Left Ventricular End-Systolic Elastance Is Incorrectly Estimated by the Use of Stepwise Afterload Variations in Conscious, Unsedated, Autonomically Intact Dogs

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Background  End-systolic elastance (Ees), the slope parameter of the end-systolic pressure (ESP)-volume (ESV) relation (ESPVR), is usually estimated in patients by producing stepwise, steady-state pharmacological afterload variations and collecting one ESP-ESV point from each step. The ESPVR is then constructed by fitting a linear equation to these points. In sedated, autonomically blocked dogs, it has been shown that when one point from control, one point from a state of increased afterload, and one point from a state of decreased afterload are used, the resulting Ees incorrectly estimates true Ees, defined as the slope of the ESPVR obtained by transient vena caval occlusion. We investigated if this was also the case in unsedated, autonomically intact dogs when the points used belonged to steady states of progressively decreasing or progressively increasing afterload pressure.

Methods and Results  In 10 conscious dogs instrumented with left ventricular (LV) endocardial sonomicrometers to measure LV volume, a LV pressure transducer, and an inferior vena cava (IVC) occluder, two protocols were carried out on separate days. In each protocol, an ESPVR was generated by IVC occlusion in the control state and in two steady-state levels of afterload change produced by stepwise infusion of nitroprusside (protocol 1, afterload decrease) and angiotensin II (protocol 2, afterload increase). In each protocol, steady-state ESP-ESV data points were averaged from the control state and from each level of afterload variation. Linear equations were fitted to the three steady-state points from each protocol, and the estimated Ees, values obtained (EesEST) were compared with the Ees values of the control ESPVRs obtained by IVC occlusion (EesTRUE). In protocol 1, EesEST underestimated EesTRUE by about 16% (EesEST, 6.49±1.55 mm Hg/mL; EesTRUE, 7.48±1.29 mm Hg/mL; P<.02). In protocol 2, EesEST overestimated EesTRUE by about 37% (EesEST, 9.99±3.97 mm Hg/mL; EesTRUE, 6.43±3.88 mm Hg/mL; P<.007).

Conclusions  In conscious, autonomically intact dogs, the use of stepwise, steady-state afterload variations to obtain ESP-ESV data points to construct the ESPVR incorrectly estimates Ees. In the case of afterload reduction, EesTRUE is underestimated an average of 16.3%, and in the case of afterload increase, EesTRUE is overestimated an average of 37.1%. These errors should be taken into account when interpreting clinical studies using this methodology. (Circulation. 1994;90:1431-1440.)

Key Words  elastance • afterload • pressure-volume relation • contractility
achieved by infusion of methoxamine, the resulting ESPVR is flatter than the control ESPVR, and therefore true $E_{os}$ is underestimated. The authors suggest that these errors may be even larger in the presence of intact autonomic reflexes, circulating catecholamines, and spontaneous uncontrolled respiration.

Although combined afterload changes have been used in some studies of this type, in many other cases, including articles published subsequent to that of Freeman et al., LV load is changed stepwise always in the same direction. In other words, in these studies the ESP-ESV data points are collected from steady states of progressively lower afterload pressure or from steady states of progressively higher afterload pressure.

Sagawa et al.32 advanced the hypothesis that if the loading change is a stepwise afterload reduction, it could lead to a false estimate of $E_{os}$. In the example given by Sagawa et al.32 (Fig. 1), a vasoconstrictor is used to produce stepwise decrease in afterload pressure, and each point collected belongs to an ESPVR with a higher slope than the previous one, because at each level of afterload reduction the baroreflex would induce an increase in inotropic state. As a result, the ESPVR constructed by connecting these data points would be much flatter than the true ESPVR corresponding to any one of the individual levels of afterload reduction and therefore would underestimate the true $E_{os}$ value of the basal state.

To extend the findings of Freeman et al, we tested this hypothesis in conscious, unsedated, autonomicomically intact dogs that were breathing normally, by comparing the true $E_{os}$ value of the basal state obtained by acute IVCO with the $E_{os}$ value estimated from three steady-state ESP-ESV data points: one corresponding to the basal state, one corresponding to a first level of afterload reduction, and one corresponding to a second level of afterload reduction. Each level of afterload reduction was achieved by infusion of sodium nitroprusside.

By applying the same protocol but using angiotensin II instead of sodium nitroprusside, we also investigated whether the ESPVR constructed on the basis of the opposite loading change, ie, stepwise afterload increases, yielded reliable estimates of true end-systolic elastance.

Methods

The surgical preparation and experiments (as well as the transportation, housing, and care of the animals) were conducted according to the guiding principles of the American Physiological Society.

Surgical preparation

Ten adult mongrel dogs of either sex, weighing 19.6±0.9 kg (mean±SD), were operated on. Anesthesia was induced using intravenous thiopental sodium (25 mg/kg) and maintained with 2% enflurane. Instrumentation has been described in detail elsewhere.33 Briefly, three pairs of ultrasonic microcrystals were positioned to measure LV internal apex-base, septum–free wall, and anteroposterior diameters; a high-fidelity pressure microtransducer (Konigsberg P7, Konigsberg Instruments) together with a fluid-filled catheter for its calibration was inserted in the LV cavity; a pneumatic cuff occluder was positioned around the inferior vena cava; a fluid-filled catheter for drug infusion was introduced into the right atrium, and pacing wires were sutured to the left atrial appendage. All cables and catheters were tunnelled subcutaneously to emerge at the interscapular space, and the thoracotomy was repaired without closing the pericardium.

Experimental Protocol

Experiments were performed 3 to 4 weeks after surgery, with the conscious, unsedated, autonomically intact dog lying on its right side. The three pairs of ultrasonic microcrystals were connected to a sonomicrometer (Triton Technology), and the ventricular fluid-filled catheter was connected to a pressure transducer (Statham P23 Db) that had been calibrated using a mercury column, with the zero reference point set at the level of the spine. The signal generated by the high-fidelity pressure microtransducer was then adjusted to match the signal provided by the fluid-filled catheter. The three diameter signals and the pressure signal were digitized on-line every 5 milliseconds over 15 seconds with an analog-digital converter (Data Translation 2801-A) coupled to a personal computer, and the calibrated pressure-volume (P-V) loops were displayed.

Protocol 1

In 7 dogs, the protocol included three experimental conditions: control, first level of afterload reduction, and second level of afterload reduction. In two dogs exhibiting physiological sinus arrhythmia during the control condition, the heart was paced (Medtronic 5325) at a heart rate (HR) that was 10% above spontaneous HR. These dogs did not exhibit arrhythmia under changed afterload conditions. After stabilization, two sets of recordings were made: first, a series of at least 10 steady-state beats for the measurement of hemodynamic parameters, and second, immediately afterward, all beats occurring during an acute, short-lasting (maximum, 12 seconds) IVCO, for the construction of the ESPVR. The nitroprusside infusion was started at a rate of 1.7 μg·kg⁻¹·min⁻¹ and then adjusted to cause a decrease in ESP of at least 10% with regard to control, which was achieved at a rate of 2.2±0.6 μg·kg⁻¹·min⁻¹. After recording the signals during steady-state conditions and IVCO, we augmented the infusion rate to produce a further decrease in ESP of at least 10% with regard to the first level of afterload reduction. This was achieved with a dose of 5.1±1.9 μg·kg⁻¹·min⁻¹. Then, the final recordings under steady-state conditions and during IVCO were made.
Protocol 2

In 3 dogs from protocol 1 and in three additional dogs, a second protocol consisting of two levels of angiotensin II-induced afterload increase was carried out on a different day. After control recordings of the steady state and the IVCO, angiotensin II was infused (4.3±1.0 μg·kg⁻¹·min⁻¹) to increase ESP at least 10% above control values. After new recordings of the steady state and the IVCO, angiotensin II infusion was augmented (9.9±3.3 μg·kg⁻¹·min⁻¹) until ESP was at least 10% higher than during the previous level of afterload increase. The final recordings of the steady state and of the IVCO were made, and the dog was killed using an overdose of thiopental sodium followed by a lethal injection of potassium chloride. Correct microcrystal positioning was verified at necropsy.

Data Analysis

The information recorded consisted of steady-state beats and those from IVCO under each experimental condition. The beats from IVCO were the first to be analyzed to calculate the parameters of the ESPVR according to the iterative method described by Kono et al. The resulting volume axis intercept (V₀) value was then used to identify the end-systolic point in each of the steady-state beats as the maximum ratio of LVP to (LVV−V₀). In all cases, LV volume (LVV) (in mL) was calculated as:

\[ LVV = ABD·APD·SFWD·π/6 \]

where ABD, APD, and SFWD are the apex-base, anteroposterior, and septum-free wall internal diameters, respectively.

The digitally calculated first derivative of LVP (dP/dt) was used as the reference signal to define end diastole (at the onset of its rapid upstroke), onset ejection (at its peak positive value), and end ejection (at its peak negative value).

For each experimental step, the beats recorded during steady-state conditions were averaged for the calculation of HR, LV ESP, peak-systolic (PSP), and end-diastolic (EDP) pressures; LV end-diastolic (EDV), onset ejection (OEV), end-ejection (EEV), and end-systolic (ESV) volumes; anteroposterior diameter at onset ejection (OE) and at end ejection (EE); and the maximum value of dP/dt (dP/dt max). Stroke volume (SV) (in mL), SV/HR (in percent), cardiac output (CO) (in L/min), and mean velocity of circumferential fiber shortening (Vcf) (in s⁻¹) were calculated using the following equations:

\[ SV = OEV−EEV \]

\[ CO = (SV·HR)/1000 \]

\[ EF = 100·(SV/OEV) \]

\[ Vcf = (APD_{OE}−APD_{EE})/(APD_{OE}/ET) \]

where ET is ejection time.

For each experimental condition, linear regression analysis was applied to beats recorded during IVCO to construct the ESPVR according to the equation:

\[ ESP = E_{es}(ESV−V_0) \]

From each ESPVR of both protocols, E₀, V₀, and the linear correlation coefficient (r) were calculated. With the same beats, Mw (the slope parameter of the relation between LV stroke work and EDV, called preload recruitable stroke work) and dE/dt max (the slope parameter of the relation between dP/dt max and EDV, which represents the maximum rate of change of LV elastance) were calculated.

In each protocol, using the average ESP-ESV points from the steady states of the control condition, the first level of afterload change, and the second level of afterload change, a new ESPVR was calculated using linear regression analysis. From this “changed-afterload” relation, the estimated E₀, and V₀ values were calculated.

In both protocols, all E₀ values obtained from IVCO were called E₀TRUE, and those estimated from linear regression analysis of the three steady-state ESP-ESV data points were called E₀EST.

Statistical Analysis

Analysis of variance for repeated measures was used to process the results corresponding to the three experimental conditions of the afterload decrease protocol (protocol 1) and the three experimental conditions of the afterload increase protocol (protocol 2). In each protocol, when the F value showed that significant differences were present, the Tukey B test was used to compare the control condition with the first and second levels of afterload modification. In each protocol, paired t tests were used to compare the estimated E₀ with the corresponding true control E₀. In all cases, a value of P<.05 was considered to indicate statistically significant differences. All results are expressed as mean±SD.

Results

Fig 2 shows the P-V loops obtained during IVCO under all experimental conditions in a dog displaying small changes in the position of the ESPVR. Fig 3, on the other hand, is an example of a dog displaying larger changes in response to loading variations.

Protocol 1

Table 1 shows the values for the hemodynamic variables and indexes of contractility as well as the correlation coefficients and number of data points of the ESPVRs. Both rates of nitroprusside infusion induced significant decreases in ESP, EDP, ESV, and EDV. A significant HR increase was observed only at the second level of afterload reduction, which also resulted in a significant fall in EF, whereas dP/dt max, Vcf, and Mw remained unchanged. On the other hand, dE/dt max increased significantly under both rates of nitroprusside infusion. Note that the dE/dt max value reported was based on six observations, since in one dog dP/dt max showed a paradoxical progressive increase during the occlusion, yielding a negative dE/dt max value. E₀ increased with nitroprusside infusion, but only at the higher infusion rate did the increase achieve statistical significance.

The individual responses of E₀ to nitroprusside infusion are illustrated in Fig 4. With the exception of dog 4 (second level of afterload reduction) and dog 5 (both levels of afterload reduction), both rates of nitroprusside infusion provoked an increase in E₀. In each panel, the estimated ESPVR resulting from connecting the three steady-state ESP-ESV data points corresponding to the three experimental conditions is shown. The individual and mean E₀ values for all four ESPVRs are listed in Table 2. Except for dog 4, E₀EST underestimated the three E₀TRUE values, including control E₀TRUE, which is the one that the tested method is purported to estimate. This was also the case for the mean E₀EST value, which is significantly lower (P<.02) than the mean control E₀TRUE. On average, E₀EST underestimated control E₀TRUE by 16.3%.
Protocol 2

Table 3 shows the values for the hemodynamic variables and indexes of contractility, as well as the correlation coefficients and number of data points of the ESPVRs.

Significant increases in ESP, EDP, ESV, and EDV were observed. Because neither HR nor SV changed, CO stayed constant. Both EF and Vcf decreased significantly with the higher rate of angiotensin II infusion. Although Mv remained unchanged, dE/dt max decreased significantly in response to the higher rate of infusion. Neither Ees nor V0 showed significant variations.

The individual responses of Ees and V0 to angiotensin II infusion are illustrated in Fig 5 and listed in Table 4. In each panel of Fig 5, the estimated ESPVR resulting from connecting the three steady-state ESP-ESV data points corresponding to the three experimental conditions is depicted, and the corresponding Ees*EST and estimated V0 values are listed in Table 4. It is seen that in all dogs Ees*EST overestimated the three Ees*TRUE values, including control Ees*TRUE, which is the one that the tested method purports to estimate. This was also the case for the mean Ees*EST, which was significantly higher (P<.007) than the mean control Ees*TRUE. On the average, Ees*EST overestimated control Ees*TRUE by 37.1%.

Discussion

Freeman et al31 were the first to show that the use of steady-state afterload variations, a method often used in the clinical setting to produce ESPVRs, yielded incorrect estimates of Ees. In sedated, autonomically blocked dogs, they demonstrated that the ESPVR obtained by fitting a linear equation to three steady-state ESP-ESV data points (one from the control condition, one from a state of nitroprusside-induced afterload reduction, and one from a state of angiotensin-induced afterload enhancement) overestimated the slope of the control ESPVR obtained by vena caval occlusion during hyperventilation-induced apnea. When methoxamine was used instead of angiotensin to increase afterload pressure, Ees was underestimated. The authors thus concluded that the results of a given study may be influenced by the agents used and suggested that these misestimations of true Ees may be even larger in the presence of intact reflexes, circulating catecholamines, and normal respiration.

The results of the present study extend the findings of Freeman et al31 by showing that in unsedated, autonomically intact dogs that are respiring normally, the use of stepwise, steady-state nitroprusside-induced afterload reductions to generate the ESPVR underestimates Ees, whereas the use of stepwise, steady-state angiotensin-induced afterload increases overestimates Ees.
The major difference between our findings and those of Freeman et al. lies in the fact that they autonomicallly blocked their dogs, so the misestimation of $E_a$ was caused by shifts in the position of the ESPVR due to the sensitivity of $V_t$ to ventricular afterload. In our autonomically intact dogs, we would expect not only parallel shifts to occur (as found by Sodums et al.\cite{1}) but also reflex changes in $E_a$. The incorrect estimation of $E_a$ by the clinical procedure requires a change in the position of the ESPVR to be brought about by a parallel shift, a change in slope, or a combination of both. The predominant factor causing the change in position probably depends on the autonomic state of the animal at the time, so we believe that the large range of responses exhibited by the ESPVRs of our animals reflects a wide range of basal autonomic states. We looked for indicators of this hypothesis by correlating $E_a$ with the hemodynamic variables, both in absolute terms and in terms of the change in the values of the variables between successive steps of both protocols. We found that the best correlation existed between $E_a$ and HR. In the case of nitroprusside, the absolute values of $E_a$ and HR correlated well under all conditions ($r=.93$), and the changes in these parameters between the successive steps also correlated well ($r=.80$), suggesting that the response to nitroprusside could have been mediated by the baroreflex resulting in positive inotropic and chronotropic effects. This was not the case for angiotensin; although the absolute values of $E_a$ and HR correlated well ($r=.88$), the changes of these parameters between the successive steps correlated poorly ($r=-.29$). We conclude that HR is a good rule-of-thumb indicator of $E_a$ but that changes in HR in response to pharmacological interventions do not necessarily reflect changes in $E_a$.

**Response to Nitroprusside**

The results of the present study show that nitroprusside infusion induced the expected fall in LV filling pressure. As a consequence, EDV decreased significantly. This decrease could not be compensated for by the increase in HR, resulting in a significant fall in CO. The ensuing response of $E_a$ to nitroprusside infusion was consistent with a baroreflex-induced increase in LV contractility. This is further supported by the significant increase in $dE/dt_{max}$ provoked by nitroprusside. $M_w$ did not accompany the changes observed in $E_a$ and $dE/dt_{max}$. However, it has been shown that $M_w$ is less sensitive to inotropic variations than $E_a$ and $dE/dt_{max}$.

The ESPVR has been found to be moderately curvilinear, with its concavity facing the volume axis.\cite{38,43} This curvilinearity is more pronounced (the line curves down faster) at low ESPs. This suggests that measurement of $E_a$ on the same curve but over a lower range of pressures could yield a higher value than when measured at normal pressures. Although in all cases the ESP-ESV data points were adequately fitted to a linear equation, a contribution of this effect to the observed
TABLE 1. Hemodynamic Variables and Indexes of Contractility for Protocol 1 (Afterload Decrease)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>NPS-1</th>
<th>NPS-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, bpm</td>
<td>143±14</td>
<td>158±28</td>
<td>167±32*</td>
</tr>
<tr>
<td>LVESP, mm Hg</td>
<td>120.6±5.6</td>
<td>101.3±4.4†</td>
<td>84.9±9.6‡</td>
</tr>
<tr>
<td>LVEDP, mm Hg</td>
<td>10.9±10.0</td>
<td>5.1±5.6*</td>
<td>2.9±3.4†</td>
</tr>
<tr>
<td>LVESV, mL</td>
<td>22.7±5.3</td>
<td>18.9±4.8†</td>
<td>17.3±4.5‡</td>
</tr>
<tr>
<td>LVEDV, mL</td>
<td>36.9±8.7</td>
<td>29.9±8.2†</td>
<td>25.6±6.5‡</td>
</tr>
<tr>
<td>SV, mL</td>
<td>14.2±7.1</td>
<td>11.1±6.5†</td>
<td>8.3±5.4‡§</td>
</tr>
<tr>
<td>CO, L/min</td>
<td>1.98±0.88</td>
<td>1.64±0.76*</td>
<td>1.29±0.71†</td>
</tr>
<tr>
<td>dP/dt max, mm Hg/s</td>
<td>3105±560</td>
<td>3406±812</td>
<td>3148±1109</td>
</tr>
<tr>
<td>EF, %</td>
<td>37.6±11.1</td>
<td>35.6±12.8</td>
<td>31.3±13.6‡</td>
</tr>
<tr>
<td>Vcf, s⁻¹</td>
<td>1.42±0.39</td>
<td>1.59±0.37</td>
<td>1.61±0.41</td>
</tr>
<tr>
<td>Ees, mm Hg/mL</td>
<td>7.75±1.29</td>
<td>10.72±5.09</td>
<td>13.16±5.93*</td>
</tr>
<tr>
<td>V₀, mL</td>
<td>6.6±5.4</td>
<td>8.0±5.7</td>
<td>8.9±6.9</td>
</tr>
<tr>
<td>Mw, mm Hg</td>
<td>90.2±7.2</td>
<td>91.3±11.7</td>
<td>89.7±11.3</td>
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<tr>
<td>dE/dt max, mm Hg/s · mL (n=6)</td>
<td>87.6±33.5</td>
<td>165.3±47.8*</td>
<td>205.5±63.9†</td>
</tr>
<tr>
<td>r</td>
<td>0.98±0.013</td>
<td>0.968±0.013</td>
<td>0.962±0.032</td>
</tr>
<tr>
<td>No.</td>
<td>14±5</td>
<td>17±6</td>
<td>13±4</td>
</tr>
</tbody>
</table>

NPS-1 indicates lower rate of sodium nitroprusside infusion; NPS-2, higher rate of sodium nitroprusside infusion; HR, heart rate; bpm, beats per minute; LVESP, left ventricular end-systolic pressure; LVEDP, left ventricular end-diastolic pressure; LVESV, left ventricular end-systolic volume; SV, stroke volume; CO, cardiac output; dP/dt max, maximum time derivative of left ventricular pressure; EF, ejection fraction; Vcf, maximum velocity of circumferential fiber shortening. Ees, end-systolic elastance; V₀, volume intercept of the end-systolic pressure-volume relation; Mw, slope of the preload recruitable stroke work relation; dE/dt max, maximum rate of change of left ventricular elastance; r, correlation coefficient for linear regression of LVESP-LVESV data points; and No., number of LVESP-LVESV points used from inferior vena caval occlusions. Values are mean±SD. *P<.05 compared with control; †P<.01 compared with control; ‡P<.05 compared with NPS-1; §P<.01 compared with NPS-1.

Fig 4. Plots of individual end-systolic pressure-volume relations (light lines) obtained during each experimental step in protocol 1 (afterload reduction). In each dog, the heavy line is the end-systolic pressure-volume relation resulting from fitting a linear equation to the pressure-volume data points (○) collected under each experimental condition (control, lower rate of nitroprusside infusion, and higher rate of nitroprusside infusion).
TABLE 2. Individual and Mean Values for True and Estimated End-Systolic Elastance for Protocol 1 (Afterload Decrease)

<table>
<thead>
<tr>
<th>Dog</th>
<th>E&lt;sub&gt;s&lt;/sub&gt; Protocol 1, mm Hg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
</tr>
<tr>
<td>1</td>
<td>7.84</td>
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<tr>
<td>2</td>
<td>6.93</td>
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<tr>
<td>3</td>
<td>8.95</td>
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<td>4</td>
<td>8.39</td>
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<td>5</td>
<td>6.77</td>
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<td>6</td>
<td>9.48</td>
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<tr>
<td>7</td>
<td>5.87</td>
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<tr>
<td>Mean</td>
<td>7.75</td>
</tr>
<tr>
<td>SD</td>
<td>1.29</td>
</tr>
</tbody>
</table>

E<sub>s</sub> indicates end-systolic elastance; NPS-1, lower rate of sodium nitroprusside infusion; NPS-2, higher rate of sodium nitroprusside infusion; and EST, estimated end-systolic elastance using stepwise, steady-state afterload reductions. *P<.01 compared with control (ANOVA plus Tukey's B); †P<.02 compared with control (paired t test).

Increases in E<sub>s</sub> should not be discarded, especially in dogs 2 and 6 at the higher rate of nitroprusside infusion, who showed a more-than-50% E<sub>s</sub> increase with regard to the previous experimental condition.

Response to Angiotensin

The hemodynamic changes observed under angiotensin II infusion may be attributed to a Starling response. In effect, LVEDV increased significantly, resulting in preservation of SV and CO despite the increases in ESP and ESV. Note that although LVEDP increased significantly under these conditions, this cannot of itself be taken as evidence for a Frank-Starling mechanism because LVEDP is not a reliable indicator of LVEDV when vasoactive drugs are used. The absence of an intact pericardium in our dogs permitted preservation of SV and CO through a Frank-Starling mechanism. This may not be the case in patients with intact pericardium; Tyberg et al showed that the elevated right atrial pressure under these circumstances may be transmitted via the pericardial cavity to the space surrounding the LV, thus attenuating the increase in LV transmural pressure and so restricting the expression of a Frank-Starling mechanism.

The changes displayed by the indexes of contractility under angiotensin infusion were not uniform. Although E<sub>s</sub> showed a slight, nonsignificant tendency to increase and M<sub>w</sub> stayed almost constant, Vcf and dE/dt<sub>max</sub> decreased significantly in response to the higher rate of infusion. The change displayed by Vcf does not necessarily reflect decreased contractility, because it has been shown that Vcf decreases in response to angiotensin-induced increases in afterload pressure. The decrease

TABLE 3. Hemodynamic Variables and Indexes of Contractility for Protocol 2 (Afterload Increase)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Ang II-1</th>
<th>Ang II-2</th>
</tr>
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<tbody>
<tr>
<td>HR, bpm</td>
<td>130±19</td>
<td>130±21</td>
<td>132±20</td>
</tr>
<tr>
<td>LVEESP, mm Hg</td>
<td>112.0±10.5</td>
<td>140.4±14.2†</td>
<td>163.8±18.6‡</td>
</tr>
<tr>
<td>LVEDP, mm Hg</td>
<td>7.4±1.9</td>
<td>11.1±2.4*</td>
<td>15.4±5.1†‡</td>
</tr>
<tr>
<td>LVEDV, mL</td>
<td>21.6±10.7</td>
<td>25.3±13.5*</td>
<td>27.8±14.0†</td>
</tr>
<tr>
<td>SV, mL</td>
<td>31.6±14.3</td>
<td>36.0±17.0*</td>
<td>38.6±17.0†</td>
</tr>
<tr>
<td>CO, L/min</td>
<td>14.9±5.9</td>
<td>14.8±4.8</td>
<td>14.3±3.6</td>
</tr>
<tr>
<td>dP/dt&lt;sub&gt;max&lt;/sub&gt;, mm Hg/s</td>
<td>3238±544</td>
<td>3261±547</td>
<td>3346±633</td>
</tr>
<tr>
<td>EF, %</td>
<td>43.0±2.7</td>
<td>40.0±4.9</td>
<td>37.1±6.9*</td>
</tr>
<tr>
<td>Vcf, s&lt;sup&gt;-1&lt;/sup&gt;</td>
<td>1.53±0.40</td>
<td>1.31±0.43</td>
<td>1.14±0.42†</td>
</tr>
<tr>
<td>E&lt;sub&gt;s&lt;/sub&gt;, mm Hg/mL</td>
<td>6.43±3.88</td>
<td>7.44±4.10</td>
<td>7.62±3.88</td>
</tr>
<tr>
<td>V&lt;sub&gt;c&lt;/sub&gt;, mL</td>
<td>-2.2±8.2</td>
<td>0.5±3.5</td>
<td>-0.2±2.8</td>
</tr>
<tr>
<td>M&lt;sub&gt;w&lt;/sub&gt;, mm Hg</td>
<td>86.8±13.0</td>
<td>95.0±14.7</td>
<td>101.7±18.6</td>
</tr>
<tr>
<td>dE/dt&lt;sub&gt;max&lt;/sub&gt;, mm Hg/s·mL</td>
<td>71.4±58.4</td>
<td>51.4±71.1</td>
<td>45.0±42.0*</td>
</tr>
<tr>
<td>r</td>
<td>0.970±0.040</td>
<td>0.983±0.017</td>
<td>0.977±0.031</td>
</tr>
<tr>
<td>No.</td>
<td>13±2</td>
<td>14±3</td>
<td>13±2</td>
</tr>
</tbody>
</table>

Ang II-1 indicates lower rate of angiotensin II infusion; Ang II-2, higher rate of angiotensin II infusion; HR, heart rate; bpm, beats per minute; LVEESP, left ventricular end-systolic pressure; LVEDP, left ventricular end-diastolic pressure; LVESV, left ventricular end-systolic volume; LVEDV, left ventricular end-diastolic volume; SV, stroke volume; CO, cardiac output; dP/dt<sub>max</sub>, maximum time derivative of left ventricular pressure; EF, ejection fraction; Vcf, maximum velocity of circumferential fiber shortening, E<sub>s</sub>, end-systolic elastance; V<sub>c</sub>, volume intercept of the end-systolic pressure-volume relation; M<sub>w</sub>, slope of the preload recruitable stroke work relation; dE/dt<sub>max</sub>, maximum rate of change of left ventricular elastance; r, correlation coefficient for linear regression of LVEESP-LVESV data points; and No., number of LVEESP-LVESV points used from inferior vena caval occlusions. Values are mean±SD.

*P<.05 compared with control; †P<.01 compared with control; ‡P<.05 compared with Ang II-1.
in $dE/dt_{\text{max}}$, which was statistically significant despite large dispersion in the data, is however difficult to explain on the basis of pure loading variations. Given the marked angiotensin-induced rise in ESP, it is reasonable to suppose that a moderate baroreflex-mediated decrease in contractility occurred, reflected only by $dE/dt_{\text{max}}$, which, as stated above, is more sensitive to inotropic variations than other indexes.

An interesting observation of this study is that although the direction of change of $E_{\text{es}}$ was the same in both protocols, $E_{\text{est}}$ resulting from connecting the three ESP-ESV data points of the nitroprusside protocol underestimated $E_{\text{es,TRUE}}$, whereas $E_{\text{est}}$ resulting from connecting the three ESP-ESV data points of the angiotensin protocol overestimated $E_{\text{es,TRUE}}$. This phenomenon reflects the relative changes in ESP and ESV observed under each protocol. During nitroprusside infusion, the mean percent change in EDV was greater than the mean percent change in ESP at the lower rate of infusion (19% and 15.7%, respectively) and very similar at the higher rate of infusion (14.4% and 15.5%, respectively). In contrast, during angiotensin infusion, the mean percent change in ESP was much greater than the mean percent change in ESV at both rates of infusion (20.3% versus 14.6%, respectively, at the lower rate, and 14.5% versus 9%, respectively, at the higher rate). Consequently, the estimated ESPVR line generated by stepwise afterload decrease was significantly flatter than its control ESPVR, and that estimated from stepwise afterload increase was significantly steeper than its control ESPVR.

Because the hemodynamic intervention (acute vena caval occlusion) used to construct the ESPVR varies the volume of the right ventricle, the role of direct ventricular interaction should be discussed. Slinker and Glantz demonstrated that in dogs with the pericardium removed (which is the case of our own dogs), direct ventricular interaction is about one fifth as important as series interaction at end diastole and only one sixth as important at end systole. Because the results of the present study refer to events taking place at end systole, it is unlikely that the misestimations of $E_{\text{es,TRUE}}$ associated with the use of $E_{\text{est}}$ could be attributed to the effect of direct ventricular interaction.

**Clinical Implications**

The results of this investigation indicate that the conclusions reached in clinical studies based on esti-
moters of E\textsubscript{es} obtained using stepwise steady-state afterload changes should be interpreted with care. When the effects of a drug or a pathophysiological situation or intervention expected to depress contractile state is assessed by the use of stepwise nitroprusside-induced afterload decreases, it must be taken into account that approximately 16\% of any observed fall in E\textsubscript{es} may be attributed to methodological error. If, on the other hand, the tested intervention is supposed to enhance contractility, the error associated with this method may offset the effect of the intervention and produce a false-negative result.

With the use of angiotensin-induced afterload increases, similar reasoning applies, but in this case the expected methodological error is approximately 37\%.

**Conclusions**

The use of stepwise, steady-state afterload reductions or enhancements to obtain ESP-EV points for the estimation of the ESPVR may result in incorrect estimation of E\textsubscript{es}. Results in conscious, unseated, automonically intact dogs indicate that in the case of nitroprusside-induced afterload reduction, true E\textsubscript{es} is underestimated by 16.3\%, and in the case of angiotensin-induced afterload increase, true E\textsubscript{es} is overestimated by about 37.1\%. These results should be taken into account when interpreting clinical studies using this methodology. We suggest that the potential clinical usefulness of E\textsubscript{es} merits the further development of those clinical protocols directed toward rapid afterload reduction, which appears to provide a clearer response than afterload increase.

**Acknowledgments**

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**References**


Left ventricular end-systolic elastance is incorrectly estimated by the use of stepwise afterload variations in conscious, unsedated, autonomically intact dogs.

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