Ventricular stroke work and efficiency both remain nearly optimal despite altered vascular loading

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De Tombe, Pieter P., Steven Jones, Daniel Burkhoff, William C. Hunter, and David A. Kass. Ventricular stroke work and efficiency both remain nearly optimal despite altered vascular loading. Am. J. Physiol. 264 (Heart Circ. Physiol. 33): H1817–H1824, 1993.—Recent clinical and animal studies have suggested that ventricular-vascular coupling normally operates at either optimal ventricular efficiency (EFF = stroke work/myocardial oxygen consumption) or stroke work (SW) and that efficiency in particular is compromised by cardiac dysfunction. These distinctions between coupling states at maximal work vs. efficiency are largely based on theoretical models. To date, there are few direct experimental data defining optimal conditions for each parameter, respectively, in the same heart or tests of whether changes from these conditions must produce significant declines in both parameters. Therefore, 10 isolated blood-perfused canine hearts were studied at varying contractilities, with the heart ejecting into a simulated three-element Windkessel model of arterial impedance. For a given isotropic state [indexed by the slope of the end-systolic pressure-volume relationship (Esv)], myocardial oxygen consumption and SW were measured over a broad range of afterload resistances. The latter was indexed by the effective arterial elastance (Ea) and ventricular-vascular interaction expressed by the ratio of Eo to Eo (Eo/Eo). On average, maximal SW occurred at Eo/Eo = 0.80 ± 0.16, whereas EFF was maximal at Eo/Eo = 0.70 ± 0.15 (P < 0.01). However, these differences were small, and both SW and EFF were ≥90% of their respective optima over a broad overlapping range of Eo to Eo ratios (0.3–1.3), corresponds with ejection fractions ranging from ~40 to ~80%). These data show that both SW and efficiency are nearly maximal under many conditions of ventricular-vascular interaction. This suggests that precise optimization of either parameter is unlikely to be a major target of cardiovascular homeostasis under many circumstances.

EXPERIMENTAL AND THEORETICAL analyses of left ventricular coupling with the arterial vascular system have yielded several hypotheses regarding the primary factors that control this interaction (3, 6). It is generally accepted that vascular properties and hemodynamic requirements are dictated by organism size and that ventricular size and strength adjust to provide the required systemic blood flow and pressure in an optimal manner (6). Theories differ with regard to what is believed to be optimized. Studies in isolated and intact animal hearts suggest that vascular and ventricular properties are matched to achieve maximal transfer of mechanical energy (6, 12, 25–27) (i.e., power or stroke work). Alternatively, theoretical analysis as well as data from conscious animals and humans suggest that ventricular metabolic efficiency, defined as the ratio of stroke work to myocardial oxygen consumption per beat, may be optimized under normal conditions (1, 3, 9, 14, 18).

These distinctions may have clinical relevance (1, 9, 19). Studies have suggested that cardiac efficiency is compromised in human congestive heart failure in favor of maximal external work, whereas the opposite appears the case in normal hearts (1, 19). Therapeutic interventions such as vasodilator therapy can thus be viewed with respect to their capacity to improve efficiency (9, 14, 15). This notion is appealing, particularly if energy delivery to the heart is compromised. Unfortunately, although conditions for maximal stroke work or power have been extensively studied (6, 12, 14, 25–28), simultaneous metabolic data are scant (5, 20, 28). The data that exist do not clearly define conditions for which efficiency is maximal, or even whether there is an optimum (20). Thus prior interpretations of clinical ventricular-vascular data have primarily been based on model predictions rather than measured data.

For the distinction between coupling states at maximal work vs. efficiency to be meaningful, optimal conditions must be reasonably different, and any change from these conditions should produce a significant decline in one or the other parameter. The present study directly tested these features by simultaneously measuring mechanical and energetic data in isolated blood-perfused canine left ventricles contracting against a computer-simulated vascular load. Although the results confirm that each parameter is optimal at different conditions of ventricular-vascular interaction, this difference is found to be quite small. Furthermore, both parameters remain near maximal over a broad overlapping range of interaction.

METHODS

Surgical preparation. Ten isolated canine ventricles were studied. The procedures used to isolate and support the canine heart have been previously described in detail (17, 22). Briefly, two mongrel dogs (25–35 kg) anesthetized with pentobarbital sodium (30 mg/kg) were used for each experiment. The support dog was premedicated with hydrocortisone (500 mg im), diphenhydramine (50 mg), indomethacin (25 mg pr), and heparin (5,000 IU). The femoral arteries and veins of the support dog were cannulated to provide perfusion of oxygenated blood to a heart isolated from a second (donor) dog. The chest of the donor dog was opened under artificial ventilation. The subclavian artery and right atrium were cannulated and connected to the perfusion system. The heart was then isolated under continuous blood perfusion, with temperature controlled at 37°C. The left ventricle (LV) was vented, the left atrium opened, and all chordae tendineae were cut. A ring adapter was sewn into the mitral annulus, and a thin latex balloon connected to a volume control system was placed within the LV chamber. Left ventricular pressure was measured inside the balloon by a microtransducer (PC-880, Millar, Houston, TX). A bipolar surface...
Coronary perfusion pressure was measured via a catheter placed through the brachiocephalic trunk into the aortic root. Two perfusion pumps (model 1215, Harvard Apparatus, South Natick, MA) maintained mean coronary perfusion pressure at 80 mmHg (2). The first pump withdrew arterial blood from the support dog at a constant rate while the second pump diverted blood flow so as to bypass the isolated heart. This arrangement maintained a fixed hemodynamic demand on the support dog, independent of coronary flow to the isolated heart, which helped stabilize the preparation. The support dog was also mechanically ventilated, and blood pH, PO₂, and PCO₂ were maintained in the normal range by adjustment of ventilation rate. The support dog was administered sodium bicarbonate and O₂ as required.

The right ventricle and atrium of the isolated heart were drained via a wide-bore cannula with side holes. The right heart was made airtight by purse string suture around the cannula at the right ventricle apex and ligation of superior and inferior vena cavae. Total coronary blood flow (excluding a small independent of coronary flow to the isolated heart, which helped stabilize the preparation. The support dog was also mechanically ventilated, and blood pH, PO₂, and PCO₂ were maintained in the normal range by adjustment of ventilation rate. The support dog was administered sodium bicarbonate and O₂ as required.

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Ventricular systolic properties were indexed by the slope of the end-systolic pressure-volume relationship (17, 22) (Eₔ). Vascular loading was indexed by the effective arterial elastance (Eₐ), peripheral arterial resistance (Rₚ), and arterial compliance (Cₚ). Vascular filling during diastole was accomplished by a simple computer-simulated circuit, consisting of a pressure source and resistance. The design and implementation details of this servo system have been previously reported, and the reader is directed to these studies for a full description (17, 23, 24).

Experimental protocol. After the preparation was completed, each heart was provided 20 min for stabilization. The primary aim was to assess sensitivities of ventricular efficiency and stroke work (SW) to changes in ventricular and arterial properties. This was achieved by varying the simulated arterial resistance over a broad range at constant left ventricular “contractility,” heart rate, and end-diastolic volume (EDV). Ventricular systolic properties were indexed by the slope of the end-systolic pressure-volume relationship (17, 22) (Eₔ). Vascular loading was indexed by the effective arterial elastance (Eₐ) (24, 25). Eₐ is approximately equal to the total mean arterial resistance divided by cardiac cycle length (24, 25). These two parameters were used to determine a ventricular to vascular coupling ratio (Eₐ/Eₔ), as previously described by Sunagawa and colleagues (25). To guarantee that a sufficient range of coupling ratios was assessed in each heart, Eₐ was first estimated (from isovolumic beats at varying volumes), and using known cycle length, eight or more Eₐ values were predetermined that would yield Eₐ-to-Eₔ ratios approximately between 0.5 and 8.0. These Eₐ values were then randomly selected and entered into the computer vascular loading model. Rₚ was held constant (0.2 mmHg·ml⁻¹·s), and Cₚ was adjusted so that the diastolic decay time constant (Rₚ·Cₚ) was fixed at 1.3 s. This latter step ensured that the pressure-volume loops had fairly well-defined diastolic and systolic corners at each of the selected afterloads. Two to three minutes of equilibration were provided between each randomly selected Eₐ value. In summary, for each experimental run, data were measured at the preselected afterload conditions with constant heart rate and EDV (Fig. 1). At each load, left ventricular pressure and volume, coronary perfusion pressure and flow, myocardial arteriovenous oxygen difference (AVO₂), and surface electrocardiogram were recorded. After a complete loading sequence was obtained, cardiac conditions were changed either by switching to a smaller or larger EDV (~50% change) or inotropic state (intracoronary infusion of dobutamine at 1–5 μg/min or CaCl₂ at 1–5 mmol/min). After a new steady-state condition was achieved, the protocol was repeated. In this manner, a total of 31 separate variable afterload runs were obtained from the 10 hearts. Data sufficient to define optimal coupling for both SW and efficiency were obtained in 26 (80%) of the afterload runs. Failure in the remaining five was due to inadequate data collection at low coupling ranges (<0.5) stemming from limitations in volume servo system at low afterload resistances (requiring large volume displacements), particularly in hearts with rapid heart rates and low Eₐ. These data could not be used to analyze for differences in the coupling ratio at optimal work vs. efficiency but were examined.

Data signals were digitized at 200 Hz and stored on diskettes for off-line analysis. At the end of the experiment the weights of the right ventricular free wall and the LV (including the septum) were measured.

Data analysis. The principal relations were those between SW or efficiency and the coupling ratio Eₐ to Eₔ. The Eₐ values used to determine this ratio for each loading condition were derived from each respective set of ejecting beats at varying afterload (i.e., Fig. 1). The end-systolic pressure-volume relationship was defined by the locus of points of the ratio maximal pressure to volume – Vₘₚ, with volume axis intercept (Vᵢₚ) determined with use of an iterative technique (17). Data were fit by linear regression with slope Eₐ. This approach assumes that afterload change in and of itself does not alter Eₐ. This is a simplification, since we recently demonstrated that afterload can modestly alter Eₐ (2). The potential impact of this simplification on the data is discussed later.

Eₐ was calculated for each pressure-volume loop as the ratio of end-systolic pressure (Pₛₑₐₜ) to stroke volume (SV = Vₘₚ – Vᵢₚ, where Vₘₚ and Vᵢₚ are maximum and minimum volume, respectively). SW was the numerically integrated area within each loop. Total mechanical work was measured by the pressure-volume area (PVA) as described by Suga et al. (11, 21). PVA was calculated by determining the area bounded by the

![Fig. 1. Example of experimental protocol. Left ventricular pressure is plotted as function of instantaneous left ventricle volume. Volumes were made to "eject" against different levels of computer-simulated arterial afterload resistance (10 levels in this example). End-systolic pressure-volume coordinates are indicated by solid circles and fit to equation: \( P_{es} = E_{es}(V_{es} - V_0) \) (dashed line), where \( P_{es} \) is end-systolic pressure, \( E_{es} \) is end-systolic elastance and equals 4.05 mmHg/ml and \( V_0 \) is volume axis intercept and equals -0.2 ml; \( r = 0.991). For each beat, area within pressure-volume loop [stroke work (SW)], myocardial oxygen consumption (MVO₂), and arterial load were determined.\]
end-systolic pressure-volume relationship and diastolic pressure-volume relationship and the systolic trajectory of the pressure-volume loop. All steady-state mechanical and energetic parameters were derived from an average of 4–6 sequential cardiac cycles.

Per beat total \( \text{MVO}_2 \) was obtained by dividing \( \text{MVO}_2 \) measured at each afterload by heart rate. LV \( \text{MVO}_2 \) was equal to total heart \( \text{MVO}_2 \) minus the \( \text{O}_2 \) consumption of the unloaded right ventricle. The latter was estimated by multiplying the unloaded \( \text{MVO}_2 \) of the whole heart by the ratio of right ventricle to total heart mass. Myocardial efficiency was defined as the ratio of SW to \( \text{Mire} \), measured at each afterload. LV \( \text{M}_{\text{a}} \) was equal to total heart \( \text{M}_{\text{ire}} \) minus the \( \text{O}_2 \) consumption of the unloaded right ventricle. The latter was estimated by multiplying the unloaded \( \text{M}_{\text{ire}} \) of the whole heart by the ratio of right ventricle to total heart mass. Myocardial efficiency was defined as the ratio of SW to \( \text{Mire} \), with both measures first converted into joules per beat (1 ml \( \text{O}_2 = 20 \text{ J} \); 1 mmHg/ml = 1.334 \times 10^{-3} \text{ J} ). The result was expressed as a percent.

Statistical analysis. To determine the \( E_a \)-to-\( E_{es} \) ratio at maximal SW and efficiency (SW/\( \text{MVO}_2 \)), data from each experimental run were fit by nonlinear regression to a Gaussian function of the form: \( \text{SW (or SW/\text{MVO}_2)} = k \cdot e^{-(\text{ln}(E_a/E_{es})^2)/\sigma^2} \), where \( \mu = \text{ln}(E_a/E_{es}) \) at the point of maximal SW or efficiency (\( \mu \) and \( \sigma \) are constants). Although this choice of fit was somewhat arbitrary, it both characterized the data well and provided a simple and direct method to estimate the optimal point. The adequacy of the nonlinear fit was indicated by the 1 - RSS-to-CSS ratio, where RSS and CSS are the residual and corrected total sum of squares, respectively. The mean value of this ratio was 0.91 ± 0.096. Comparisons of \( \mu \) values derived from the Gaussian fits were made by paired t testing (13). The pooled data were also fit to a Gaussian function. Statistical analyses, including linear and nonlinear regressions, were performed using commercial software (SYSTAT, Evanston, IL). Data are presented as means ± SD. Where appropriate, paired or unpaired Student’s t test was used for comparisons, with significance accepted at the \( P < 0.05 \) level.

RESULTS

Figure 2 displays an example of SW and metabolic efficiency (SW/\( \text{MVO}_2 \)) vs. \( R_a \) (Fig. 2, left) and the same variables vs. coupling ratio (\( E_a/E_{es} \); Fig. 2, right) for a typical heart. The corresponding bottom panels display the same data on a semilogarithmic scale, with each variable normalized to its optimal value. Plots as functions of \( R_a \) are shown, since this was the principal independent variable. Characterization of this change by the \( E_a \)-to-\( E_{es} \) ratio enabled adjustment for between run and interheart variations in contractile state, thus facilitating group data analysis. As shown in Fig. 2, the two representations yielded virtually identical qualitative results. Both SW and efficiency demonstrated clear optima at coupling ratios slightly below 1.0 (resistance of 1.2 mmHg/ml or 1,600 dyn s cm⁻⁵). Maximal metabolic efficiency was 8.5% in this example, typical of the data overall (9.4 ± 5.6%). The semilogarithmic plots more clearly demonstrate the broad range of coupling ratios (and resistances) over which both variables are optimal. The curves in these lower plots are the Gaussian fits to the data.

Table I provides data for a typical data run for each heart. Absolute values for SW, efficiency, calculated mean arterial pressure, and \( \text{MVO}_2 \) at optimal work are given, along with ranges for these and other parameters obtained by varying resistance. \( E_{es} \) values span a somewhat broader and higher range than typical of isolated hearts, reflecting inotropic support provided by intracoronary infusion of CaCl₂ or dobutamine (see METHODS).
Table 1. Values for hemodynamic parameters measured at low and high resistances and at maximal stroke work, and peak efficiency obtained in a representative data run for each heart

<table>
<thead>
<tr>
<th>Dog</th>
<th>HR, min⁻¹</th>
<th>Ees/100 g, mmHg/ml-100 g⁻¹</th>
<th>Range of Resistance and Hemodynamic Parameters*</th>
<th>Measured at Maximal Stroke Work</th>
<th>Peak Efficiency, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Resistance, mmHg/ml⁻¹·s</td>
<td>SV, ml</td>
<td>SW, mmHg/ml</td>
</tr>
<tr>
<td>1</td>
<td>150</td>
<td>5.3</td>
<td>0.67–14.0</td>
<td>20.4–3.7</td>
<td>1,860–519</td>
</tr>
<tr>
<td>2</td>
<td>167</td>
<td>9.4</td>
<td>0.41–5.4</td>
<td>25.5–9.2</td>
<td>2,207–1,350</td>
</tr>
<tr>
<td>3</td>
<td>128</td>
<td>5.0</td>
<td>0.34–11.7</td>
<td>32.6–5.1</td>
<td>2,217–569</td>
</tr>
<tr>
<td>4</td>
<td>133</td>
<td>6.1</td>
<td>0.33–11.2</td>
<td>27.4–4.7</td>
<td>1,534–471</td>
</tr>
<tr>
<td>5</td>
<td>90</td>
<td>7.0</td>
<td>0.77–11.9</td>
<td>29.7–8.3</td>
<td>2,536–1,232</td>
</tr>
<tr>
<td>6</td>
<td>136</td>
<td>14.7</td>
<td>0.18–16.5</td>
<td>12.4–3.0</td>
<td>899–337</td>
</tr>
<tr>
<td>7</td>
<td>150</td>
<td>11.0</td>
<td>0.44–5.6</td>
<td>90.4–8.5</td>
<td>1,592–584</td>
</tr>
<tr>
<td>8</td>
<td>100</td>
<td>3.9</td>
<td>0.53–19.0</td>
<td>20.0–2.7</td>
<td>1,264–195</td>
</tr>
<tr>
<td>9</td>
<td>90</td>
<td>6.9</td>
<td>0.44–23.6</td>
<td>26.8–3.1</td>
<td>1,421–321</td>
</tr>
<tr>
<td>10</td>
<td>150</td>
<td>14.8</td>
<td>0.26–3.7</td>
<td>29.1–4.7</td>
<td>2,163–1,729</td>
</tr>
</tbody>
</table>

Mean 129.4 8.4 0.437± 12.3± 24.9± 5.3± 1,749.7± 70.7± 24.2± 122.8± 0.1282± 0.1520± 63.1 0.1526 9.4
±SD ±27.3 ±3.9 ±0.18 ±6.3 ±5.8 ±2.5 ±482 ±516 ±5.6 ±19.3 ±0.041 ±0.044 ±146 ±0.629 ±5.6

HR, heart rate; Ees, end-systolic elastance; SV, stroke volume; SW, stroke work; mABP, mean arterial blood pressure; MVO₂, myocardial oxygen consumption. The broad range of Ees reflects the use of intracoronary inotropic support. * Minimum and maximum resistances are provided along with corresponding SV, SW, mABP, and MVO₂ values measured at these resistances. † Mean ± SD of low parameters; ‡ mean ± SD of high parameters.

In most cases, these values were not that dissimilar from what is observed in more intact preparations.

Gaussian relations were fit to the data obtained from each afterload run (n = 26) to determine coupling ratios at optimal SW vs. efficiency. There was a small but significant difference between the loading conditions (coupling ratio) at each optimum, with maximal SW/MVO₂ occurring at a lower afterload resistance relative to Ees (Eₐ-to-Ees ratio = 0.696 ± 0.15) than SW (0.80 ± 0.16, P < 0.0001). Figure 3 displays the Eₐ to Ees ratio at peak SW vs. peak efficiency for each data run. Whereas most data points fell above the identity line (greater coupling ratio at maximal SW), this difference was frequently very small.

Pooled data with mean Gaussian fits are displayed in Fig. 4. Each run was normalized to its optimal value (defined by nonlinear fit). As was true for individual runs, pooled data also yielded a significantly larger coupling ratio of 0.77 (95% confidence interval: 0.73–0.81) for maximal SW vs. 0.685 (0.65–0.72) for maximal SW/MVO₂ (P < 0.05). Although maximal SW and efficiency occurred at slightly different afterloads, there was considerable overlap. This is more directly depicted by averaged relations determined from the group data (Fig. 5). Portions of each relation that fall at or above the dotted line in Fig. 5 delineate the range of coupling ratios at which both work and efficiency were ≥90% of optimal. This range was broad, spanning an Eₐ-to-Ees ratio of...
0.3–1.3 and includes values that have been reported both for normal human hearts (near 0.6) (1, 9, 19) and conscious dogs (near 1.0) (12), as well as in acute cardiac depression and human cardiomyopathy (near 1.3) (1, 9). This coupling range translates into an ejection fraction range from ~40 to 80%.

**Impact of Ees and EDV.** The 26 individual relations relating SW or SW/MVo₂ to Ees/Ees ratio were obtained in hearts at varying preload volumes, heart rates, and contractilities, as summarized in Table 2. Prior theory and experimental data from the isolated heart has shown that neither EDV, Ees, nor heart rate alters the coupling ratio at maximal SW (3, 25). However, analogous data for efficiency do not exist, although theory predicts an influence (3, 10). Therefore, we assessed these dependencies in the present data using the following multiple linear regression model: Ees/Ees ratio = b₀ + b₁ × EDV + b₂ × Ees + b₃ × HR, where HR is heart rate. Results are provided in Table 3. This analysis confirmed the lack of sensitivity of coupling ratio at maximal SW to EDV, HR, or Ees. However, for efficiency, there was a significant negative dependence on Ees. Thus the Ees/Ees ratio at maximal efficiency was lowest at high contractilities and increased (getting closer to that for optimal SW) at reduced contractility.

**DISCUSSION**

The interaction between the heart and the vascular loading system determines the external work and metabolic efficiency with which the heart performs that work. Prior theoretical and some experimental data suggested that work and efficiency could not both be maximized under a given set of conditions. Extension of these concepts to intact human subjects has led to the notion that precisely which parameter is maximal may have both clinical and therapeutic significance (1, 9, 15, 19). The present data appear to weaken this notion. Although work and efficiency are indeed optimized at slightly different afterload resistances (work peaking at a slightly higher resistance than SW/MVo₂), this difference is generally small. Furthermore, the sensitivity of both parameters to changes in resistance is sufficiently low that both parameters can exceed 90% of their respective maximal values over a broad loading range. Thus, under physiological and even some pathophysiological states, both parameters remain near optimal.

**Ventricular efficiency optimization.** To our knowledge this is the first study in which an optimum for metabolic efficiency (SW/MVo₂), as function of Rₐ, has been measured. Early studies of loading effects on cardiac efficiency were performed by Sarnoff and co-workers (18), although the artificial loading methods used made this data difficult to interpret. A more recent study was reported by Elzinga and Westerhof (5) in isolated cat hearts, in which ventricular and arterial properties were defined by mean pressure-flow relations. Elzinga and Westerhof (5) found that work and efficiency were optimized at different mean flows. However, the lower Rₐ range was limited in this study, since arterial and coronary perfusion pressure were dependent on the pumping action of the left heart. Consequently, MVo₂ data were not obtained at sufficiently high flows to define the optimal point of metabolic efficiency in most of the hearts. This was not a problem in the present study, since coronary perfusion was independently controlled. Furthermore, by maintaining heart rate in a more physiological range in many hearts, we were able to reduce arterial impedance sufficiently for more direct determination of conditions at optimal efficiency in nearly 80% of the experiments.

Prior experiments have shown (26), and theory predicts (3), that the ventricular-arterial coupling conditions (Ees/Ees rates) at maximal SW are independent of EDV or contractile state (Ees). This was found in the present

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Coefficient</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>SW</td>
<td>0.802±0.208</td>
<td>0.001*</td>
</tr>
<tr>
<td>EDV</td>
<td>−0.002±0.004</td>
<td>0.657</td>
</tr>
<tr>
<td>Ees</td>
<td>−0.000±0.008</td>
<td>0.280</td>
</tr>
<tr>
<td>HR</td>
<td>0.001±0.001</td>
<td>0.436</td>
</tr>
<tr>
<td>Efficiency (SW/MVo₂)</td>
<td>0.095±0.150</td>
<td>0.001*</td>
</tr>
<tr>
<td>EDV</td>
<td>−0.010±0.004</td>
<td>0.380</td>
</tr>
<tr>
<td>Ees</td>
<td>−0.018±0.007</td>
<td>0.012*</td>
</tr>
<tr>
<td>HR</td>
<td>0.000±0.001</td>
<td>0.802</td>
</tr>
</tbody>
</table>

SW/MVo₂ ratio of SW to MVo₂, Ees, arterial elastance. Data were fit by multiple linear regression to Ees/Ees ratio at maximal SW (or SW/MVo₂) = b₀ + b₁ × EDV + b₂ × Ees + b₃ × HR to test for the influence of EDV (b₁), Ees (b₂), and HR (b₃) on the Ees/Ees coupling ratio at optimal SW or SW/MVo₂ (b₀ is a constant). * P < 0.05 by multiple linear regression.

**Table 3. Multiple regression analysis of effect of EDV, Ees and HR on the Ees-to-Ees ratio at maximal SW and efficiency**

**Table 2. Range of cardiac size and systolic function**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ees, mmHg·ml·100 g⁻¹</td>
<td>8.69±4.45</td>
<td>3.46–24.9</td>
</tr>
<tr>
<td>EDV, ml</td>
<td>25.7±18.9</td>
<td>7.9–41.1</td>
</tr>
<tr>
<td>HR, min⁻¹</td>
<td>136.5±97.3</td>
<td>85–167</td>
</tr>
<tr>
<td>MassLV, g</td>
<td>143.8±20.4</td>
<td>112–172</td>
</tr>
<tr>
<td>MassLV, g</td>
<td>54.5±3.0</td>
<td>42–72.3</td>
</tr>
</tbody>
</table>

EDV, end-diastolic volume; MassLV, MassLV, mass of left ventricle and right ventricle, respectively.
study as well. Similar analysis also predicts the opposite to be the case for coupling at peak ventricular efficiency (3, 10). The present data are the first to confirm this experimentally, showing a significant negative correlation between the $E_a$-to-$E_v$ ratio at peak efficiency and contractile state ($E_v$). This indicates that as the contractile state of the heart is decreased, the coupling ratio at optimal SW and efficiency converge, consistent with the model prediction (10). This runs counter to the notion that an increase in $E_a$-to-$E_v$ ratio with heart failure necessarily indicates that the heart is working further away from optimal efficiency in favor of external work, as suggested by recent studies (1, 9, 19). Rather, this observation raises the possibility that both normal and moderately diseased ventricular-arterial coupling may occur without critically compromising either cardiac work or efficiency.

Myocardial efficiency is often defined in several ways (11, 15, 21). This study focused on a common definition that varies with afterload resistance, namely the $MVO_2$ cost of delivering SW. This is not to imply that metabolic efficiency of cardiac chemomechanical energy conversion is similarly variable. Rather a variable amount of the mechanical energy generated by the ventricle is liberated to perform external work, whereas the remaining mechanical “potential” energy is presumably dissipated as heat (11, 21). This explains the relatively low efficiencies as given in Table 1. The sum of both internal potential energy and SW work yields PVA, which is linearly related to $MVO_2$ (11, 17, 21). The inverse slope of this relation is cardiac chemomechanical conversion efficiency and is relatively insensitive to arterial load. In the present study, this efficiency averaged 27.1 ± 12.4%, similar to prior data from our laboratory (2).

Yet another form of efficiency, called work efficiency, relates external work to total potential external work (i.e., PVA) (7, 12, 15, 19). This has become popular, particularly in clinical studies, due to the relative ease of measuring PVA as opposed to $MVO_2$ in vivo. Unlike SW/$MVO_2$, which is optimized at a physiological resistance, the SW-to-PVA ratio increases monotonically with declining afterload and is maximal at zero load. Thus, this ratio is never “optimized” except at a non-physiological load. This is demonstrated in Fig 6, which compares the two efficiency ratios as functions of the $E_a$-to-$E_v$ ratio, both derived from the present data. The SW-to-PVA ratio yields a lower coupling ratio for “maximal” efficiency than that obtained from SW/$MVO_2$. This likely contributed to greater apparent disparities in loading conditions for maximal SW vs. SW/$PVA$ (9, 12, 19) compared with what we report for SW vs. SW/$MVO_2$. In absolute terms, the SW/PVA is also much greater than SW/$MVO_2$ (averaging 76.0 ± 6.7% in the present study) because it ignores the $MVO_2$ costs of excitation-contraction coupling and basal metabolism. For all these reasons, we do not believe it is a particularly useful efficiency expression.

Comparison with prior data. The coupling ratio at optimal SW reported in the present study is somewhat lower than previously reported by Sunagawa et al. (25), although similar to that observed in conscious animals...
afterloads, \( P_{es} = SW/SV \) underestimates true \( P_{es} \), whereas as resistance is reduced (declining \( P_{es} \)), the opposite is observed.

Several reports have suggested that the in situ heart and arterial system operate in a manner such that SW generation by the heart is maximal (6, 12, 14, 25–27). For example, in a recent study in the conscious chronically instrumented dog, Little and Cheng (12) found that the in vivo heart operates close to the point of maximal SW. This result is consistent with studies in anesthetized animals (4, 14, 26, 27). On the other hand, Piene and Sund (4) found in the cat right ventricle that metabolic efficiency and not SW appeared maximized. This observation is consistent with our previous theoretical predictions (3) and the recent observations by Sasayama et al. (1, 9, 19), who found \( E_{a} \)-to-\( E_{es} \) ratio of close to 0.5 in human subjects. These and other recent reports might be interpreted to indicate that metabolic efficiency, rather than SW, is optimized in intact circulations. The present data provides an important perspective to the investigative search for what is or is not optimized under different conditions. Work and efficiency are both nearly maximal over a broad loading range, spanning physiological and pathophysiological values. Hence, we conclude that precise optimization of either parameter is likely of little consequence in the normal or moderately abnormal circulation. Instead, homeostasis in the intact system more likely centers on control of blood pressure, circulating volume, and oxygenation and can ignore ventricular SW or efficiency, since both should remain near maximal under many conditions. This built-in “safety net” is likely compromised only in severe ventricular or vascular disorders.

Experimental design. We recognize that one must be quite cautious when extrapolating isolated heart results to more intact or human data. However, it is nearly impossible to adequately measure the necessary variables without the controls afforded by the isolated-heart preparation. There are several specific aspects of the isolated-heart preparation that should be considered.

Coronary perfusion pressure was held constant, whereas in the intact circulation, this pressure would vary with ventricular-arterial interaction. This might reduce work at the lowest afterloads due to a fall in coronary perfusion pressure, making optimization curves appear less shallow. The contractile state of the isolated heart is often less than observed in situ. Because the optimum afterload resistance for metabolic efficiency (SW/M\( V_{O2} \)) was affected directly by contractile state (Table 2), whereas this was not true for SW, the disparity between optimum afterload resistance for SW or SW/M\( V_{O2} \) in the intact circulation might be larger than appreciated from the current data. However, we expressly provided inotropic support in many of the runs so that the mean \( E_{es} \) was \(-9.0 \text{ mmHg/ml, well within the range reported in conscious dogs (12).} \) Lastly, the computer-simulated arterial impedance is a simplified model and does not encompass the full impedance characteristics of the natural arterial system. The framework of elastance matching assumes that \( E_{es} \) is load independent. However, recent results from this laboratory in the isolated blood-perfused canine heart (2), and others in the in situ heart (7, 8), indicate that ejection can yield an \( E_{es} \) that exceeds that predicted by a load-independent \( E_{es} \). Specifically, we recently reported that reducing \( E_{a} \) in the isolated heart can result in an increase in \( E_{es} \). Applying this to the present study would mean that as \( E_{a} \) is lowered, \( E_{es} \) might increase slightly, making the \( E_{a} \)-to-\( E_{es} \) ratio even lower than that calculated, assuming a fixed \( E_{es} \). The opposite would hold for an increase in \( E_{a} \). The effect would be to broaden the \( E_{a} \)-to-\( E_{es} \) vs. SW (or efficiency) relations even further. If anything, assuming a fixed \( E_{es} \) underplays the flat nature of these relations.

In conclusion, our study confirms that both SW and SW/M\( V_{O2} \) efficiency are optimal at a specific, but slightly different, ventricular-vascular coupling conditions. However, this difference is small, and the relations between SW or SW/M\( V_{O2} \) and coupling ratio are broad with considerable overlap. It would seem therefore unlikely that optimization of either parameter plays a major role in normal control of the circulation or ventricular-vascular coupling. Stated another way, homeostatic mechanisms can essentially ignore the heart without actively compromising its efficiency or external work.

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