Systemic vascular resistance: an unreliable index of left ventricular afterload

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ABSTRACT  Systemic vascular resistance (SVR) is a frequently used clinical index of left ventricular afterload. However, SVR may not adequately assess left ventricular afterload (i.e., ventricular internal fiber load during systole) since it reflects only peripheral vasomotor tone. In contrast, left ventricular end-systolic wall stress ($\sigma_{es}$) reflects the combined effects of peripheral loading conditions and left ventricular chamber pressure, dimension, and wall thickness. To determine the relationship between SVR and $\sigma_{es}$, left ventricular afterload and contractility were pharmacologically altered in eight dogs instrumented with central aortic microtip and Swan-Ganz thermodilution catheters. Left ventricular wall thicknesses and dimensions were measured from two-dimensionally targeted M mode echocardiograms. Aortic, right atrial, and left ventricular end-systolic pressures as well as cardiac output were recorded. SVR and $\sigma_{es}$ were determined under control conditions as well as during infusions of nitroprusside, methoxamine, dobutamine, and norepinephrine. Control data acquired before each drug infusion were similar. When compared with baseline values, SVR underestimated the magnitude of change in left ventricular $\sigma_{es}$ by (1) 22% when afterload alone was decreased (nitroprusside), (2) 54% when afterload alone was increased (methoxamine), and (3) 50% when afterload was decreased and contractility was augmented (dobutamine). Most importantly, when afterload was minimally decreased in association with augmented contractility (norepinephrine), SVR increased by 21% while $\sigma_{es}$ fell by 9%. Thus, discordant changes in left ventricular afterload (i.e., $\sigma_{es}$) and SVR can occur during pharmacologic interventions. SVR is an unreliable index of left ventricular afterload, reflecting only peripheral arteriolar tone rather than left ventricular systolic wall force. This emphasizes the fact that a true measure of left ventricular afterload must consider the interaction of factors internal and external to the myocardium.


OVERALL left ventricular systolic performance is inversely related to the force opposing ventricular fiber shortening (i.e., afterload). This fundamental property of the myocardium becomes critically important in interpreting variables of left ventricular shortening in patients suspected of having contractile abnormalities. In the clinical setting, the most commonly used measure of ventricular afterload is systemic vascular resistance (SVR). However, SVR is a measure of vasomotor tone that reflects only the nonpulsatile component of peripheral load. In contrast, left ventricular systolic wall stress reflects the combined effects of peripheral loading conditions and factors internal to the heart. Recently, the wall stress at end-systole ($\sigma_{es}$) has been shown to be directly related to end-systolic dimension and volume. As such, $\sigma_{es}$ is a major determinant of overall left ventricular performance and can be considered the afterload that limits ventricular fiber shortening at end-ejection.

To determine the relationship between total left ventricular muscle load (i.e., wall stress) and SVR, an instrumented canine preparation was studied during alterations in left ventricular afterload alone (with nitroprusside and methoxamine) and during combined changes in left ventricular afterload and contractile state (with dobutamine and norepinephrine).

Methods

Animal preparation and instrumentation. Eight closed-chest mongrel dogs (18.5 to 35 kg) were premedicated with subcutaneous morphine (5 mg/kg) followed by anesthesia with intravenous $\alpha$-chloralose (100 mg/kg). After endotracheal intubation, room air ventilation was maintained with a Harvard volume respirator. Arterial blood gases (Corning 165.2 Analyzer) were measured to ensure physiologic respiratory support. A No. 8F Swan-Ganz catheter connected to a Statham P231D transducer was advanced via the right external jugular vein into
the pulmonary artery for measurements of thermodilution cardiac output (Columbus Instruments) and of pulmonary arterial and pulmonary capillary wedge pressures. A second catheter was advanced from the external jugular vein into the right atrium for measurement of right atrial pressure and for injection of the iced saline boluses required for determinations of cardiac output. A high-fidelity micromanometer-tipped catheter (Millar, Texas) was advanced via the left femoral artery and positioned in the ascending aorta just above the aortic valve. Central aortic pressure tracings were obtained and used for measurements of left ventricular ejection time and end-systolic pressure (Pes). The femoral vein was cannulated with a large-bore catheter that was used for infusion of intravenous drugs and fluids. The electrocardiogram, core body temperature, and central aortic pressures were monitored throughout the experiment. The micromanometer-tipped catheter was electronically zeroed in a 37°C water bath and calibrated with a mercury manometer before insertion. All other pressure measurements were made with fluid-filled catheters with the transducer zeroed to midchest level. The total preparation time before initial measurements were obtained was approximately 90 min.

Experimental design. Each animal was premedicated with intravenous atropine (0.010 to 0.015 mg/kg body weight) to abolish the vagally mediated bradycardia commonly associated with morphine-chloralose anesthesia. Ultrasound imaging (Hewlett-Packard, Andover, MA) was performed with a 5 MHz ultrasound transducer with the beam directed just off the tip of the anterior leaflet of the mitral valve. Recordings were obtained at end-expiration with the dogs in a right lateral position. Animals with narrow chests were used to facilitate ease of echocardiographic imaging. Simultaneous left ventricular two-dimensional and targeted M mode echocardiograms, electrocardiogram, and mean right atrial and high-fidelity central aortic pressures were recorded under baseline conditions. Thermodilution cardiac outputs were obtained in triplicate at the time of echocardiographic and pressure recordings.

Afterload manipulation without alteration of contractile state. Once baseline recordings were obtained, afterload manipulation without alteration in contractile state was accomplished with infusions of either the α1-specific agonist methoxamine or with the vasodilator nitroprusside. Methoxamine (infusion rate = 15 μg/kg/min) was used when baseline mean aortic pressure was 125 mm Hg or less. This protocol was followed for four dogs. At this dose, methoxamine caused a 2 to 4 mm Hg/min increase in left ventricular systolic pressure. The left ventricular response to the pressor challenge was assessed with recordings obtained every 1 to 2 min until peak systolic pressure increased 30 to 60 mm Hg above baseline. At that time the infusion of methoxamine was discontinued; the peak pressor effect lasted 2 to 5 min. Nitroprusside (initial dose 0.25 μg/kg/min) was given when baseline mean aortic pressure was greater than 125 mm Hg. Four dogs were studied with this drug. Recordings were made 5 min after initiation of the drug infusion. The infusion rate was titrated until mean arterial pressure fell by 20% to 30% of the baseline value in association with a change in heart rate of less than 10 beats/min. At this point, the infusion of nitroprusside was discontinued. Multiple data points were collected during the nitroprusside titration phase.

Alteration of contractile state. After baseline hemodynamics were reestablished, all eight dogs received sequential intravenous infusions of dobutamine and norepinephrine. Dobutamine, which has a half-life of 2 to 3 min, was infused at 5 μg/kg/min for 8 min to allow establishment of steady-state pharmacokinetics. Pressures, cardiac outputs, and echocardiographic recordings were then obtained. Thirty minutes after completion of the infusion of dobutamine a new set of baseline data was recorded. This was followed by an infusion of 0.15 μg/kg/min of norepi-

neprinone. After 8 min, simultaneous pressures, cardiac outputs, and echocardiographic recordings were obtained.

Data analysis. The peak of the R wave of the electrocardiogram and the dicrotic notch of the high-fidelity central aortic pressure tracing were used to designate end-diastole and end-systole, respectively. Left ventricular end-systolic and end-diastolic dimensions (Des and Ddi) and wall thicknesses (hw and hdi) were measured from the echocardiographic recordings as the mean value of three to five cardiac cycles. The left ventricular percent fractional shortening (CMD) was calculated as Des minus Ddi divided by Ddi. The left ventricular Pes and ejection time were measured from the high-fidelity central aortic pressure tracings in the standard fashion and taken as the average of 5 beats. Left ventricular ejection time (LVET) was corrected to a heart rate of 60 beats/min by dividing by the square root of the preceding RR interval. The rate-corrected left ventricular mean velocity of fiber shortening (VcfM)10 was calculated as:

$$\text{Wall stress} = [\text{pressure}] \times [\text{geometric factor}]$$

$$V_{\text{cfM}} = \frac{\% \Delta D}{\text{LVET}} \times \frac{\% \Delta D}{\sqrt{\text{RR}}}$$

Left ventricular σes was calculated as the product of Pes and a geometric factor that includes Des and hdi. The following angiographically validated formula11 was used:

$$\sigma_{\text{es}} = (P_{\text{es}}) \left( \frac{D_{\text{es}}}{(h_{\text{di}})(1 + h_{\text{di}})} \right)$$

where σes is in g/cm², Pes is in mm Hg, Des and hdi are in cm, and 0.34 is a factor to convert Pes from mm Hg to g/cm². SVR was calculated as the mean aortic minus mean right atrial pressure times the conversion factor 80 dyne-cm⁻²/mm Hg divided by the thermodilution-determined cardiac output.12

In all dogs, the same micromanometer-tipped catheter and recording system were used. In six of the eight dogs studied, comparisons were made between initial and end-of-study data for zero position and overall gain. In five of the six animals, no differences were noted. In the remaining dog, a 2 mm Hg shift in the zero position without a change in overall gain was present.

Statistical analysis. Each dog served as its own control. The paired t test was used to assess the hemodynamic changes induced by each drug relative to their respective control values. Left ventricular contractile state was measured with the use of the load-independent relationship between σes and VcfM (σes-VcfM).10 For each animal this relationship was determined by linear regression analysis (least squares method) with a minimum of four data points acquired under baseline contractility conditions over a wide range of afterload (σes) generated by either methoxamine or nitroprusside. In addition, all 44 data points obtained in the eight dogs under baseline contractility conditions were used to construct the mean regression line and 95% confidence limits for the σes-VcfM relation. For any individual σes-VcfM point acquired during either dobutamine or norepinephrine infusion, the vertical distance above or below this mean regression line was used as an estimate of contractile state.9,12 This allowed comparisons to be performed at the same level of afterload (i.e., σes) for control σes-VcfM points and data acquired during dobutamine or norepinephrine infusion.

Interobserver and intraobserver coefficients of variation were
TABLE 1
Hemodynamics during afterload manipulation without altered left ventricular contractility

<table>
<thead>
<tr>
<th></th>
<th>NP</th>
<th>C&lt;sub&gt;NP&lt;/sub&gt;</th>
<th>C&lt;sub&gt;METH&lt;/sub&gt;</th>
<th>Percent change from NP to METH</th>
<th>C&lt;sub&gt;NP&lt;/sub&gt;</th>
<th>C&lt;sub&gt;METH&lt;/sub&gt;</th>
<th>Percent change from NP to METH</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>95 ± 11</td>
<td>89 ± 16</td>
<td>6</td>
<td>98 ± 20</td>
<td>94 ± 12</td>
<td>-4</td>
<td></td>
</tr>
<tr>
<td>P&lt;sub&gt;m&lt;/sub&gt; (mm Hg)</td>
<td>143 ± 18</td>
<td>103 ± 27</td>
<td>-28</td>
<td>114 ± 8</td>
<td>164 ± 8</td>
<td>+44</td>
<td>&lt;.05 &lt;.001 &lt;.001 &lt;.001</td>
</tr>
<tr>
<td>P&lt;sub&gt;a&lt;/sub&gt; (mm Hg)</td>
<td>154 ± 13</td>
<td>114 ± 14</td>
<td>-26</td>
<td>125 ± 10</td>
<td>176 ± 9</td>
<td>+41</td>
<td>&lt;.05 &lt;.001 &lt;.001 &lt;.001</td>
</tr>
<tr>
<td>G</td>
<td>1.53 ± 0.18</td>
<td>1.15 ± 0.21</td>
<td>-25</td>
<td>1.64 ± 0.07</td>
<td>2.16 ± 0.06</td>
<td>+32</td>
<td>&lt;.01 &lt;.001 &lt;.01 &lt;.01</td>
</tr>
<tr>
<td>CO (l/min)</td>
<td>5.3 ± 1.1</td>
<td>6.0 ± 0.9</td>
<td>+13</td>
<td>5.1 ± 0.5</td>
<td>5.0 ± 0.5</td>
<td>-2</td>
<td>&lt;.05 &lt;.001 &lt;.001 &lt;.001</td>
</tr>
<tr>
<td>Vcf&lt;sub&gt;f&lt;/sub&gt; (circuit/sec)</td>
<td>1.07 ± 0.09</td>
<td>1.26 ± 0.10</td>
<td>+18</td>
<td>1.05 ± 0.09</td>
<td>0.80 ± 0.09</td>
<td>-24</td>
<td>&lt;.01 &lt;.001 &lt;.001 &lt;.001</td>
</tr>
<tr>
<td>SVR (dyne-sec-cm&lt;sup&gt;-5&lt;/sup&gt;)</td>
<td>2126 ± 331</td>
<td>1379 ± 132</td>
<td>-35</td>
<td>1710 ± 93</td>
<td>2521 ± 265</td>
<td>+48</td>
<td>&lt;.001 &lt;.001 &lt;.001 &lt;.001</td>
</tr>
<tr>
<td>σ&lt;sub&gt;es&lt;/sub&gt; (g/cm&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>80 ± 16</td>
<td>44 ± 13</td>
<td>-45</td>
<td>69 ± 9</td>
<td>128 ± 7</td>
<td>+86</td>
<td>&lt;.001 &lt;.001 &lt;.001 &lt;.001</td>
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</tbody>
</table>

NP = nitroprusside; METH = methoxamine; C<sub>NP</sub> = prenitroprusside control; C<sub>METH</sub> = premethoxamine control; HR = heart rate; P<sub>m</sub> = mean aortic pressure; G = end-systolic geometric factor (for equation see text); CO = cardiac output.

Computed for both the Vcf<sub>f</sub> and σ<sub>es</sub> with the following formulas:

\[ \sigma_{es} = \sqrt{\frac{n}{\sum (d_{i})^2}} \]

\[ \%CV = (100) \left( \frac{\sigma_{es}}{\bar{\xi}} \right) \]

where n = number of observations; d<sub>i</sub> = difference between measurements; \%CV = coefficient of variation (percent); \bar{\xi} = average of all measurements. The intraobserver coefficients of variation were 3.9% and 3.8% for Vcf<sub>f</sub> and σ<sub>es</sub>, respectively. The interobserver coefficients of variation were 7.3% for Vcf<sub>f</sub> and 7.6% for σ<sub>es</sub>.

Results

The hemodynamic data obtained under baseline contractility conditions before and during afterload manipulation with nitroprusside or methoxamine are summarized in table 1. Similar data recorded before and during dobutamine and norepinephrine infusions are listed in table 2. Representative two-dimensional and targeted M mode echocardiographic images are shown in figure 1.

Control data. The four dogs with control aortic mean pressures of 125 mm Hg or less received methoxamine while the other four dogs (i.e., those with aortic mean pressures >125 mm Hg) received nitroprusside. As expected, aortic mean pressure, left ventricular end-systolic pressure, and SVR were higher for the dogs subsequently given nitroprusside. There were no differences between the nitroprusside and methoxamine groups with respect to heart rate, cardiac output, Vcf<sub>f</sub>, σ<sub>es</sub>, or the geometric factor found in the formula for σ<sub>es</sub>.

The hemodynamic data acquired from the eight dogs were similar under control conditions before dobutamine and before norepinephrine. For a given animal, the σ<sub>es</sub>-Vcf<sub>f</sub> points obtained under these two control conditions fell on the linear regression line generated

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TABLE 2
Hemodynamics during augmentation of left ventricular contractility

<table>
<thead>
<tr>
<th></th>
<th>DB</th>
<th>C&lt;sub&gt;DB&lt;/sub&gt;</th>
<th>NE</th>
<th>Percent change from C&lt;sub&gt;DB&lt;/sub&gt; to NE</th>
<th>C&lt;sub&gt;NE&lt;/sub&gt;</th>
<th>Percent change from C&lt;sub&gt;NE&lt;/sub&gt; to DB</th>
<th>DB vs NE</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>97 ± 18</td>
<td>111 ± 15</td>
<td>+14</td>
<td>100 ± 22</td>
<td>100 ± 15</td>
<td>0</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>P&lt;sub&gt;m&lt;/sub&gt; (mm Hg)</td>
<td>130 ± 22</td>
<td>154 ± 32</td>
<td>+18</td>
<td>131 ± 18</td>
<td>177 ± 29</td>
<td>+35</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>P&lt;sub&gt;a&lt;/sub&gt; (mm Hg)</td>
<td>141 ± 22</td>
<td>172 ± 32</td>
<td>+21</td>
<td>143 ± 24</td>
<td>189 ± 29</td>
<td>+32</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>G</td>
<td>1.63 ± 0.09</td>
<td>1.01 ± 0.07</td>
<td>-38</td>
<td>1.58 ± 0.08</td>
<td>1.09 ± 0.09</td>
<td>-31</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CO (l/min)</td>
<td>5.3 ± 0.8</td>
<td>7.3 ± 0.9</td>
<td>+38</td>
<td>5.9 ± 1.7</td>
<td>6.4 ± 1.4</td>
<td>+8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Vcf&lt;sub&gt;f&lt;/sub&gt; (circuit/sec)</td>
<td>1.05 ± 0.11</td>
<td>1.50 ± 0.21</td>
<td>+43</td>
<td>1.06 ± 0.11</td>
<td>1.41 ± 0.17</td>
<td>+34</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>SVR (dyne-sec-cm&lt;sup&gt;-5&lt;/sup&gt;)</td>
<td>1895 ± 285</td>
<td>1652 ± 348</td>
<td>-13</td>
<td>1834 ± 540</td>
<td>2228 ± 493</td>
<td>+21</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>σ&lt;sub&gt;es&lt;/sub&gt; (g/cm&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>80 ± 25</td>
<td>59 ± 18</td>
<td>-26</td>
<td>77 ± 16</td>
<td>70 ± 15</td>
<td>-9</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>

DB = dobutamine; NE = norepinephrine; C<sub>DB</sub> = predobutamine control; C<sub>NE</sub> = prenorepinephrine control; other abbreviations are as in table 1.

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by "pure" afterload manipulation with nitroprusside or methoxamine. This established the fact that left ventricular contractility had returned to a baseline level before dobutamine and norepinephrine infusions. This is illustrated for a representative dog in figure 2.

Data acquired during pharmacologic manipulations

Physiologic determinants of SVR. Figure 3 shows percent change from control for mean aortic pressure, cardiac output, and SVR. Nitroprusside decreased mean aortic pressure by 28% (p < .01) without associated changes in cardiac output or heart rate. This resulted in a 35% decrease in SVR (2126 ± 331 to 1379 ± 132 dyne-sec-cm⁻², p < .01). Methoxamine increased mean aortic pressure by 44% (p < .001), while cardiac output and heart rate remained unchanged. This resulted in a 48% rise in SVR (1710 ± 93 to 2521 ± 265 dyne-sec-cm⁻², p < .001). Dobutamine increased mean aortic pressure by 18% (p < .05) and cardiac output by 38% (p < .001). The rise in cardiac output was predominant and in part reflected a 14% increase in heart rate (p < .05). SVR fell by 13% (1895 ± 285 to 1652 ± 348 dyne-sec-cm⁻², p < .01). Finally, norepinephrine increased SVR by 21% (1834 ± 540 to 2228 ± 493 dyne-sec-cm⁻², p < .001), reflecting a 35% rise in mean aortic pressure (p < .001) without significant changes in cardiac output or heart rate.

Physiologic determinants of σes. Figure 4 shows percent change from control in Pes, the left ventricular geometric factor, and σes. Nitroprusside decreased Pes by 26% (p < .01) in conjunction with a 25% fall in the left ventricular geometric factor (p < .01). This resulted in a 45% decline in σes (80 ± 16 to 44 ± 13 g/cm², p < .01). Methoxamine increased all of these variables, with a 41% rise in Pes (p < .001) and a 32% rise in the left ventricular geometric factor (p < .01). The net result was an 86% increase in σes (69 ± 9 to 128 ± 7 g/cm², p < .001). In contrast, when contractility was augmented with dobutamine, Pes increased by 21% (p < .01) while the left ventricular geometric factor decreased by 38% (p < .01). This resulted in a 26% decline in σes (80 ± 25 to 59 ± 18 g/cm², p < .01). Finally, norepinephrine increased Pes by 32% (p < .01) and decreased the left ventricular geometric factor by 31% (p < .01), leading to a 9% fall in σes (77 ± 16 to 70 ± 15 g/cm², p < .12).

Relationship between changes in SVR and σes. Figure 5 shows a side-by-side comparision of the mean changes in SVR and σes after each of the four drugs. With peripheral vasodilation produced by nitroprusside, SVR underestimated the magnitude of change in left ventricular afterload by 22% (p < .05). When vasocostriction was induced by methoxamine, SVR again underestimated the change in σes (this time by 54%, p < .05). When afterload was decreased and contractility was augmented with dobutamine, a 50% disparity in the change in SVR and σes was evident (p < .01). Most importantly, norepinephrine, which minimally decreased afterload while augmenting contractility, resulted in changes in SVR and σes that were different in magnitude and discordant in direction (p < .001).

FIGURE 1. Two-dimensional echocardiogram (top of A) and targeted M mode echocardiograms (bottom of A and B) obtained from a dog in the current study. Panel A was taken from a videotape still frame while panel B came from hardcopy. ECG = electrocardiogram; IVS = interventricular septum; AOP = aortic pressure; LVPW = left ventricular posterior wall.
Effects on left ventricular force-velocity-shortening relations

**Overall left ventricular performance.** Figure 6 shows the maximal effect of each drug intervention on overall left ventricular performance as measured by Vcf, Vcf decreased with methoxamine (p < .01) and increased with nitroprusside (p < .01), dobutamine (p < .001), and norepinephrine (p < .001).

**Left ventricular contractile state.** Figure 7 shows the relationship between $\sigma_{es}$ and Vcf for the entire study group under control conditions. The diagonal solid line shows the mean value for this relation generated over a wide range of $\sigma_{es}$ values obtained under baseline control conditions as well as during methoxamine or nitroprusside infusion. The curved lines are the 95% confidence limits for this relation. Data points above these limits indicate increased contractility while points below indicate decreased contractility. For any $\sigma_{es} - Vcf$ data point, the vertical distance to the mean regression line represents the deviation in Vcf units at a given level of afterload (i.e., $\sigma_{es}$). Since Vcf incorporates heart rate and is preload independent, comparisons of the deviations of Vcf from the mean regression line can be used to assess left ventricular contractility independent of changes in loading conditions induced by various pharmacologic interventions. With these concepts as a framework, figure 8 shows the individual and average $\sigma_{es}$-Vcf data points obtained with dobutamine and norepinephrine. All points are above the 95% confidence limits for the mean $\sigma_{es}$-Vcf relation, indicating a significant positive inotropic effect of both drugs. The vertical distance, measured in Vcf units, to the mean regression line for the average $\sigma_{es}$-Vcf point obtained during dobutamine (open square) and norepinephrine

![Figure 2](image_url)

**Figure 2.** Data from a representative dog showing left ventricular (LV) $\sigma_{es}$ plotted against Vcf. The linear regression lines generated under control conditions (C;METH) and during methoxamine (METH) infusion are shown. Points obtained under predobutamine control (C;DOB) and prenorepinephrine control (C;NE) conditions fell on the line generated by "pure" afterload manipulation. This established the fact that LV contractility had returned to the baseline level before dobutamine and norepinephrine infusions.

![Figure 3](image_url)

**Figure 3.** Plot of the major physiologic determinants of SVR. Values are shown as percent change from control. $P_m$ = aortic mean pressure; CO = cardiac output; NP = nitroprusside; METH = methoxamine; DOB = dobutamine; NOREPI = norepinephrine; *p < .05; **p < .01; ***p < .001.
Discussion

Our results demonstrate that alterations in left ventricular afterload (i.e., $\sigma_{es}$) are not adequately reflected by SVR. To understand why SVR is an unreliable measure of left ventricular afterload, it is necessary to examine the concept of afterload itself.

Left ventricular afterload as measured by systolic wall stress. Afterload is defined as the force opposing ventricular fiber shortening during left ventricular ejection.$^{1,2,7}$ It is not synonymous with peripheral arterial pressure, peripheral vasomotor tone, or SVR. Rather, it can be more appropriately thought of as left ventricu-

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FIGURE 4. Plot of the mean percent change from control values for left ventricular $P_{es}$, end-systolic geometric factor (G), and $\sigma_{es}$. Other abbreviations as in figure 2.

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FIGURE 5. Comparison of the mean percent change from control values for SVR and $\sigma_{es}$ during nitroprusside (NP), methoxamine (METH), dobutamine (DOB), and norepinephrine (NOREPI) infusions. Note the discordant changes with norepinephrine.
lar wall stress during ejection. It includes factors both internal and external to the myocardium. According to La Place’s principle, left ventricular wall stress is directly related to chamber dimension and pressure and inversely related to wall thickness.\textsuperscript{1, 6-8, 11} During the ejection phase of the cardiac cycle, the left ventricular dimension decreases while ventricular pressure and wall thickness increase. Normally, left ventricular afterload (i.e., wall stress) reaches its peak within the first one-third of ventricular ejection and then declines throughout the remainder of systole.\textsuperscript{6, 8, 9, 11} This occurs despite rising ventricular pressure throughout most of the ejection period, and emphasizes the importance of the decline in left ventricular size and increase in wall

**Figure 6.** Effects of the four drug interventions on overall left ventricular performance as measured by Vcf. Abbreviations as in figure 2.

**Figure 7.** Relationship between left ventricular (LV) \( \sigma_w \) and Vcf for the entire study group under control conditions. See text for detailed description.
thickens (i.e., geometric factors) as determinants of instantaneous systolic wall stress. By end-ejection, wall stress is generally less than 50% of its peak value.\(^{3,9}\) Left ventricular systolic wall stress can be divided into several components, each of which has specific physiologic significance. These include: (1) peak systolic wall stress, which is one of the most important stimuli for left ventricular hypertrophy in chronic pressure overload states such as systemic hypertension, valvular aortic stenosis, or coarctation of the aorta,\(^6,11,14-16\) (2) integral of left ventricular systolic wall stress over time, which along with heart rate and contractile state is a major determinant of myocardial oxygen requirements,\(^17,18\) (3) \(\sigma_{es}\), which defines the limiting force to left ventricular fiber shortening. This is demonstrated by the fact that ventricular ejection ends when instantaneous myocardial force reaches the maximal or isometric value for the existing chamber size, thickness, and pressure.\(^7,8,10,19-22\) The \(\sigma_{es}\) is a measure of this load. For a given level of contractility, it is the wall stress at end-systole rather than the load throughout the course of ventricular ejection that is inversely related to the overall extent and mean velocity of fiber shortening. Accordingly, absolute values for peak, mean, and integral of left ventricular systolic force (i.e., wall stress) can vary without altering events at end-systole.\(^7,20\)

In this study, the physiologic determinants of \(\sigma_{es}\) (i.e., end-systolic pressure and the left ventricular geometric factor) decreased when afterload was reduced with nitroprusside and increased when afterload was augmented with methoxamine (figure 4). This reflects the direct linear relationship between \(P_{es}\) and \(D_{es}\) when contractile state is maintained constant over a wide range of afterload.\(^23-25\) In contrast, when contractility was augmented with either dobutamine or norepinephrine, \(P_{es}\) increased (+21% and +32%, respectively) while the left ventricular geometric factor decreased (−38% and −31%, respectively). These discordant changes between \(P_{es}\) and the left ventricular geometric factor reflect the increased slope and leftward shift in the \(P_{es}-D_{es}\) relation that occur with a positive inotropic intervention.\(^24,25\) This means that relative to control values, \(D_{es}\) is smaller for any \(P_{es}\). Since there is conservation of left ventricular mass, the decrease in \(D_{es}\) is associated with an increase in end-systolic wall thickness. The net result is a decline in the left ventricular geometric factor that more than counterbalances the rise in \(P_{es}\), leading to a 26% fall in \(\sigma_{es}\) with dobutamine and a 9% fall with norepinephrine (figure 4).
Left ventricular afterload as measured by SVR. For years SVR has been used as a measure of ventricular afterload. It is defined by analogy to Ohm’s law as the ratio of mean pressure drop to total flow across the systemic vascular bed. This assumes that the cardiovascular system is a “DC” circuit that generates constant pressure and flow throughout systole and diastole. However, the left ventricular is a pulsatile rather than steady-state pump that works against an internal load consisting of pressure and geometric factors plus an external load consisting of pulsatile and nonpulsatile components. The relative importance of each of these components depends on multiple factors, including the inertial properties of blood, the elasticity, viscosity, and geometry of arteries and the viscous properties of blood in small vessels. Since SVR incompletely assesses the ventricle’s internal and external loads, it is not surprising that conditions exist in which SVR is an unreliable measure of left ventricular afterload. Results from the current study confirm this fact by showing that SVR underestimates the magnitude of change in afterload (1) by 22% when afterload alone is decreased (nitroprusside), (2) by 54% when afterload alone is increased (methoxamine), and (3) by 50% when afterload is decreased and contractility is augmented (dobutamine). Most importantly, when afterload is minimally decreased in association with augmented contractility (with norepinephrine), SVR fails to accurately predict either the magnitude or direction of change.

Effects of dobutamine and norepinephrine on left ventricular contractility. The relationship between left ventricular σ and the Vcf is a sensitive measure of contractility that incorporates heart rate and afterload while being preload independent. This overcomes the load- and rate-dependent limitations of traditional indexes of left ventricular systolic performance such as ejection fraction, percent fractional shortening, and mean velocity of fiber shortening. In our study, dobutamine increased Vcf by 43%, while norepinephrine increased it by 34% (figure 5). These changes in overall performance were associated with a greater afterload-reducing effect for dobutamine than for norepinephrine (-34% vs -9%, p < .05). When changes in left ventricular afterload were incorporated into the data analysis, both sympathomimetic drugs were shown to be equipotent positive inotropes (figure 8). Thus, assessment of left ventricular mechanics by the approach outlined in this investigation allowed separation and quantitation of the multiple hemodynamic effects of each of the cardioactive agents studied.

Methodologic considerations. A detailed discussion of the methods used in this study has been presented previously. However, several issues specific to the current investigation should be addressed. First, all animals studied had symmetrically contracting left ventricles without evidence of regional wall motion abnormalities on two-dimensional echocardiographic imaging. It was therefore assumed that the targeted M mode echocardiograms were representative of global left ventricular performance. Second, it was assumed that the alterations in left ventricular afterload induced by nitroprusside and methoxamine occurred without associated changes in ventricular contractility. This seems reasonable since heart rate remained unchanged with both drugs, suggesting that a large outflow of catecholamines did not occur. Finally, left ventricular meridional rather than circumferential wall stress was used to measure ventricular afterload. In normally shaped hearts, both of these components of total wall force are important determinants of ventricular shortening characteristics. Although their absolute values may differ in magnitude, their usefulness as measures of left ventricular afterload are comparable.

In accordance with this concept are the results of the animal study by Little et al. in which ultrasonic crystals and a left ventricular micromanometer catheter were used to assess left ventricular mechanics before and after infusion of 10 μg/kg/min dobutamine. For comparable changes in left ventricular pressure, proportionally similar changes in left ventricular long- and short-axis dimensions were noted. This suggests that meridional and circumferential wall stresses also changed in a proportionally similar manner with a catecholamine challenge. Thus, it appears that either analysis of wall stress would have resulted in similar findings in our study.

Clinical implications. SVR is an unreliable measure of left ventricular afterload, as demonstrated by its inability to accurately assess afterload changes associated with pharmacologic interventions. In the clinical setting, changes in SVR do not necessarily reflect left ventricular loading conditions since the true measure of ventricular afterload must consider the interaction of factors internal and external to the myocardium.

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