Single-beat estimation of right ventricular end-systolic pressure-volume relationship

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METHODS

Preparation. The experiments were done in accordance with the “Guiding Principles in the Care and Use of Animals” approved by the American Physiological Society. Details of our preparation have been published previously (4). Briefly, 28 mongrel dogs (mean wt 24 kg) were anesthetized with sufentanil (10 μg/kg iv) and α-chloralose (80 mg/kg iv), fol-

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Followed by infusions of sufentanil (1 μg·kg⁻¹·h⁻¹) and α-choleralose (20 mg·kg⁻¹·h⁻¹), and ventilated with 40% O₂ and 5 cmH₂O end-expiratory pressure. RV pressure was monitored with a micromanometer catheter (Millar Instruments; Houston, TX) and instantaneous pulmonary blood flow with a transit-time ultrasonic flow probe (Transonic Systems; Ithaca, NY). Cardiac output and RV ejection fraction were measured with a fast-response thermodilution pulmonary artery catheter (Baxter-Edwards; Irvine, CA) (30). A clamp was placed around the pulmonary artery upstream from the flow probe, ~1 cm away from the pulmonary valve. The chest was closed but no attempt was made to restore negative pleural pressure. Hypoxic pulmonary vasoconstriction was enhanced by aspirin (20 mg/kg iv) (4).

Protocol. In the first part of the study, flow and pressures were recorded during several beats before and during the first beat after the proximal pulmonary artery was clamped (Fig. 2). In each dog, the procedure was repeated at each combination of normal or low preload and normal or high afterload with normal or low or high myocardial contractility (12 combinations). Preload was decreased by inflating a balloon in the inferior vena cava to reduce venous return. Afterload was increased by reducing the inspired oxygen to 10% to cause hypoxic pulmonary vasoconstriction. Contractility was increased by dobutamine (5–10 μg·kg⁻¹·min⁻¹ iv) and decreased by propranolol (1 mg/kg iv). In the second part of the study, flow and pressures were recorded to determine ESPVR for each dog and to assess RV contractility and coupling efficiency. Contractility, preload, and afterload were modified by the same procedures as before. Because we found flow reduction and hypoxia to cause sympathetic stimulation, we also increased the afterload by constricting the proximal pulmonary artery and assessed the effects of flow reduction, hypoxia, and constriction before and after α- and β-adrenergic blockade with phentolamine (2 mg/kg iv + 50 μg·kg⁻¹·h⁻¹) and propranolol (2 mg/kg iv) (4).

Data analysis. Ventricular and arterial components of coupling, Eₜₚ and Eₚ, were determined from about five signal-averaged consecutive beats. First, RV end-diastolic volume was calculated as the ratio of stroke volume to ejection fraction (end-diastolic volume does not affect Eₜₚ or Eₚ; see Discussion). The decrease of RV volume during systole was computed by integration of the instantaneous pulmonary arterial flow, assuming that blood flowing through the proximal pulmonary artery was ejected from the RV. Second, the RV pressure-volume loop (limited to isovolumic contraction, ejection and isovolumic relaxation) was constructed from instantaneous RV pressure and volume. Third, Pₘₚₓ was determined by fitting the equation P = a + b·sin(c·t + d), where P is pressure and t is time, to RV pressure values before the maximal first derivative of pressure development over time (dP/dt) and after minimal dP/dt (Fig. 3, left) (26). Coefficients a–d were computed by a least-square nonlinear fitting routine by using the Levenberg-Marquardt procedure. Pₘₚₓ was obtained as Pₘₚₓ = a + 2 b. Fourth, the ESPVR line was drawn from Pₘₚₓ down and tangent to the pressure-volume curve, i.e., from predicted isovolumic beat end systole to actual ejection beat end systole (Fig. 3, right) (27). The arterial effective elastance line was drawn from end systole to end diastole. Fifth, Eₚ was computed as the slope of the ESPVR line, and Eₜₚ as the absolute slope of the arterial elastance line (17).

Statistics. Results are expressed as means ± SE. Predicted and observed values were compared by correlation analysis. Changes in contractility, preload, and afterload were tested by analysis of variance and analysis of contrasts. P values <0.05 were accepted as indicating statistical significance.

RESULTS

Pₘₚₓ prediction. Observed Pₘₚₓ values were obtained in 136 of the 144 instances. Failures were related to premature beats triggered by the clamping procedure. Predicted Pₘₚₓ values were obtained in 114 instances. Failures were mainly related to RV pressure tracing artifacts due to catheter knocking against the ventricular wall at low preload or during dobutamine infusion. The automated fitting procedure failed in eight instances. Overall, 106 pairs of values were available for correlation analysis. In each dog, a strong correlation was observed between observed and predicted

![Image](http://ajpheart.physiology.org/)

Fig. 1. Principle of single-beat end-systolic pressure-volume relation (ESPVR) determination. The ESPVR is assumed linear and afterload independent. Trace ABCDA is the pressure-volume curve of a normal ejecting beat, with end diastole in point A and end-systole in point C. In a traditional approach, a progressive increase of afterload at same preload yields the end-systolic points I, J, and K, and the ESPVR is defined as the CIJK line. In the present approach, the computed maximal pressure of an isovolumic beat at same preload (ABLABA) yields the end-systolic point L, and ESPVR is defined as the CL line.

![Diagram](http://ajpheart.physiology.org/)

Fig. 2. Example of proximal pulmonary arterial (PA) clamping procedure. The beat recorded just after the clamping is isovolumic, as verified by the absence of flow in the artery, and begins at the same end-diastolic volume and pressure (press) as the normal ejecting beats. RV, right ventricular.
Fig. 3. Determination of ventricular end-systolic elastance (E\(_{es}\)) and arterial effective elastance (E\(_{a}\)). Left: end-systolic pressure of an isovolumic beat is computed by sine wave extrapolation from the ejecting beat by using pressure values recorded before maximal first derivative of pressure development over time (dP/dt) and after minimal dP/dt. Right: this maximal RV pressure of isovolumic beats (P\(_{max}\)) is drawn on the RV pressure-volume diagram. The ESPVR line is drawn from P\(_{max}\) down and tangent to the pressure-volume curve, i.e., from predicted isovolumic beat end systole to actual ejecting beat end systole (defined by the contact point of pressure-volume curve and ESPVR line). The effective arterial elastance line is drawn from end systole to end diastole. E\(_{es}\) is the slope of the ESPVR line, and E\(_{a}\) is the absolute slope of the arterial elastance line.

\[ P_{max} = r = 0.98 \pm 0.02, P < 0.001 \] Regression lines had intercepts of 1 ± 2 mmHg and slopes of 0.87 ± 0.06 (Fig. 4). Predicted P\(_{max}\) thus consistently overestimated observed P\(_{max}\) by ~15%.

Baseline and inotropic changes. Baseline hemodynamics and blood gas values were normal (Table 1). E\(_{es}\) was 1.1 ± 0.1 mmHg/ml, E\(_{a}\) was 0.8 ± 0.1 mmHg/ml, and E\(_{es}/E_{a}\) was 1.6 ± 0.4. Dobutamine increased cardiac output and systemic arterial pressure. It increased E\(_{es}\) to 2.0 ± 0.2 mmHg/ml, did not affect E\(_{a}\), and increased E\(_{es}/E_{a}\) to 2.5± 0.5. Propranolol did not change cardiac output and decreased systemic arterial pressure. It did not affect E\(_{es}\) or E\(_{a}\) significantly, but decreased E\(_{es}/E_{a}\) to 0.9 ± 0.2.

Preload and afterload changes. Venous return reduction decreased cardiac output and all intravascular pressures and increased heart rate (Table 2). It did not affect E\(_{es}\), increased E\(_{a}\) from 0.6 ± 0.1 to 1.3 ± 0.2 mmHg/ml, and decreased E\(_{es}/E_{a}\) from 2.0 ± 0.3 to 1.1 ± 0.2 mmHg/ml. E\(_{es}\) tended to increase in dogs with moderate hypotension and tachycardia due to baroreceptor-induced adrenergic stimulation. It tended to decrease in dogs with severe hypotension and tachycardia, possibly due to decreased coronary flow. After adrenergic blockade, venous return reduction still decreased cardiac output and pressures, but no longer had an effect on heart rate, E\(_{es}\), E\(_{a}\), or E\(_{es}/E_{a}\). Hypoxia increased pulmonary arterial pressure and cardiac output (Table 3). It increased E\(_{es}\) from 1.0 ± 0.1 to 1.3 ± 0.2 mmHg/ml and E\(_{a}\) from 0.7 ± 0.1 to 1.1 ± 0.2 mmHg/ml and did not affect E\(_{es}/E_{a}\). After adrenergic blockade, hypoxia still increased E\(_{es}\), but decreased E\(_{es}/E_{a}\) from 1.4 ± 0.2 to 1.1 ± 0.1 mmHg/ml. Pulmonary artery constriction increased pulmonary arterial pressure and decreased cardiac output (Table 4). It increased E\(_{es}\) from 1.2 ± 0.2 to 2.0 ± 0.4 mmHg/ml and E\(_{a}\) from 1.0 ± 0.1 to 2.6 ± 0.5 mmHg/ml and decreased E\(_{es}/E_{a}\) from 1.6 ± 0.5 to 0.9 ± 0.1. After adrenergic

Table 1. Effects of dobutamine and propranolol on right ventricular-arterial coupling

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Dobutamine</th>
<th>Propranolol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flow, l/min</td>
<td>2.8± 0.3</td>
<td>4.0 ± 0.6*</td>
<td>2.4 ± 0.2</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>89± 9</td>
<td>99 ± 13</td>
<td>103 ± 7</td>
</tr>
<tr>
<td>P(_{es}), mmHg</td>
<td>103 ± 5</td>
<td>118 ± 10*</td>
<td>83 ± 4*</td>
</tr>
<tr>
<td>P(_{pa}), mmHg</td>
<td>15 ± 2</td>
<td>18 ± 2*</td>
<td>15 ± 3</td>
</tr>
<tr>
<td>E(_{es}), mmHg/ml</td>
<td>1.07 ± 0.11</td>
<td>2.00 ± 0.23*</td>
<td>0.94 ± 0.11</td>
</tr>
<tr>
<td>E(_{es}), mmHg/ml</td>
<td>0.86 ± 0.12</td>
<td>0.91 ± 0.14</td>
<td>1.24 ± 0.20</td>
</tr>
<tr>
<td>E(<em>{es}/E</em>{a})</td>
<td>1.64 ± 0.39</td>
<td>2.49 ± 0.51*</td>
<td>0.91 ± 0.20*</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 12. HR, heart rate; P\(_{es}\), systemic arterial pressure; P\(_{pa}\), pulmonary arterial pressure; E\(_{es}\), right ventricular end-systolic elastance; E\(_{a}\), pulmonary arterial effective elastance. *P < 0.05 vs. baseline.

Table 2. Effects of venous return reduction on right ventricular-arterial coupling

<table>
<thead>
<tr>
<th></th>
<th>Before Adrenergic Blockade</th>
<th>After Adrenergic Blockade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flow, l/min</td>
<td>3.6 ± 0.3</td>
<td>2.3 ± 0.2*</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>87 ± 7</td>
<td>127 ± 10*</td>
</tr>
<tr>
<td>P(_{es}), mmHg</td>
<td>90 ± 4</td>
<td>69 ± 6*</td>
</tr>
<tr>
<td>P(_{pa}), mmHg</td>
<td>16 ± 1</td>
<td>12 ± 1*</td>
</tr>
<tr>
<td>E(_{es}), mmHg/ml</td>
<td>1.03 ± 0.09</td>
<td>1.07 ± 0.13</td>
</tr>
<tr>
<td>E(_{es}), mmHg/ml</td>
<td>0.62 ± 0.09</td>
<td>1.29 ± 0.16*</td>
</tr>
<tr>
<td>E(<em>{es}/E</em>{a})</td>
<td>2.01 ± 0.32</td>
<td>1.07 ± 0.23*</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 16. *P < 0.05 vs. baseline.
investigated only by Maughan et al. (20) using isolated hearts and linear ESPVR. ESPVR slopes in isovolumic beats were found to be once flatter (2.26 vs. 2.60 mmHg/ml) and once steeper (2.68 vs. 2.50 mmHg/ml) than in ejecting beats. Recalculations from their individual data (20, Table 2) show similar end-systolic pressures in ejecting and isovolumic beats at end-systolic volumes of 40 ml (83 ± 7 vs. 85 ± 7 mmHg) and 60 ml (135 ± 11 vs. 138 ± 11 mmHg). This result suggests that RV ESPVR is the same for ejecting and isovolumic beats, and thus is afterload independent in the investigated volume ranges.

**P_{\text{max}} prediction.** In isolated hearts, Sunagawa et al. (26) determined by Fourier analysis that the pressure-time relationship of a left ventricular isovolumic beat is very close to a sine wave. Accordingly, they found a good correlation between P_{\text{max}} observed during an isovolumic beat and P_{\text{max}} predicted by sine wave extrapolation from the isovolumic parts of an ejecting beat. The same assumption could be incorrect in the RV, due to its crescent shape and its asynchrony contraction pattern, or not be true in vivo due to ventricular interdependence or pericardial constraint. We therefore verified the assumption for the in vivo RV with the use of ejecting and isovolumic beats beginning at the same end-diastolic volume. We found excellent individual correlations between observed and predicted P_{\text{max}} (r = 0.98 ± 0.02). Predicted P_{\text{max}} overestimated observed P_{\text{max}}, a finding that we had anticipated. The lower P_{\text{max}} during our “isovolumic” beats was attributed to the pulmonary valve opening and to minimal ejection from the RV into the pulmonary artery up toward the clamping device. In this situation, observed P_{\text{max}} should be lower than predicted P_{\text{max}} and the difference should increase in proportion to the generated ventricular pressure. This is exactly what we observed. These results suggest that predicted P_{\text{max}} is very close to the P_{\text{max}} of a true isovolumic beat. The single-beat method used in the left ventricle (27) can thus also be used in the RV to determine the ESPVR and assess the inotropic state.

**Baseline and inotropic changes.** Baseline RV E_{\text{es}} values were ~1.1 mmHg/ml, in keeping with values of 1.2 mmHg/ml reported in dogs with sonomicrometry (12). E_{\text{a}} was ~0.7 mmHg/ml, reflecting the low pulmonary arterial pressure and resistance. E_{\text{es}}/E_{\text{a}} was ~2, which Table 4. Effects of pulmonary artery constriction on right ventricular-arterial coupling

<table>
<thead>
<tr>
<th>Flow, l/min</th>
<th>Before Adrenergic Blockade</th>
<th>After Adrenergic Blockade</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Hypoxia</td>
</tr>
<tr>
<td>3.4 ± 0.3</td>
<td>2.8 ± 0.3</td>
<td>2.3 ± 0.2</td>
</tr>
<tr>
<td>98 ± 12</td>
<td>116 ± 11*</td>
<td>91 ± 8</td>
</tr>
<tr>
<td>88 ± 7</td>
<td>76 ± 9</td>
<td>70 ± 9</td>
</tr>
<tr>
<td>18 ± 2</td>
<td>29 ± 3*</td>
<td>17 ± 2</td>
</tr>
<tr>
<td>0.11 ± 0.12</td>
<td>0.23 ± 0.50*</td>
<td>0.13 ± 0.16</td>
</tr>
</tbody>
</table>

*Values are means ± SE; n = 8. P < 0.05 vs. baseline.
is remarkably similar to the values reported for left ventricular-aortic coupling (6, 15). According to Burkhoff et al. (5), $E_{es}/E_a$ values of 2 are associated with a maximal ratio between mechanical work production and myocardial oxygen consumption. Our results thus confirm that the RV is optimally matched to its afterload in the normal state. They also confirm that intrinsic mechanical properties of the right and left ventricles are similar, and that the apparent differences result from the much lower RV afterload (5, 8). Dobutamine increased $E_{es}$ and $E_{es}/E_a$, whereas propranolol decreased $E_{es}/E_a$. The absence of effect of propranolol on $E_{es}$ indicates a low sympathetic tone, probably resulting from the anesthesia, normal blood volume and normal aortic pressure (in view of the decrease in $E_{es}/E_a$, the absence of changes in $E_{es}$ and $E_a$ could also result from a type 2 error due to a large individual variability). We conclude that our method adequately detects dobutamine-induced inotropic changes, and thus can be used to assess RV contractility.

Preload and afterload changes. Venous return reduction increased $E_a$, due to the increase in pulmonary vascular resistance and impedance (4). $E_{es}$ remained unaffected, due to variable individual effects of adrenergic stimulation. Accordingly, adrenergic blockade inhibited all effects of venous return on $E_{es}$ and $E_{es}/E_a$. Active (hypoxic) vasoconstriction and passive (mechanical) arterial constriction increased $E_a$. They also increased $E_{es}$, possibly due to adrenergic stimulation. However, both of them still increased $E_{es}$ after adrenergic blockade. Such an adrenergic-unrelated $E_{es}$ response to increased afterload is quite consistent with homeometric autoregulation or Anrep effect (22). Recent studies (10, 19) reported RV homeometric autoregulation in animals with increased afterload due to respiratory distress syndrome or to pulmonary arterial occlusion. The Anrep effect is mediated by changes in intracellular calcium sensitivity and concentration and is unaffected by propranolol but inhibited by verapamil (29, 32). We therefore tried to prevent the $E_{es}$ response by verapamil, but additional verapamil depressed contractility so much that pulmonary arterial constriction resulted in rapid death. Contractility-unrelated effects of afterload on $E_{es}$ therefore cannot be completely excluded, but our results are entirely consistent with the assumption that single-beat-derived $E_{es}$ is a load-independent index of RV contractility in clinically relevant ranges of preload and afterload.

Perspectives. To our knowledge, the present method is the first permitting assessment of RV contractility and RV arterial coupling without measuring RV volume or modifying preload or afterload. We used actual RV end-diastolic volume in our calculations, but any arbitrary value can be used without affecting $E_{es}$ or $E_a$ (see Fig. 3). Pulmonary arterial velocity and flow can be obtained by noninvasive Doppler and magnetic resonance techniques. The present method is thus already applicable to patients during right heart catheterization. When Doppler techniques will be able to generate RV pressure signals of sufficient quality, as they do for the left ventricle, the present method will be applicable to patients in a completely noninvasive way.

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