Mechanical Matching of the Left Ventricle With the Arterial System in Exercising Dogs

Kiyoshi Hayashida, Kenji Sunagawa, Mitsu ru Noma, Masaru Sugimachi, Hiroshi And o, and Motoomi Nakamura

We investigated how changes in ventricular contractility and arterial properties associated with exercise influence the energy transmission from the left ventricle to the arterial system. On six chronically instrumented dogs preconditioned to run on a treadmill, we imposed exercise loads of various degrees by altering the speed and slope of the treadmill (up to 7 km/hr and 20% slope). We evaluated ventricular contractility by end-systolic elastance (Ees) and arterial properties in terms of the effective arterial elastance (Ea). Ea was estimated by the ratio of mean aortic pressure to stroke volume. With exercise, Ees significantly increased from 7.6±1.7 to 10.9±2.6 mm Hg/ml (p <0.005), and Ea tended to increase from 4.9±1.4 to 6.7±1.8 mm Hg/ml (p =0.068), whereas the ratio of Ees to Ea remained fairly constant (from 0.69±0.26 to 0.63±0.21, NS). The mechanical optimality index, defined as the ratio of stroke work to its theoretically derived maximal value, was 0.93±0.07 at rest and 0.92±0.08 at peak exercise. Similarly, the metabolic optimality index, defined as the ratio of cardiac oxygen consumption to stroke work conversion efficiency and its theoretical maximal value, was 0.98±0.02 at rest and 0.99±0.01 at peak exercise (NS).

We conclude that external work of the left ventricle of these dogs was at a near maximal level for a given preload during exercise as well as at rest without compromising the conversion efficiency of metabolic energy to stroke work. (Circulation Research 1992;71:481–489)

KEY WORDS  • ventricular arterial matching  • end-systolic elastance  • effective arterial elastance

The cardiovascular system is designed to provide adequate blood flow to peripheral tissues and thus support the normal function of these tissues. Since adequate cardiac output for peripheral perfusion can be achieved by multiple combinations of ventricular contractility and loading conditions, it is likely that the cardiovascular control system chooses a unique combination of ventricular contractility, heart rate, and arterial properties according to some optimization criteria. The fact that the myocardium uses a large amount of metabolic energy throughout normal life suggests that the optimum coupling of the ventricle with the arterial system may be achieved on the basis of energy conversion and transmission efficiency of ventricular ejection. Indeed, stroke power output of the normal excised feline left or right ventricle was found to be maximum when the ventricle was loaded with normal arterial impedance.1–3 Also, in the open-chest cat, the stroke power output of the left ventricle was found to be maximum at normal arterial impedance.4–6 In the canine left heart, external work was expected to be nearly maximal under normal loading conditions,7,8 as was indeed the case.9–12 Although all these studies have indicated that the external work or mechanical efficiency is well optimized in anesthetized as well as conscious animals, it is not known whether the maximization principle of external work holds in conscious animals under exercise stress, when the metabolic demand of myocardium is greatly increased.

The purpose of this investigation, therefore, was to evaluate the effect of exercise on mechanical energy transmission from the left ventricle to the arterial load. We used chronically instrumented dogs preconditioned to run on a treadmill and demonstrated that the external work of the ventricle was fairly well maximized during exercise as well as at rest.

Materials and Methods

Surgical Preparation

We used six adult mongrel dogs (18±3 kg) preconditioned to run voluntarily on a treadmill. The dogs were anesthetized with sodium pentobarbital (30 mg/kg i.v.), intubated, and artificially ventilated with room air through a volume-cycled respirator (model SN-480-4, Shinano, Tokyo). The chest was opened at the fourth left intercostal space under sterile conditions. After a pericardiotomy, the heart was suspended in a pericardial cradle. A high-fidelity pressure transducer (model P-7, Konigsberg Instruments, Inc., Pasadena, Calif.) was inserted into the left ventricle through a small incision at the apex. An electromagnetic flow probe (model MFV-2100, Nihon Koden, Tokyo) was placed around the aortic root. A catheter was inserted into the left internal thoracic artery to measure arterial pressure.
We inserted a catheter into the left atrium to calibrate the left ventricular pressure transducer. After exteriorizing the left ventricular pressure and the flow probe cables at the posterior neck through a subcutaneous tunnel, we closed the chest and allowed the dogs to recover for about 10 days.

Protocol

After the dogs had completely recovered from surgery, we imposed an exercise stress of various degrees with a treadmill. The exercise stress was varied stepwise in random order from complete standstill to maximal speed (7 km/hr) with a 20% slope while recordings were made of left ventricular pressure, aortic pressure, and left atrial pressure. When the hemodynamic condition was judged to have reached a steady state for a given level of exercise stress, we digitized these analog signals on-line at 200 Hz with a 12-bit resolution and stored them on the hard disk of a dedicated laboratory computer system (DEC PDP 11/44, Maynard) for subsequent analyses.

Estimation of Ventricular and Arterial Elastance

To analyze the influence of exercise on the transmission of mechanical energy of the ventricle to the arterial system, we treated both the ventricle and the arterial system as elastic chambers; the end-systolic elastance ($E_{es}$) represented ventricular properties, and the effective arterial elastance ($E_{a}$) represented arterial loading properties. $E_{es}$ is the slope of the end-systolic pressure-volume relation, $E_{a}$ is the slope of the end-systolic pressure-stroke volume relation.

Since contractility of the ventricle rapidly changed with exercise, we applied a modified single-beat $E_{es}$ estimation technique, which made it possible to estimate $E_{es}$ beat by beat without the necessity of altering the loading conditions of the ventricle. As shown in Figure 1, we predicted isovolumic left ventricular pressure (LVP) by using the Gauss-Newton nonlinear curve-fitting technique to fit its isovolumic portion to the sinusoidal function that follows, thus determining constants A, B, C, and D:

$$LVP = A \cdot \sin(Bt+C) + D$$  \hspace{1cm} (1)\

where $t$ is time. Drawing a tangential line from the predicted isovolumic peak left ventricular pressure to the right corner of the pressure-ejected volume loop (obtained by the time integration of aortic flow and measured left ventricular pressure) yields the end-systolic pressure-stroke volume relation line. The slope of this line represents $E_{es}$. We used this single-beat estimation technique throughout the experiment. For a given level of exercise stress, when we judged that the hemodynamic state had reached a steady state, we sampled instantaneous left ventricular pressure and aortic flow for several seconds to get between eight and 20 consecutive beats, and we estimated $E_{es}$ for every beat. We then took an average of them. The beat-to-beat variation (i.e., normalized SD by mean) of the estimated $E_{es}$ was approximately 10% of its mean value. Asoh et al. reported that the standard error of the $E_{es}$ estimation by this technique relative to that by the actual aortic clamping was found to be less than 0.5 mm Hg/ml. The same technique has been independently validated in patients by Takeuchi et al.

By definition, $E_{a}$ is determined by the ratio of the end-systolic pressure to stroke volume. Since end-systolic pressure determined by the single-beat estimation was close to mean arterial pressure as shown in Figure 2, we approximated $E_{a}$ as the ratio of mean arterial pressure to stroke volume. This is equivalent to approximating $E_{a}$ by the ratio of total arterial resistance ($R$) to a cardiac cycle length ($T$): $E_{a} = R/T$.

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**FIGURE 1.** Left panel: Prediction of isovolumic left ventricular pressure (LVP). The solid line shows measured LVP, and the dashed line shows predicted isovolumic LVP that was obtained by fitting the isovolumic portions of the measured LVP to the sinusoidal function with offset using a nonlinear curve-fitting technique (see text for details). Right panel: Estimation of end-systolic elastance ($E_{es}$). Drawing a tangential line from the predicted peak LVP to the right corner of the end-systolic pressure ($P_{es}$)-ejected volume loop obtained by the integration of aortic flow and measured LVP yields the $P_{es}$-ejected volume relation line. The slope of this line represents $E_{es}$.

**FIGURE 2.** Plot showing estimated end-systolic pressure ($P_{es}$) by the single-beat end-systolic elastance estimation technique (see text) compared against mean arterial pressure ($P_{m}$) in 55 points obtained from six dogs ($P_{es}=0.88P_{m}+18$, $r=0.89$, $p<0.001$). Different symbols correspond to different dogs. As can be seen, $P_{es}$ was close to $P_{m}$, as evidenced by a narrow distribution along the line of identity (the dotted line). The standard error of the estimate was 5 mm Hg.
FIGURE 3. For the purpose of determining stroke volume (SV) and external work of the left ventricle, we treated both the ventricle and arterial system as elastic chambers. The diagram shows ventricular end-systolic elastance (Ees) as the slope of the end-systolic pressure–volume relation. Vo is end-systolic unstressed volume. The effective arterial elastance (Ea) is the slope of the end-systolic pressure–SV relation. Ea can be approximated by the ratio of arterial resistance to one cardiac cycle length. The diagonal line that runs from end-diastolic volume (Ved) represents the Ea line. The intersection between the ventricular and Ea line gives the end-systolic volume (Ves) and thus SV. The hatched area stands for stroke work (SW) of the ventricle, which represents the external work done by the ventricle against the arterial system. Only 50% of SV was stored by the effective Ea. SW can be approximated by Equation 2 (see text for details).

Evaluation of the Efficiency of Left Ventricular External Work

Illustrated in Figure 3 is the basic framework of ventriculoarterial coupling and its relation to stroke work (SW). Detailed explanations of the ventriculoarterial coupling using the elastance model of the ventricle and arterial system and its application to estimate external work have been given elsewhere. In brief, assuming a constant left ventricular pressure during ejection (i.e., isobaric contraction), SW of the ventricle can be approximated as

\[ SW = (V_{ed} - V_o)^2 \frac{E_a}{(1 + E_a/E_{es})^2} \]  

(2)

where \( V_{ed} \) is end-diastolic volume and \( V_o \) is end-systolic unstressed volume. According to this framework, only 50% of SW would be stored at end systole by \( E_a \). By differentiating Equation 2 with respect to \( E_a \), one can show that SW becomes maximal when \( E_a \) equals \( E_{es} \). Substituting \( E_a \) in Equation 2 with \( E_{es} \) yields

\[ SW_{max} = (V_{ed} - V_o)^2 \frac{E_{es}}{4} \]  

(3)

where \( SW_{max} \) represents maximal SW. Because actual contractions were not exactly isobaric and mean systolic pressure was somewhat higher than end-systolic pressure, the estimated SW with Equation 2 in this investigation was slightly but consistently lower than actually measured (~20% at most). The condition at which SW becomes maximal (i.e., \( E_a = E_{es} \)), however, remained unaltered.10

We indexed mechanical optimality (\( Q_{mch} \)) by taking the ratio of SW to \( SW_{max} \) as

\[ Q_{mch} = \frac{SW}{SW_{max}} \]  

(4)

Substituting Equations 2 and 3 into Equation 4 yields

\[ Q_{mch} = \frac{4E_a}{E_{es}(1 + E_a/E_{es})^2} \]  

(5)

Therefore, once we know \( E_a/E_{es} \), we can evaluate \( Q_{mch} \) of the ventricular ejection by Equation 4. Note that \( Q_{mch} \) becomes unity (i.e., maximal) when \( E_a/E_{es} \) is unity.

Statistical Analysis

All values are given as mean±SD. For the comparison of the mean, we used the paired t test. A value of \( p<0.05 \) was considered significant.

Results

Changes in Hemodynamic Variables

Basic hemodynamic variables are summarized in Tables 1 and 2. Illustrated in Figure 4 are changes in hemodynamic variables associated with exercise. All variables were shown as a function of cardiac output. The top plots show a representative case, and the bottom plots show the pooled data at rest and at peak exercise stress. With increases in the exercise load,
cardiac output increased from 1.8±0.5 to 3.5±1.1 l/min (p<0.005) (the left panel of Figure 4), and heart rate increased from 108±17 to 199±31 beats per minute (p<0.005), whereas arterial blood pressure increased less markedly from 77±4 to 110±22 mm Hg (p<0.05) (the middle panel of Figure 4). Thus, arterial resistance decreased significantly by approximately 30% from 2.8±0.6 to 2.1±0.6 mm Hg sec/ml (p<0.05) (the right panel of Figure 4).

Changes in $E_\text{es}$ and $E_a$

Figure 5 illustrates the effect of exercise on the elastance of the left ventricle and the arterial system. The top plots show a set of data obtained from a representative dog (dog 4 on Tables 1 and 2). As can be seen in the top left panel, in response to exercise, $E_\text{es}$ increased with cardiac output. This trend was true for all animals examined. A linear regression analysis indicated that the average slope of the cardiac output versus

<table>
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<tr>
<th>Dog No.</th>
<th>$E_\text{es}$ (mm Hg/ml)</th>
<th>$E_a$ (mm Hg/ml)</th>
<th>$E_\text{es}/E_a$</th>
<th>CO (l/min)</th>
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<td>9.3</td>
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<tr>
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<tr>
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<td>11.5</td>
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<tr>
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<td>10.9</td>
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<td>3.5</td>
</tr>
<tr>
<td>SD</td>
<td>1.8</td>
<td>2.6</td>
<td>0.26</td>
<td>1.1</td>
</tr>
</tbody>
</table>

$E_\text{es}$, effective arterial elastance; $E_a$, end-systolic elastance; CO, cardiac output; Ex, after exercise.

*p=0.068 vs. control value (rest) by two-tailed t test.

†p<0.005 vs. control value (rest).
FIGURE 5. Plots showing data obtained from a representative case (dog 4 in Tables 1 and 2) under various exercise levels (top) and the pooled data at rest and at peak exercise (bottom). Left panels: Effect of exercise on the left ventricular end-systolic elastance (Ees). CO, cardiac output. With increases in exercise load, Ees increased from 7.6±1.7 to 10.9±2.6 mm Hg/ml (p<0.005). Middle panels: Effect of exercise on the effective arterial elastance (Ea). With increases in exercise load, increases in heart rate overwhelmed decreases in arterial resistance, which in turn increased Ea from 4.9±1.4 to 6.7±1.8 mm Hg/ml (p=0.068). Right panels: Effect of exercise on the ratio of Ea to Ees (Ea/Ees). The ratio was not significantly altered by exercise (0.69±0.26 vs. 0.63±0.21, NS). See text for details.

The Ees relation in six dogs was 2.10±0.64 mm Hg·ml⁻¹·(l/min)⁻¹. The correlation coefficient varied between 0.85 and 0.94 (mean, 0.89), with a value of p<0.01 in all animals. As shown in the top middle panel of Figure 5, Ees also increased with cardiac output. This trend was observed in all animals except one. The average slope of the cardiac output versus Ees relation in five dogs was 1.40±0.66 mm Hg·ml⁻¹·(l/min)⁻¹. The correlation coefficient varied between 0.43 and 0.85 (mean, 0.66) (p<0.01 in three dogs and p<0.1 in two dogs). In one dog (dog 3), Ees decreased with increases in cardiac output (r=0.85, p<0.01). This dog had an unusually high heart rate to begin with at the resting condition. The decrease in arterial resistance overrode the increase in heart rate in response to exercise (see "Discussion").

The top right panel of Figure 5 shows the effect of exercise on Ees/Ees. As can be seen, the ratio remains fairly constant irrespective of changes in cardiac output. This was true in all animals examined.

The bottom plots of Figure 5 show the pooled data at rest and at peak exercise. With increases in the exercise load, Ees significantly increased from 7.6±1.7 to 10.9±2.6 mm Hg/ml (p<0.005) (the bottom left panel), and Ees also increased from 4.9±1.4 to 6.7±1.8 mm Hg/ml (the bottom middle panel). In the pooled data, however, statistical significance of the increase in Ees with cardiac output was marginal (p=0.068), because Ees did not increase with cardiac output in dog 3. As shown in the bottom right panel, Ees/Ees remained fairly constant (0.69±0.26 versus 0.63±0.21, NS).

Efficiency of Energy Transmission of Ventricular Ejection

Shown in Figure 6 is the effect of exercise on Qmch, defined in "Materials and Methods" as the ratio of SW to the theoretically derived SWmax. Qmch was estimated from Equation 4 using experimentally measured Ees/Ees. The top panel shows a representative case. As can be seen, Qmch remained almost unity irrespective of the level of exercise. The bottom panel shows the pooled data. Qmch was 0.92±0.07 at rest and 0.92±0.08 (p=NS) at peak exercise and was maintained at near unity.

Discussion

Effect of Exercise Stress on Ventricular Arterial Elastance

We have shown that both Ees and Ees increased with increases in exercise load in chronically instrumented dogs. Ees was linearly correlated with cardiac output. Similarly, Ees also increased linearly with increases in cardiac output, except for one animal. Increases in Ees indicate augmentation of myocardial contractility, whereas increases in Ees reflect a more complex physiological response. Since Ees can be approximated by the ratio of total arterial resistance to cardiac cycle length,10,11 relative changes in these two factors determine Ees. During exercise stress, both the total arterial resistance and cardiac cycle length decreased. There-
fore, whether $E_a$ decreased or increased depended solely on the changes in arterial resistance relative to those in heart rate. The fact that $E_a$ increased with exercise in most animals reflected that the reduction in the total arterial resistance was overridden by the reduction in cardiac cycle length. In one dog (dog 3), however, $E_a$ decreased with increases in cardiac output. Because this dog had an unusually high heart rate to begin with at the rested condition, its heart rate was unable to increase as much as the other dogs. Therefore, the decrease in arterial resistance override the increase in heart rate in response to exercise.

**Mechanical Optimality of Ventricular Ejection**

As we have indicated, the external work of the left ventricle is closely related to the ratio of $E_a$ to $E_{ao}$ ($E_a/E_{ao}$). $Q_{mch}$ becomes maximal when $E_a/E_{ao}$ is unity. A numerical analysis of Equation 5 indicated that $Q_{mch}$ was rather insensitive to changes in $E_a/E_{ao}$. $Q_{mch}$ was higher than 0.90 when $E_a/E_{ao}$ varied between 0.52 and 1.92. When $E_a/E_{ao}$ was higher than 2.0 or lower than 0.5, $Q_{mch}$ decreased. We have shown in this experiment that $E_a/E_{ao}$ at rest was between 0.52 and 1.92 (0.69±0.26). In other words, $Q_{mch}$ was more than 0.9 (0.93±0.07); thus, external work of the ventricle was nearly maximized for a given level of preload.

With increases in the exercise load, $E_a/E_{ao}$ remained fairly constant (peak exercise, 0.63±0.21) despite the fact that both $E_a$ and $E_{ao}$ increased. $Q_{mch}$ remained high (0.92±0.08). Thus, external work of the left ventricle was always nearly maximized during exercise as well as at rest under the tested conditions.

**Metabolic Optimality of Ventricular Ejection**

Although in this investigation we did not directly measure the oxygen consumption of the myocardium ($V_O_2$), the tight relation between the pressure–volume area (PVA) and $V_O_2$ made it possible to estimate the efficiency of the left ventricle as a biological machine that transforms metabolic energy to external cardiac work. Suga and his associates have extensively studied the relation between $V_O_2$ and PVA circumscribed by the end-systolic and end-diastolic pressure–volume relation. According to their data, the end-systolic PVA is linearly related to $V_O_2$ of the left ventricle. The relation can be formulated as

$$V_O_2 = A \cdot PVA + B \tag{6}$$

where $A$ is the slope and $B$ the intercept. Changes in contractility alter the intercept $B^{23}$ while hardly affecting slope $A$. Using this relation, one may estimate the left ventricular $V_O_2$, assuming isobaric contraction if the end-systolic pressure–volume relation, end-diastolic pressure–volume relation, and stroke volume are known. In our experiment, we measured the linearized slope of the end-systolic pressure–volume relation and stroke volume. Since PVA under the end-diastolic pressure–volume relation is small relative to the total PVA, ignoring this area enabled us to estimate PVA of the left ventricle and thus provided us with an estimate of $V_O_2$. Using $V_O_2$ thus estimated, we could evaluate metabolic efficiency of ventricular ejection, which is defined as the ratio of SW to $V_O_2$. To evaluate optimality, we defined the metabolic optimality index ($Q_{mnb}$) as

$$Q_{mnb} = \frac{SW/V_O_2}{(SW/V_O_2}_{max} \tag{7}$$

where the numerator represents the metabolic efficiency of ventricular external work and the denominator is its theoretical maximal value. Therefore, the unity $Q_{mnb}$ represents the left ventricle, which requires minimal $V_O_2$ to generate a given amount of SW. This index is identical to that proposed by Burkhoff and Sagawa. Illustrated in Figure 7 is the effect of exercise on $Q_{mnb}$. As can be seen, $Q_{mnb}$ was near unity (0.98±0.02) at rest and remained almost at unity during exercise (0.99±0.01), which is to say that ventricular ejection was indeed metabolically optimal during exercise as well as at rest.

**Mechanical and Metabolic Optimality as a Function of $E_a/E_{ao}$**

Burkhoff and Sagawa analyzed the efficiency of ventricular ejection using a model of the ventriculoarterial-coupled system. As shown in the top panel of Figure 8, it was clear that as suggested by Sunagawa et al., $Q_{mnb}$ is unity when $E_a/E_{ao}$ is unity. $Q_{mnb}$ is higher than 0.9 when $E_a/E_{ao}$ changes between 0.52 and 1.92. On the other hand, $Q_{mnb}$ reaches unity when $E_a/E_{ao}$ is approximately 1/2. $Q_{mnb}$ is higher than 0.9 when $E_a/E_{ao}$ varies between 0.25 and 1.0. To simultaneously make these efficiency indexes above 0.9, $E_a/E_{ao}$ should be approximately between 0.5 and 1.0. As shown in the shaded area in the top panel of Figure 8, this was exactly the range of that observed in this experiment. The fact that both $Q_{mch}$ and $Q_{mnb}$ are relatively insensitive to changes in $E_a/E_{ao}$ made it possible to simultaneously maximize these indexes and thus allowed animals to maintain the ventriculoarterial-coupled system at its optimal condition.

![Figure 6](http://circres.ahajournals.org/Download/1992/71/3/486_Figure6.png)
FIGURE 7. Top panel: Plot showing effect of exercise on the metabolic optimality index (Qmb). CO, cardiac output. Qmb (which is defined by Equation 7 in the text) is near unity at all exercise levels. Different symbols correspond to different dogs. Bottom panel: Plot of pooled data showing that Qmb is 0.98±0.02 at rest and 0.99±0.01 at maximal exercise level. Qmb did not significantly change with exercise. See text for details.

By observing Ea/Ees, we could learn how close the operating point is to its optimum. By observing Qmch and Qmb, we could evaluate how efficient ventriculoarterial coupling is. What is truly important is not the closeness of the operating point to its optimum but the efficiency of the ventriculoarterial coupling. Thus, the observed natural response, which apparently failed to adjust Ea/Ees to 0.5 or unity but succeeded in maximizing both Qmch and Qmb (>0.9), was teleologically sound.

Illustrated in the bottom panel of Figure 8 are Qmch and Qmb, as functions of the ejection fraction. The ejection fraction was estimated using the coupling framework developed by Sunagawa and colleagues.10,13 With this framework, stroke volume (SV) is expressed by

\[ SV = \frac{E_{es}}{E_a + E_{es}} (V_{es} - V_o) \]  

where \( V_{es} - V_o \) is the effective preload. Should we define the ejection fraction as the ratio of SV to \( V_{es} - V_o \), the ejection fraction (EFe) becomes

\[ EFe = \frac{E_{es}}{E_a + E_{es}} \]

Thus, Qmch becomes maximal when the ejection fraction is 50%. If the ejection fraction as defined above is between 34% and 66%, Qmch would be above 0.9. Qmb becomes maximal when the ejection fraction is approximately 67%. If the ejection fraction is between 50% and 80%, Qmb would be above 0.9. Thus, both Qmch and Qmb reach near maximal values when the ejection fraction varies between 50% and 66% (i.e., optimal ejection fraction). As can be seen in the bottom panel of Figure 8, the estimated ejection fraction (the shaded area) of exercising dogs in this experiment was matched with the optimal ejection fraction.

FIGURE 8. Top panel: The mechanical and metabolic optimality index (Qmch and Qmb, respectively) computed as a function of arterial elastance (Ea)/end-systolic elastance (Ees). Qmb was computed for the heart with Ees of 10 mm Hg/ml and effective end-diastolic volume (i.e., end-diastolic volume minus end-systolic unstressed volume) of 25 ml. Qmch reaches a maximum when Ea equals Ees (i.e., Ea/Ees = 1), whereas Qmb reaches a maximum when Ea is approximately Ees/2. The shaded range represents the Ea/Ees actual value (mean±1 SD) obtained in this experiment. Note that Qmch and Qmb are close to unity in the shaded range (modified from Burkhoff and Sagawa7). Bottom panel: Mechanical and metabolic optimality index as a function of the ejection fraction (EF). EF is estimated using the framework of ventricular arterial coupling approximating both the left ventricle and arterial system by the elastic chambers.10,13 EF represents the ratio of stroke volume to effective preload, i.e., end-diastolic volume minus end-systolic unstressed volume. As can be seen, Qmch reaches a maximum when EF equals 50%. On the contrary, Qmb becomes maximal when EF is 67%. The shaded range represents estimated EF at rest and during exercise in this experiment (mean±1 SD).

Clinical Significance

The result of this investigation may have some clinical relevance. If ventricular contractility fails to increase in response to exercise, as in patients with heart failure, increasing heart rate and decreasing arterial resistance inevitably increase Ees/Ea, which in turn decreases Qmch. The deterioration of mechanical optimality in the left ventricle with poor contractility has been demonstrated in animals12 and in patients.24 Administration of positive inotropic agents and/or vasodilators would decrease Ees/Ea and thus improve Qmch.

In left ventricular hypertrophy, such as in patients with hypertension or aortic stenosis, both Ees and Ea would increase.25,26 If this is the case, Qmch is likely to be maintained. On the contrary, in case of hypertrophic cardiomyopathy, since the increase in Ees is unrelated to the afterload,27 the resultant Ees/Ea would decrease. This results in a decrease in Qmch. The use of β-blockers or calcium channel antagonists for these patients would depress Ees and thus would improve Qmch.

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If the relation between VO2 and end-systolic PVA is maintained under these pathological conditions, the effect on Qned is similar to the effect on Qmch, as discussed above. Whether the PVA–VO2 is maintained under the pathological conditions remains to be seen.

Accuracy of Ees and Ea Estimation

In this experiment, accurate estimations of Ees and Ea are essential. We estimated Ees using a single-beat estimation technique. The estimation error was approximately 10% in open-chest dogs15 if we compared the estimated Ea against that obtained by the actual aortic occlusion.18 Under the exercising condition, however, heart rate increased and arterial resistance decreased. Thus, the dynamic properties of the ventricle and arterial system such as ventricular internal resistance and arterial wave reflection would manifest and significantly modulate ejecting ventricular pressure. The single-beat estimation technique, on the other hand, analyzes only the isovolumic phases of ventricular pressure. Therefore, the estimated Ea by this technique would inherently be relatively insensitive to changes in ventricular pressure during ejection.

Two other problems would also affect the accuracy of Ea estimation. One is the load dependence of the end-systolic pressure–volume relation, and the other is its nonlinearity.28,29 However, as Little et al30 demonstrated, we do think that this load dependence and nonlinearity did not prevent the end-systolic pressure–volume relation from being well approximated by a straight line or the Ees from providing a useful index of the contractile state. Indeed, Igarashi et al31 reported that, in open-chest dogs, Ees determined from the aortic occlusion method was close to that determined from five steady-state contractions. Thus, we believe that the single-beat estimation technique would provide us a reasonably accurate estimate of Ees.

A numerical analysis indicated that a 10% error in estimating Ees could result in errors of up to 2% in the estimation of Qmch and Qned. Therefore, the quantitative contribution of the estimation error of Ees did not significantly affect the result and thus the conclusion of this experiment.

Once the end-systolic pressure–volume relation was determined, we could determine end-systolic pressure. Since stroke volume was directly measured by electromagnetic flowmetry, Ees, which is defined as the ratio of end-systolic pressure to stroke volume, was rather accurately estimated. The dynamic properties of the ventricle and arterial system could affect the end-systolic pressure versus mean arterial pressure relation. In this series of experiments, however, as shown in Figure 2, they correlated highly linearly. Therefore, we used mean arterial pressure instead of end-systolic pressure to facilitate a simple, yet accurate, estimation of effective arterial elastance.

Recently, Little and Cheng32 reported that mean Ea and Ees were 6.9±3.1 and 7.2±2.7 mm Hg/ml, respectively, in conscious dogs. In our data, the values were 4.9±1.4 and 7.6±2.6 mm Hg/ml, respectively. Neither Ea nor Ees was significantly different between the studies (unpaired t test). They reported that Ees/Ea, which was the reciprocal value of what we reported, was 0.96±0.20. For the purpose of comparison, we also estimated Ees/Ea. The estimated Ees/Ea in this study was 1.65±0.64, which was marginally larger than that of reported (unpaired t test, two-tailed p=0.050). There are a couple of possible reasons that may contribute to this difference. First, in their study they estimated ventricular volume and stroke volume using a sonomicrometric technique. In our study, we used an electromagnetic flowmeter to estimate stroke volume. This difference in the volume estimation technique will be partly responsible for the difference in Ees/Ea. Second, in estimating Ea, they used end-systolic pressure, whereas we used mean aortic pressure. Although these pressures were fairly close (see Figure 2), the end-systolic pressure under the control condition was slightly yet significantly higher than the mean aortic pressure (78.7±4.3 versus 86.8±4.4 mm Hg, p<0.005) (Table 1). This approximation of the end-systolic pressure by the mean aortic pressure could contribute to the difference in Ees/Ea at least under the control condition. Finally, we estimated Ees from a steady-state pressure–volume loop and estimated isovolumic peak pressure for a given end-diastolic volume, whereas Little and Cheng32 estimated Ees from multiple pressure–volume loops while decreasing preload. This difference in changes in loading condition would systematically affect Ees, and thus Ees/Ea through the aforementioned loading condition dependence and curvilinearity of the end-systolic pressure–volume relation.

Limitations

There are several limitations in this investigation. First, we have shown that external work of the left ventricle in conscious dogs was nearly maximal for a given level of preload irrespective of exercise stress. This unique feature is teleologically sound; however, we are not certain whether this maximization is intended by the cardiovascular regulatory system. Needless to say, further investigations are required to uncover the principle target of cardiovascular regulation.

Second, we have not investigated what mechanism was responsible for the maximization of external work. With exercise, increases in sympathetic tone result in increases in ventricular contractility and heart rate. Increases in metabolic demand in skeletal muscle decrease arterial resistance. As we indicated, the constant ratio of Ea to Ees could not be achieved unless three parameters, Ees, heart rate, and arterial resistance, changed in a concordant fashion. Exactly how the neurohumoral system plays a role in adjusting Ees and Ea remains to be seen.

Finally, in this investigation, we analyzed the ventriculoarterial matching, exclusively focusing on steady hemodynamic states. Under physiological conditions, however, there may well be transient exercise stress as well as steady-state exercise stress. There is no a priori reason to believe that the matching between the ventricle and the arterial system should take place, even transiently, just like static matching. Further investigation on transient ventriculoarterial matching remains to be seen.

Conclusion

We conclude that 1) external work of the left ventricle of dogs at rest is nearly maximal, 2) external work remains nearly maximal during exercise in spite of marked changes in cardiac contractility and hemody-
dynamics, and 3) the conversion efficiency of metabolic energy to SW does not appear to be compromised during exercise.

References

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