Baltimore, Maryland.

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Address for correspondence: David A. Kass, MD, Division of Cardiology, Carnegie 538, Johns Hopkins Hospital, 600 N. Wolfe Street, Baltimore, MD 21205.

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†Dr. Sagawa died on August 22, 1989.
and extent of altered systolic function, assessed by the ESPVR, during acute regional ischemia in situ. Acute coronary occlusions of the left anterior descending or left circumflex artery were made at proximal and distal sites to vary the ischemic region over a wide range. The influence of autonomic reflexes on ESPVR change with ischemia was examined by studying two animal groups either with or without autonomic blockade. We tested whether factors such as the extent and location of ischemia, baseline end-systolic elastance, ambient peak systolic pressure, and reflex activation significantly and independently influenced changes in ESPVR during ischemia. Our experimental results were then compared with predictions based on a previously proposed two-elastance model$^1$ of regional ischemia.

**Methods**

**Preparation**

Thirteen mongrel dogs of either sex (20–25 kg) were anesthetized with sodium thiopental (17.6 mg/kg) and chloralose-urethane (13.6 and 136 mg/kg), and were ventilated on a volume respirator (Harvard Apparatus, South Natick, Massachusetts). The chest was opened by a median sternotomy, and the heart was suspended in a pericardial cradle. Silk threads were placed loosely around the left anterior descending (LAD) and circumflex (CIRC) arteries proximal and distal to the first or second major branch. A micromanometer-tipped catheter (PC-350, Millar, Houston, Texas) was advanced through a guiding tube sutured to the left atrium and positioned in the mid–left ventricle for pressure recording. Additional catheters were placed in the left atrial appendage for microsphere injection, the right ventricle through a jugular vein for volume signal calibration, and a femoral artery for peripheral blood pressure recording and arterial reference sampling during microsphere injection. An inferior vena cava balloon-occlusion catheter was used to transiently lower preload and generate ESPVRs. The region at the sinus node was compressed with a clamp to minimize heart rate changes during coronary occlusion (in the unblocked animals) without abolishing an atrial (or sinus) rhythm.

The conductance catheter technique has been previously described in detail.$^{10-12}$ Briefly, an 8F eight electrode conductance (volume) catheter (Webster Labs, Baldwin, California) was introduced through the left carotid artery and advanced along the left ventricular long axis to the apex. A stimulator/signal processor (Sigma V, Leycom, Oegstgeest, The Netherlands) provided a 40 $\mu$A, 20 kHz current field between the two catheter electrodes at the apex and just above the aortic valve, and measured voltages at each of six equally spaced intervening electrodes along the long axis. The voltages were converted to conductances (assuming a constant current), which were directly proportional to chamber volume. Catheter placement required examination of each segmental pressure-volume (P-V) loop to confirm that each of the individual segments (sequential electrode pairs) was intracavitary and displayed normal counterclockwise P-V motion. In addition, the catheter was imaged by two-dimensional echocardiography to confirm proper orientation along the longitudinal axis and position of the distal tip at the apex.

Myocardial blood flow determinations were made using 9–11 $\mu$m spheres radiolabeled with one of Ce$^{141}$, Sn$^{113}$, Nb$^{95}$, or Sc$^{46}$ suspended in dextran and mixed with Tween 80 (New England Nuclear). The microspheres were vibrated for 5 minutes on a vortex mixer before injection. Approximately 2 million microspheres were injected into the left atrium through an indwelling catheter. Simultaneous reference arterial samples were withdrawn at a constant rate (2.16 ml/min) by a calibrated pump. Real-time P-V loop display and eight-channel A-D conversion (at 200 Hz) were performed with a 16-bit microcomputer system (model 232A, Halcom, Maryland). Data were stored on removable hard disks for subsequent analysis.

**Experimental Protocol**

Two animal groups were studied. In seven dogs (unblocked) autonomic reflexes were intact, whereas in six additional animals (blocked), reflexes were eliminated by hexamethonium chloride (35 mg/kg) and bilateral cervical vagotomy. This dose of hexamethonium assured adequate and lasting blockade, however, it also induced vasodilation and myocardial depression.$^{10}$ Arterial pressure was supported by intravenous fluids (normal saline and hetastarch). In addition, a single bolus of amrinone HCl (2 mg/kg) was provided to help sustain the preparation during this period. The preparation was allowed to stabilize for at least 30 minutes.

After obtaining baseline hemodynamics, myocardial blood flow, and ESPVR determinations, a coronary artery site was occluded with the snare occluder. Repeat ESPVR, and microsphere blood flow determinations were made after 3 minutes of...
occlusion, and the snare occluder was then released with at least 20–30 minutes provided for return to baseline. Repeat baseline recordings of all hemodynamic variables and ESPVRs were made before each subsequent occlusion. Each animal underwent a total of four occlusions, one at each of the previously isolated artery sites (distal and proximal LAD and CIRC), and the order of occlusion was fully randomized. In two unblocked animals, ventricular fibrillation occurred on reperfusion of proximal occlusions and was treated with direct current countershock for an additional 30 minutes before further data recording. Autonomically blocked animals did not demonstrate any significant arrhythmias with coronary occlusion.

**Volume Signal Calibration**

Volume catheter signal calibration was performed by the hypertonic saline technique, previously described in detail.10–12 Concentrated (>15-fold normal) saline (1–2 ml) was rapidly injected into the right ventricle with ventilation held at end expiration. The resulting transient change in chamber blood conductivity without true volume change enabled theoretical calculation of the catheter signal at zero blood conductivity. This value (parallel conductance) represented the contribution of the heart muscle and surrounding structures to the total signal. The value was subtracted to yield absolute volume. Each parallel conductance (Vp) determination was the average of at least three separate estimates. The coefficient of variation for multiple estimates was 4.1±3%. Vp was redefined several times during each experiment, and volumes were calibrated accordingly. To assess for possible alterations in Vp during regional ischemia, hypertonic saline calibrations were made before and during 19 acute ischemic periods (six animals). The Vp values (42.7±3.1 ml) at baseline did not differ significantly from values obtained during coronary occlusion (AVp=+1.2±1.0 ml, p=NS).

**ESPVR Determination**

ESPVR was determined using previously described techniques.10,13 The first 7–11 beats (after an initial 4 mm Hg fall in peak left ventricular pressure [LVP]) to avoid beats potentially influenced by early right ventricular [RV] parallel conductance change10 were used (average of 9.7±2 beats/ESPVR [n=104]). The ESPVR was defined by the linear relation: Pes=Ees(Ves–Vo), where Pes and Ves are the end-systolic pressure and volume, respectively, Ees is the end-systolic elastance, and Vo is the volume-axis intercept. Vo was determined by an iterative technique.13 Whereas Vo provided information regarding ESPVR placement along the volume axis, it was not statistically useful in characterizing ESPVR shift because it was derived from linear extrapolation. For this purpose, comparisons were made of end-systolic volume at the highest end-systolic pressure common to both baseline and ischemic ESPVRs (ΔVes).

**Ischemic Zone Size Determination**

Estimation of ischemic zone size used the same technique previously described in an isolated heart study.1 Briefly, following KCl arrest, hearts were removed, fixed in formalin, and then sliced into five approximately 1-cm-thick short-axis sections. Each section was further divided into 16 equally radially spaced segments. Segments were counted for radioactivity in a well-type scintillation counter (Packard Model N5986). Segments were defined as ischemic if flow was reduced to less than 50% of baseline. On average, flow reduction in these segments was greater than 80%. The overall extent of ischemia (ischemic zone size) was calculated as the sum total mass of all ischemic segments divided by total left ventricular mass.

**Statistical Analysis**

Multiple linear regression analysis was used to test the independent influences of reflex status (REFLEX), ischemia extent (%IM), occlusion site (SITE) (e.g., anterior versus posterolateral ischemia), baseline end-systolic elastance (Ees_base), peak systolic pressure (PSP), and pressure change during ischemia (ΔPSP) on both the change in ESPVR slope (ΔEes) and volume shift (ΔVes). The general linear model used was:

\[
ΔEes \text{ (or } ΔVes) = C_1 + C_2 \text{REFLEX} + C_3 \%IM + C_4 \text{SITE} + C_5 Ees_{base} + C_6 PSP + C_7 ΔPSP
\]

with, a constant (C_1) and six linear coefficients (C_2–C_7). The site of coronary occlusion, as well as presence or absence of reflex blockade, was coded using dummy variables (i.e., 0=LAD, 1=CIRC). Examination of the regression-coefficient correlation matrix, as well as use of stepwise analysis, identified the principal independent significant contributors to the regression equation, and a new model with only those parameters was then fit to the data. Residual plots graphically displayed the influence of a given factor after adjustment for other significant cofactors. Analysis of covariance was also used to test influences of REFLEX or %IM on other regression relations.

With the exception of three occlusions (three separate animals) in which microsphere data could not be interpreted, probably due to poor mixing, each animal contributed four points to the overall regressions. The resulting 49 observations were not strictly statistically independent; however, randomization of occlusion sequence and the natural variability of experimental conditions and coronary anatomic distribution within a given dog limited clustering of any given animal-results data and enabled the data to be pooled in this manner.

Mean hemodynamic data were analyzed by repeated measures ANOVA, with the Bonferroni correction for
TABLE 1. Baseline Hemodynamics in Reflex Unblocked and Blocked Animal Groups

<table>
<thead>
<tr>
<th></th>
<th>Unblocked</th>
<th>Blocked</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>133.1±12.4</td>
<td>111.9±22.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peak systolic pressure</td>
<td>111.7±12.4</td>
<td>86.8±9.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>End-diastolic volume</td>
<td>21.9±8.7</td>
<td>33.5±12.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>End-systolic volume</td>
<td>11.9±6.1</td>
<td>16.0±9.7</td>
<td>0.076</td>
</tr>
<tr>
<td>End-systolic elastance</td>
<td>16.2±8.9</td>
<td>6.3±2.4</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are mean±SD of all four baselines. Differences between blocked and unblocked groups (p values given) are assessed by unpaired t tests.

multiple comparisons where appropriate. Statistical analyses were performed on a 16-bit 286 personal computer using SYSTAT statistical software.

Results

Mean Hemodynamic Responses

Mean baseline data for blocked and unblocked animal groups are provided in Table 1. There was no significant trend (by repeated measures ANOVA) between the four baseline measures (one before each respective occlusion), therefore, the results were pooled for purposes of the table. Heart rate (HR), PSP, and Ees were significantly greater in the unblocked versus the blocked group, whereas end-diastolic volume was significantly less. These differences were largely due to the vasodilating and myocardial depressant effect of hexamethonium autonomic blockade. There was a slight difference in the average %IM, as defined by flow reduction (see Methods) between unblocked and blocked groups (26.2±9.1, unblocked; 31.5±8.9, blocked; p=0.044), which may have related to the lower resting systolic pressures in the latter group.

Changes in PSP and HR due to ischemia (ΔPSP and ΔHR) were essentially comparable between occlusions. Table 2 provides mean changes in these variables during ischemia, with data alternatively grouped by site (LAD versus CIRC occlusion), location (proximal versus distal), or reflex status. None of these grouping comparisons revealed significant differences in ΔPSP during ischemia, a result also confirmed by repeated measures ANOVA (p=0.494). Average heart rate change was small and similar in blocked versus unblocked groups and distal versus proximal occlusions. CIRC occlusion tended to lower HR slightly more than LAD occlusion (p=0.026), but only by several beats per minute. On average, CIRC occlusion yielded a slightly larger ischemic region (31.5±9.5% LV mass) than did LAD occlusion (25.8±8.4%, p=0.033), consistent with canine coronary artery anatomy.

Figure 2 displays examples of P-V loops at baseline and during regional ischemia in blocked (B and D) and unblocked (A, C, E, and F) dogs with both distal (A–C) or proximal (D–F) coronary occlusion. The ESPVRs were highly linear (mean r value, 0.98±0.018) in the measured data range. IVC occlusion typically reduced systolic pressure by 22±8.4 mm Hg (varying with ESPVR slope) and provided an average of 10 beats for analysis. The data demonstrate the variety of responses occurring with acute regional ischemia in vivo. In some ventricles, ischemia predominately shifted the ESPVR rightward with little to no slope change (A and B), whereas Ees was reduced in others (C and D), and a combination of both changes was observed in still others (E and F). This variability of response suggested that several factors might simultaneously influence the observed ESPVR change.

Influence of Ischemia on Ees

To identify those factors principally influencing Ees alteration during ischemia, we used a multiple linear regression model (Table 3). REFLEX, SITE, %IM, Ees_{base}, PSP, and ΔPSP were the six factors tested. Of these parameters, %IM, Ees_{base}, and REFLEX significantly influenced Ees change during ischemia. The correlation matrix of the coefficients revealed little codependence between baseline Ees and %IM (r²=0.067), or between either coefficient and REFLEX (these values are noted by asterisk in the correlation matrix, Table 3). Thus, each variable

TABLE 2. Influence of Regional Ischemia on Changes in Peak Systolic Pressure and Mean Heart Rate

<table>
<thead>
<tr>
<th>SITE effect</th>
<th>ΔPSP</th>
<th>p</th>
<th>ΔHR</th>
<th>p</th>
<th>%IM</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAD</td>
<td>−8.2±9.6</td>
<td>0.317</td>
<td>+0.1±3.1</td>
<td>0.026</td>
<td>25.8±8.4</td>
<td>0.033</td>
</tr>
<tr>
<td>CIRC</td>
<td>−11.4±9.5</td>
<td>0.317</td>
<td>−2.3±5.1</td>
<td>0.026</td>
<td>31.5±9.5</td>
<td>0.033</td>
</tr>
</tbody>
</table>

REFLEX effect

| Unblocked    | −9.8±6.4 | 0.812| −0.5±2.6 | 0.284| 26.2±9.1 | 0.044|
| Blocked      | −10.4±11.5| 0.812| −1.8±5.5 | 0.284| 31.5±8.9 | 0.044|

LOCATION effect

| Distal       | −7.4±7.0 | 0.07 | −1.3±3.9 | 0.938| 22.2±6.9 | 0.001|
| Proximal     | −11.6±9.2| 0.07 | −1.2±4.8 | 0.938| 34.3±7.2 | <0.001|

With the exception of a small reduction in heart rate during CIRC occlusion compared with LAD, none of the comparisons were significant.

IM, average extent of ischemia; ΔPSP, peak systolic pressure; ΔHR, mean heart rate; LAD, left anterior descending (artery); CIRC, circumflex (artery); Unblocked, absence of reflex blockade; Blocked, presence of reflex blockade; Distal and Proximal, location of ischemia in artery.
largely contributed independently to overall Ees change. The largest and most strongly predictive factor was Eesbase, whereas %IM had a smaller and more variable influence. Interestingly, neither PSP nor ΔPSP due to ischemia were significant predictors of the Ees change. Although ambient systolic pressure could be an important determinant of ΔEes due to regional ischemia, the present data were collected over a sufficiently matched range of pressures (Figure 2), and this was not an important factor.

Figure 3A displays the effect of %IM on ΔEes with unblocked data shown with open circles and blocked data with closed ones. Most occlusions led to some reduction in Ees, although the amount of

![Table 3](http://circ.ahajournals.org/)

**Table 3. Multiple Regression Analysis of Determinants of Change in Ees (ΔEes) With Ischemia**

<table>
<thead>
<tr>
<th>Coefficient</th>
<th>SEE</th>
<th>t</th>
<th>p (two tail)</th>
<th>Mult r</th>
<th>Eesbase</th>
<th>REFLX</th>
<th>%IM</th>
<th>SITE</th>
<th>PSP</th>
<th>ΔPSP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>10.2</td>
<td>3.34</td>
<td>1.36</td>
<td>3.05</td>
<td>4.72</td>
<td>0.004</td>
<td>0.001</td>
<td></td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Eesbase</td>
<td>-0.77</td>
<td>-0.78</td>
<td>0.053</td>
<td>-14.53</td>
<td>-14.17</td>
<td>&lt;0.001</td>
<td>0.852</td>
<td>-0.025*</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>REFLX</td>
<td>4.0</td>
<td>3.15</td>
<td>2.86</td>
<td>3.52</td>
<td>3.68</td>
<td>0.001</td>
<td>0.894</td>
<td>0.543*</td>
<td>-0.355</td>
<td>1.00</td>
</tr>
<tr>
<td>%IM</td>
<td>-0.155</td>
<td>-0.14</td>
<td>0.040</td>
<td>-3.89</td>
<td>3.73</td>
<td>&lt;0.001</td>
<td>0.919</td>
<td>-0.299*</td>
<td>0.067</td>
<td>0.172*</td>
</tr>
<tr>
<td>SITE</td>
<td>1.17</td>
<td>0.693</td>
<td>1.69</td>
<td>0.97</td>
<td>0.031</td>
<td>-0.021</td>
<td>-0.010</td>
<td>-0.313</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>PSP</td>
<td>-0.044</td>
<td>0.037</td>
<td>-1.19</td>
<td>0.238</td>
<td>-0.917</td>
<td>-0.082</td>
<td>-0.681</td>
<td>-0.029</td>
<td>-0.025</td>
<td>1.00</td>
</tr>
<tr>
<td>ΔPSP</td>
<td>0.064</td>
<td>0.051</td>
<td>1.25</td>
<td>0.217</td>
<td>0.579</td>
<td>0.196</td>
<td>0.379</td>
<td>0.175</td>
<td>-0.040</td>
<td>-0.599</td>
</tr>
</tbody>
</table>

*pLow correlations between significant factors.

REFLX, reflex status; SITE, occlusion site; %IM, ischemic zone size; Eesbase, baseline end-systolic elastance; PSP, peak systolic pressure; ΔPSP, PSP change during ischemia; SEE, standard error of the coefficient estimate.

Overall regression r was 0.923, with F=44.4, p<0.0001. Left portion of table provides individual regression coefficients and respective standard errors, t, and p values. Values in parentheses represent results of select regression analysis incorporating only factors identified as significant. Factors are listed in order of greatest to least significant contribution to overall regression. Incremental contribution to overall regression r value (Mult r) is shown for significant factors. Right portion of table is correlation matrix of the coefficients.
change varied widely. For the unblocked group, with baseline Ees values that tended to be more homogeneous, ΔEes and %IM were correlated (ΔEes = -0.13%IM + 1.1, SEE = 1.7, r = 0.58). In contrast, the unblocked group had a much wider range of Eesbase values, and there was no apparent relation between the variables. However, ΔEes could be adjusted for Eesbase and REFLEX using the multiple regression coefficients:

$$Ees_{Adjusted} = \Delta Ees - 6.39 + 0.782 \Delta Ees_{base} - 3.15 \cdot \text{REFLEX}$$  

(2)

Note: These coefficients derive from a regression model containing only the three significant factors, their values are shown in parentheses in Table 3. This resulted in a single relation (Figure 3B) defined by: $Ees_{Adjusted} = -0.142%IM + 0.005$, SEE = 2.3, $r = 0.50$, $p < 0.001$), with a significant dependence of ΔEes on %IM in both animal groups.

Although %IM was varied by occluding at multiple vessel sites within each heart, Eesbase demonstrated natural variation between animals. As a group, reflex-blocked animals had lower resting Ees than unblocked animals (Table 1), and differences in anesthesia level, resting sympathetic tone, and heart size all probably contributed to the total range of baseline values.

The extent to which Eesbase influenced the change in Ees during regional ischemia is displayed in Figure 4A. The data demonstrated a significant correlation between the two variables, with a greater fall in Ees present in hearts with higher Eesbase values. Active reflexes offset this dependence by significantly shifting unblocked data rightward compared with blocked data ($p < 0.001$, by ANOVA). As noted above, ΔEes could be adjusted for %IM and REFLEX by rearranging Equation 2 as follows:

$$\Delta Ees_{Adjusted} = \Delta Ees - 6.39 + 0.14%IM - 3.15 \cdot \text{REFLEX}$$  

(3)

Regression of ΔEesAdjusted versus Eesbase (Figure 4B) revealed a single linear relation (ΔEesAdjusted = -0.78Eesbase - 0.005, SEE = 2.4, $r = 0.94$, $p < 0.0001$). Thus, independent of REFLEX or %IM, the Eesbase more than any other parameter, strongly predicted Ees change during regional ischemia.

Influence of Ischemia on Ees

As the examples in Figure 2 demonstrated, regional ischemia shifted ESPVRs rightward, whether much slope change was observed or not. Assessing this shift by the ESPVR Vo (as in previ-
TABLE 4. Multiple Regression Analysis of Determinants of End-Systolic Volume Shift (ΔVes) at Common End-Systolic Pressure

<table>
<thead>
<tr>
<th>Coefficient</th>
<th>SEE</th>
<th>t</th>
<th>p (two tail)</th>
<th>Mult r</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>-0.69 (-2.58)</td>
<td>6.92 (1.86)</td>
<td>-0.10 (-1.39)</td>
<td>0.920 (0.171)</td>
</tr>
<tr>
<td>%IM</td>
<td>0.44 (0.477)</td>
<td>0.069 (0.064)</td>
<td>6.38 (7.467)</td>
<td>&lt;0.001 (0.001)</td>
</tr>
<tr>
<td>SITE-APSP</td>
<td>-0.16 (-0.269)</td>
<td>0.15 (0.085)</td>
<td>-1.09 (-3.17)</td>
<td>0.283 (0.003)</td>
</tr>
<tr>
<td>ΔEes-PSP</td>
<td>-0.02 (-0.002)</td>
<td>0.008 (0.001)</td>
<td>-1.88 (-2.17)</td>
<td>0.067 (0.035)</td>
</tr>
<tr>
<td>SITE</td>
<td>1.540</td>
<td>1.936</td>
<td>0.795</td>
<td>0.431</td>
</tr>
<tr>
<td>REFLEX</td>
<td>-2.034</td>
<td>1.860</td>
<td>-1.09</td>
<td>0.281</td>
</tr>
<tr>
<td>ESPVR</td>
<td>-0.01</td>
<td>0.076</td>
<td>-0.138</td>
<td>0.891</td>
</tr>
<tr>
<td>ΔPSP</td>
<td>-0.155</td>
<td>0.104</td>
<td>-1.49</td>
<td>0.145</td>
</tr>
</tbody>
</table>

REFLEX, reflex status; SITE, occlusion site; %IM, ischemic zone size; Eesbase, baseline end-systolic elastance; PSP, peak systolic pressure; ΔPSP, PSP change during ischemia; SEE, standard error of the coefficient estimate.

Overall regression multiple r was 0.82, F=12.26, p<0.001. Regression coefficient data are shown as in Table 3. Correlations between significant cofactors were uniformly small (r<0.028). Cross term (ΔEes-PSP) represents anticipated effect of ESPVR slope change on ΔVes, which is dependent both on the magnitude of slope change and level of systolic pressure. See text for details.

Discussion

The principal findings of the present study are that in ejecting in vivo hearts, acute regional ischemia shifts the ESPVR rightward by an amount that correlates with %IM, much like the response in isolated isovolumic ventricles. However, in contrast to data previously reported in isolated1 and in vivo2 hearts, Ees frequently falls during ischemia. This change is primarily dependent on Eebsbase, with a smaller influence of %IM and REFLEX.

Regional Ischemia and ESPVR

A correspondence between increasing extent of regional ischemia and gradual worsening of global LV systolic function is well known,14-16 However, studies using indexes such as ejection fraction or dP/dtmax are limited by the ability of such studies to separate changes in global function due to altered loading from changes due to ventricular systolic performance. Furthermore, these indexes cannot be easily related to (or predicted from) an integration of ischemic and nonischemic regional properties.

The ESPVR provides a means of resolving these deficiencies. The relation is relatively load insensitive, and therefore, much less influenced by volume dilation often accompanying acute ischemia.14,17 In addition, description of the chamber by a volume elastance enables prediction of the net ESPVR from
the simple addition of two hypothetical regional elastances; an ischemic region arrested in diastole, and a “normal” region of residual myocardium.1

In isolated blood-perfused isovolumic beating hearts, Sunagawa et al1 found that regional ischemia produced a nonlinear ESPVR, with a shallow slope in the low P-V range that became increasingly steep and approached control values at higher, more physiologic, ranges. The net result was an apparent rightward shift of the ESPVR with little change in slope (local Ees) when measured at normal operating pressures (Figure 1). The extent of this shift was found to correlate with %IM. In the one previous in vivo study, Little and O’Rourke2 examined changes in the ESPVR after 2-minute occlusions of the CIRC artery in sedated closed-chest dogs. They found little change in Ees, and a rightward shift in ESPVR during ischemia. In this study, however, the %IM was neither systematically varied nor assessed. The present investigation extended these previous observations by providing data on ischemic zone size, and testing the potential additional impact of autonomic reflex activation, ischemia location, and baseline conditions on the ESPVR response.

**Alterations in Ees**

The greatest difference between the present data and those of previous ESPVR studies1,2 lay in the changes of Ees, as both previous experimental studies had not revealed significant ESPVR slope change with ischemia. In contrast, we found a striking dependence of ΔEes with ischemia on its baseline value, with larger reductions (regardless of %IM) in hearts with higher initial Ees. In isolated hearts, Ees generally ranges 3–5 mm Hg/ml (the mean was 4.5 mm Hg/ml for the Sunagawa study1), which is low compared with in vivo hearts.10,13 The mean Eesbase for the study of Little2 was 6.9±2.1 mm Hg/ml, but this included only one animal with a value greater than 7.2. (In this animal, Eesbase=10.7 mm Hg/ml, and fell to 8.9 mm Hg/ml with ischemia.) The present study demonstrated that in these lower ranges of Eesbase, Ees is altered a relatively small amount by regional ischemia (Figure 4A), and what changes do occur are further minimized if reflexes are not fully blocked. This latter point may be relevant when comparing our data with those of Little2 in which atropine and propranolol (rather than a ganglionic blocker) were used to inhibit reflexes.

The broader range of Eesbase values obtained in the present study resulted from studying both blocked (contractility depressed) and unblocked hearts, and from natural fluctuations in the sympathetic tone of open-chest anesthetized preparations. This is supported by the significant disparity in Eesbase between the two groups (Table 1) and the greater variation between repeated baselines in unblocked hearts (coefficient of variation [SD/mean×100]=25%) as compared with blocked animals (13%). Ees also has chamber-size depen-

dence,18 and smaller heart mass probably contributed to some of the Ees variation (particularly the highest values).

Another factor that could have contributed to greater Ees changes in the present compared with previous studies was a larger extent of ischemia. The average rightward ESPVR shift with ischemia in the Little and O’Rourke2 study was 9.2 ml, which correlates with approximately 25% ischemic mass (by data from the present study [Figure 5A]). In this range (Figure 3A), the effect of %IM per se is small and more variable than at higher %IM values.

Finally, although it is true that the lower the Ees at which ESPVRs are determined, the greater the potential for Ees change, our regression analysis did not reveal a significant relation between resting systolic pressure or pressure change and ΔEes (Table 3). In addition, the resting PSP in the unblocked group was very similar to that reported in the previous in vivo study.2 Thus, it is unlikely that ambient systolic pressures were an important factor in explaining the differences between the present and previous study results.

Given the dependence of ΔEes on baseline level, one could question the relevance of this effect to conscious preparations or humans in whom background sympathetic stimulation (and Ees) is lower than in open-chest preparations. However, Ees values of 8 or more mm Hg/ml are frequently obtained even in closed-chest19,20 or conscious21 dogs, and in this range, regional ischemia can induce reductions of more than 50% (Figure 4B). In conscious humans, in whom Ees values can vary with chamber size or hypertrophy,22 we have also found a significant dependence of ΔEes during coronary occlusion (by angioplasty balloon) on Eesbase (ΔEes=-0.71Eesbase, r=0.92, p<0.001) very similar to that of the present study.23 Thus, the present data appear quite relevant even to intact human physiologic responses.

**Experimental Versus Model Predictions of Altered Ees**

To help interpret the isolated heart ESPVR response to regional ischemia, Sunagawa et al1 proposed a two-compartment model of regional ischemia. The regionally ischemic ventricle was represented as a sum of two hypothetical (end-systolic) volume elastances, an ischemic compartment (Ees) and a “normal” remote compartment (Ees). The ischemic region was assigned the passive properties of the original chamber diastolic P-V relation24 and scaled in volume by the percent of ischemia (%IM). The Ees for the ischemic region was the slope of this nonlinear relation at any given pressure. The remote (normal) region was assumed to maintain normal systolic properties, so that its ESPVR was equal to the baseline relation for the preischemic ventricle, also scaled in volume (by 100-%IM). To obtain the net chamber ESPVR, both elastances were combined in parallel as follows:
At low systolic pressures, the net ESPVR was dominated by the far more compliant ischemic region, resulting in little end-systolic pressure rise but increases in end-systolic volume. At normal or high systolic pressures, the diastolic P-V relation became steeper, and $E_{es}$ was determined more by the remote region elastance. This behavior occurred only after the ischemic compartment had been initially preferentially filled, thus, the net ESPVR was shifted to the right with an apparent increase in Vo (Figure 1).

The model fit the isolated heart data quite well, supporting the experimental finding of little change in $E_{es}$ in the high P-V range, as well as a theoretical dependence of $\Delta V_{es}$ on $%IM$. A rightward ESPVR shift required no more than that the ischemic region be more compliant than the normally contracting remote region. This was very consistent with a large body of experimental data demonstrating systolic wall thinning and bulging in acutely ischemic regions. Furthermore, although muscle creep in the ischemic region might also have contributed to rightward ESPVR shifts, this phenomenon was not necessary to explain them.

In addition to predicting rightward ESPVR shift, the two-elastance model also predicted that the ESPVR slope ($E_{es}$) would be reduced particularly as the baseline elastance value increased. Combining the two compartments, one can show that the change in $E_{es}$ will be (Appendix A):

$$\Delta E_{es} = E_{es} - E_{es} \left( \frac{1}{R} \frac{E_{ed}(P)}{E_{es}(P)} \right)$$

(4)

where, $R$ is the fraction of ischemic mass ($R = %IM/100$), and $E_{ed}(P)$ is the end-diastolic elastance at a given systolic pressure ($P$). From this relation, it can be seen that as $E_{es}$ increases, so does the expected change in $\Delta E_{es}$. This prediction makes sense because $E_{es}$ indicates chamber stiffness, and the stiffer the heart is initially, the greater the net effect on that stiffness if a portion of the wall is replaced with more compliant muscle.

To use this two-elastance model to predict the $E_{es}$ relation, values for $%IM$ and $E_{ed}(P)$ were required. Even though $%IM$ varied considerably for the experimental data, by using $\Delta E_{es}$ (from Equation 2), this trend was accounted for, and an average $%IM$ could be inserted in the model (average $%IM = 35\%$). To estimate $E_{ed}(P)$ (the slope of the end-diastolic P-V relation at a systolic pressure [$P$]), the diastolic P-V curve was assumed to be a monoexponential: $P_{ed} = \alpha e^{\beta V_{ed}}$. Then,

$$E_{ed}(P) = d(P_{ed})/d(V_{ed}) = \alpha \beta e^{\beta V_{ed}} = \beta P + \alpha \beta$$

(5)

Using typical coefficients for $\alpha$ (9.0 mm Hg) and $\beta$ (0.023/ml), derived from our data (yields a $P_{ed}$ of 23 mm Hg at 60 ml volume), and measuring $E_{ed}(P)$ at a systolic pressure of 100 mm Hg (the average for the data), Equation 5 yielded an estimate for $E_{ed}(P=100)$ of 2.5 mm Hg/ml.

The results of the model analysis are shown in Figure 6A. The dotted line is the model prediction, whereas the solid points are the actual experimental results. Using these simple assumptions, there was a remarkably close concordance between theoretical model and experimental results.

A similar comparison of model prediction versus experimental data for the relation between $%IM$ and $\Delta E_{es}$ is shown in Figure 6B. The experimental results shown previously in Figure 3B are here displayed as mean±SEM averaged at more than 5% increment ranges, respectively, of $%IM$. Again, the effect of varying $E_{es}$ was accomplished by using Equation 3, enabling a single average value (10 mm Hg/ml) to be used in the model prediction. Model prediction and experimental data for this relation also agreed well.

Additional Factors

In addition to $E_{es}$ and $%IM$, the presence or absence of reflex blockade also influenced the extent of $\Delta E_{es}$ with regional ischemia. There was a significant difference in mean PSP between the two animal groups (Table 1); therefore, it was possible that the influence of blockade was largely mediated by lowered ambient systolic pressures (due to hexamethonium). This, however, was tested by including PSP and $\Delta$PSP in the regression model, and no consistent direct correlation between $\Delta E_{es}$ or $\Delta V_{es}$
and PSP was found. This raises the possibility that reflex activation effects may in part act by stimulating remote myocardium to compensate for the ischemic insult. 

$\Delta V_{\text{es}}$ was significantly dependent on $\Delta P_{\text{SP}}$ but only during CIRC and not LAD occlusions. This was true despite the fact that average $\Delta P_{\text{SP}}$ was similar for both sets of occlusions (Table 2). Thus, there was a small occlusion-site effect that influenced the extent of rightward ESPVR shift. This change was mirrored by a slightly greater increase in end-diastolic volume with ischemia during CIRC compared with LAD occlusions, (+6.1±3.8 ml [LAD] versus +8.9±4.2 ml [CIRC], $p=0.012$), and may relate to differences in central versus peripheral vascular volume distribution with posterolateral versus anterior wall ischemia.

The two-compartment model does not take into account any interactions between ischemic and remote regions,2,5,26 potential influences of local myocardial geometry and, thus, ischemia-site dependencies,5,7 or changes in ischemic regional diastolic properties during coronary occlusion.29 Despite these oversimplifications, the predicted results (Figure 6) compared favorably with the observed data. Although the precise model parameters can be varied to some extent and still fit the observed data, the results displayed in Figure 6 suggest that, by and large, the additional factors noted herein are likely to have secondary rather than primary effects on global systolic function during regional ischemia.

**Experimental Limitations**

One limitation of the present data that could have affected assessments of autonomic reflex influences, relates to the open-chest anesthetized nature of the preparation. The level of reflex activation in this setting is certainly different from an intact conscious animal. However, pentobarbital anesthesia does not eliminate autonomic reflexes, and although the ambient sympathetic tone in the unblocked group was probably above that of a conscious animal, reflex changes could and did still occur. The fact that mean heart rate was little changed (Table 2) resulted both from a direct attempt to stabilize HR (by mechanically crushing the sinus node region), as well as varying occlusion site (posterolateral ischemia tended to lower HR, whereas anterior wall ischemia raised it slightly).4 Had reflex increases in HR occurred, they might have altered the net ESPVR response by varying the contractile state of the remote region.20 By comparing with data obtained after hexamethonium blockade and vagotomy, reflex influences could still be discerned, recognizing that they might further differ in a conscious state.

As discussed in the materials and methods section, the volume catheter signal calibration requires estimation of the parallel conductance. We assessed $V_{\text{p}}$ in six hearts before and during the ischemic period (total, 24 occlusions), and the changes were small and not statistically significant. Furthermore, even small errors in $V_{\text{p}}$ estimation would not appreciably influence the $E_{\text{es}}$ calculation, but would introduce some errors into the $V_{\text{p}}$ shifts.

In vivo ESPVRs are generally determined over a much narrower loading range than isolated heart data, therefore, derived parameters such as $E_{\text{es}}$ should be compared carefully. In the present data, the average use of 10 beats per ESPVR and the consistently high degree of ESPVR linearity over the data range obtained, resulted in a small SEE of $E_{\text{es}}$ ($\pm 6.4 \pm 0.4\%$). Furthermore, in more than 80% of the occlusions, the $\% \Delta E_{\text{es}}$ fell well outside the 95% confidence limits around the baseline value. We have recently reported that ESPVRs can be nonlinear,13 and this could potentially influence the slope values. Nearly all ESPVRs before and after ischemia, however, were determined within overlapping pressure-load ranges. In addition, $E_{\text{es}}$ generally fell during ischemia, whereas curvilinearity considerations would, if anything, predict a steepening of local $E_{\text{es}}$.

Both $\Delta E_{\text{es}}$ and $\Delta V_{\text{es}}$ varied with $\%IM$, however, there was clear scatter among the data. This could relate to errors of ischemic mass determination. Although the microsphere technique is commonly used, it is recognizably an approximation method. Flow inhomogeneity at the border region can introduce errors, and because the border zone increases with overall increasing $\%IM$, the extent of this error can, itself, vary. The 50% flow-reduction definition for separating control and ischemic regions was chosen to be the same as that used in the previous isolated heart ESPVR–regional ischemia study.1

**Implications**

The present data indicate that the ESPVR response to regional ischemia is not solely a parallel shift of the relation, but rather is more complex and determined by several important and measurable factors. The most prominent of these factors are the $E_{\text{es base}}$ and $\%IM$. The extent to which experimentally determined influences of both $E_{\text{es base}}$ and $\%IM$ on $\Delta E_{\text{es}}$ are predicted by a simple two-compartment model is impressive, suggesting potential use of the model despite its recognized simplifying assumptions. Increasing interest in the global functional sequela of coronary occlusion8,9,25,31 and reperfusion in humans, and the development of similar volume-catheter techniques for assessment of P-V relations in humans,9,22 make the present data clinically pertinent. The present study should provide useful insights for interpreting similar data in future animal, as well as human, investigations.

**Appendix A**

The relation between the control elastance, $E_{\text{es base}}$, of the normal ventricle and the elastance of the regionally ischemic ventricle, $E_{\text{es I}}$, can be derived as follows. As Sunagawa et al11 did in their two-
compartment model, assume that an R fraction (R = %IM/100) of the wall of a given ventricle becomes totally ischemic, completely losing contractile properties (ischemic compartment), whereas the remaining (1 - R) fraction of the wall maintains its normal contractile properties (normal compartment). Then the elastance for the normal compartment can be written as:

\[ E_{es} = Ees/(1-R) \]  

(B1)

The end-systolic P-V relation for the ischemic compartment is assumed to be the same curvilinear end-diastolic P-V relation of the normal ventricle, except for the difference in size. Let \( E_{ed}(P) \) represent the end-diastolic elastance of the normal ventricle that varies as a function of pressure (P) due to the nonlinearity of the relation. Then the elastance of the ischemic compartment \( E_{es} \) is:

\[ E_{es} = E_{ed}(P)/R \]  

(B2)

The combined compliance of the two interconnected compartments is the sum of the two compartmental compliances. Because elastance is the reciprocal of compliance, the combined elastance for the regionally ischemic ventricle (E_{es}) is:

\[ 1/E_{es} = 1/E_{es} + 1/E_{es} \]  

(B3)

Substituting Equations B1 and B2 into this expression, we obtain:

\[ 1/E_{net} = 1 - R/E_{es} + R/E_{ed}(P) \]  

(B4)

Rearranging,

\[ E_{net} = [E_{es} - E_{ed}(P)]/[R(E_{es} + (1-R)E_{ed}(P))] \]  

and because,

\[ \Delta Ees = E_{es} - E_{net} \]

then,

\[ \Delta Ees = E_{es} - E_{es} \]  

(B5)

Equation B6 shows that for a given extent of ischemia R and a given diastolic elastance, \( E_{ed}(P) \), \( \Delta Ees \) will increase with greater \( E_{es} \). In addition, for a given \( E_{es} \) and \( E_{ed}(P) \), \( \Delta Ees \) will increase with increasing R.

This analysis focused on Ees changes; however, the same model can be used to predict shifts in Vo (see reference no. 1).

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