Left Ventricular Contractility and Energetic Cost in Disease Models

— An approach from the pressure-volume diagram —

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Left ventricular contractility and the energetic cost of contraction were assessed in various disease models in experimental animals utilizing frameworks of $E_{\text{max}}$ (left ventricular contractility index) and pressure-volume area (PVA, a measure of total left ventricular mechanical energy expenditure) derived from the pressure-volume (P-V) diagram. Under various contractile conditions, PVA linearly correlates with myocardial oxygen consumption per beat ($\text{VO}_2$) in a load-independent manner. The reciprocal of the slope of the linear $\text{VO}_2$-PVA relation indicates “contractile efficiency” (the energy transduction efficiency from oxygen to total mechanical energy). It was similar between dog and rabbit hearts (about 40%) and was not significantly affected by enhanced contractility with calcium, epinephrine, or cardiac cooling, or by depressed contractility with propranolol, decreased coronary perfusion pressure, or stunned myocardium. However, in thyrotoxic rabbit hearts contractile efficiency was significantly depressed compared to normal hearts. On the other hand, the $\text{VO}_2$ intercept of the $\text{VO}_2$-PVA relation (PVA-independent $\text{VO}_2$), which reflects $\text{VO}_2$ for non-mechanical activities such as excitation-contraction coupling and basal metabolism, positively correlates with $E_{\text{max}}$. Therefore, the ratio of an increase in PVA-independent $\text{VO}_2$ to an increase in $E_{\text{max}}$ indicates “oxygen cost of contractility”. Oxygen cost of contractility was higher in stunned myocardium than in normal hearts, suggesting that the energy cost of calcium handling is elevated in stunned myocardium. Thus, using the frameworks of $E_{\text{max}}$ and PVA, we can interconnect cardiac mechanics and energetics. Further, using the concepts of contractile efficiency and oxygen cost of contractility, we can approach the pathogenesis of variously altered contractile conditions.

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In the research field of cardiac mechanics and energetics, two important parameters have been derived from the left ventricular (LV) pressure-volume (P-V) diagram: $E_{\text{max}}$ and pressure-volume area (PVA)! As shown in Fig. 1A, $E_{\text{max}}$ is the slope of the end-systolic pressure-volume relation (ESPVR) and a load-independent index of ventricular contractility. PVA is a specific area in the P-V diagram circumscribed by the ESPVR, end-diastolic P-V relation, and the systolic P-V trajectory, and has been considered a measure of the

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Fig. 1. Schematic illustrations of left ventricular systolic pressure-volume area (PVA) in the pressure-volume diagram (Panel A) and the relation between myocardial oxygen consumption per beat (VO₂) and PVA (Panels B-E). PVA is the area surrounded by the end-systolic (ESPVR) and end-diastolic pressure-volume relations (EDPVR) and the systolic pressure-volume trajectory. It consists of both potential energy (PE) and external work (EW) in an ejection contraction (Panel A) and potential energy alone in an isovolumic contraction (not shown). The VO₂-PVA relation is linear with a positive VO₂ intercept value (Panel B). The reciprocal of the slope reflects contractile efficiency of mechanical activities, while the VO₂-intercept (or PVA-independent VO₂) reflects oxygen requirements for excitation-contraction (E-C) coupling and basal metabolism (Panel C). Enhanced contractility with calcium or epinephrine increases VO₂ for E-C coupling (Panel D), resulting in upward shifts of the VO₂-PVA relation without changing the slope (Panel E). The relation between the VO₂-intercept and Emax during an isotropic intervention is linear (Panel F), and the slope indicates oxygen cost of contractility.

Total mechanical energy generated during a cardiac contraction. Using these two parameters, we have assessed LV contractility and the energetic cost of contraction in various disease models in experimental animals.

Methods

Background

Previous studies have shown that PVA correlates linearly with myocardial oxygen consumption per beat (VO₂) in a load-independent manner (Fig. 1B)²,³ The reciprocal of the slope of the linear VO₂-PVA relation is called “contractile efficiency”¹,⁴ and indicates energy transduction efficiency from oxygen to total mechanical energy generated by a LV contraction (Fig. 1C). On the other hand, the VO₂-intercept of the VO₂-PVA relation (PVA-independent VO₂) mainly consists of VO₂ for excitation-contraction (E-C) coupling and for basal metabolism².⁵

Enhanced ventricular contractility or Eₘₐₓ with calcium or epinephrine increases VO₂ for E-C coupling without affecting contractile efficiency, resulting in a parallel upward shift of the VO₂-PVA relation (Fig. 1D). VO₂ for basal metabolism is not affected by enhanced contractility with calcium or epinephrine. When LV contractility is enhanced in several steps as in Fig. 1E, the increases in PVA-independent VO₂ linearly correlate with the increases in Eₘₐₓ (Fig. 1F). The slope of the linear relation between PVA-independent VO₂ and Eₘₐₓ is called “oxygen cost of contractility”⁶ and indicates oxygen requirement in E-C coupling for a unit increase in Eₘₐₓ.

Using the frameworks of Eₘₐₓ and PVA, we assessed contractile efficiency and oxygen cost of contractility in various disease models in dog and rabbit hearts.

Heart Preparation

Experiments were performed in isolated, blood-perfused dog or rabbit hearts supported by cross-circulation with an intact animal. The surgical procedures of the cross-circulated heart preparation of the dog or rabbit have been described in detail previously²,³ After cross-circulation was started, a thin balloon was inserted into the LV of the isolated heart and connected to our custom-made volume servo pump (dog study) or to a microsyringe (rabbit study) to control and measure the LV volume. Coronary blood flow and coronary arteriovenous oxygen content difference were measured to calculate myocardial oxygen consumption per beat (VO₂).

Experimental Protocol

In the dog study, LV pressure, volume, coronary blood flow, and arteriovenous oxygen content difference were measured during either isovolumic or ejection contractions.
under various LV end-diastolic volumes to calculate LV $E_{\text{max}}$, PVA and VO$_2$. In the rabbit study, similar measurements were made during isovolumic contractions only. The pathological conditions we examined were; 1) lowered coronary perfusion pressure produced by constricting the coronary arterial perfusion tube (dog)$^6$ 2) stunned myocardium produced by 15 min global ischemia followed by 120 min reperfusion (dog)$^5$ 3) cardiac cooling induced by placing the coronary perfusion tubes in a cold water bath (dog)$^7$ 4) congestive heart failure induced by chronic rapid pacing at a rate of 250 beats/min (dog)$^8$ 5) thyrotoxicosis induced by daily injection of 1-thyroxine (rabbit)$^4$ We also examined the effects of various positive and negative inotropic drugs on $E_{\text{max}}$ and the VO$_2$-PVA relation.

RESULTS

Due to the negative inotropic effect of propranolol, $E_{\text{max}}$ decreased by $48 \pm 11\%$, and the VO$_2$-PVA relation shifted downward in a parallel manner. With coronary perfusion pressure reduced from $82 \pm 8$ mmHg to $32 \pm 6$ mmHg, $E_{\text{max}}$ decreased by $56 \pm 14\%$ and the VO$_2$-PVA relation shifted downward with a slight decrease in the slope. In stunned myocardium, $E_{\text{max}}$ decreased from control by $37 \pm 23\%$, whereas the VO$_2$-PVA relation did not shift downward. In contrast, cardiac cooling increased $E_{\text{max}}$ by $46 \pm 13\%$, while the VO$_2$-PVA relation did not show any shift. In pacing-induced heart failure, the ESPVR was depressed and showed downward convexity. When PVA was calculated according to a parabolic fit to the ESPVR, the VO$_2$-PVA relation was linear and depressed downward in an approximately parallel manner. In the thyrotoxic rabbit heart, the ESPVR was upward convex. Although $E_{\text{max}}$ was similar to the normal heart, the VO$_2$-PVA relation shifted upward with a steepened slope. In each pathological condition, we assessed both contractile efficiency and the oxygen cost of contractility.

Contractile Efficiency

Fig. 2 lists mean values for contractile efficiency calculated from the slope of the linear VO$_2$-PVA relation in various conditions. In dog hearts, neither the mode of contraction (isovolumic or ejection contraction) nor positive inotropic drugs (calcium, epinephrine, or OPC-8212) changed contractile efficiency$^1$. Decreased contractility by either propranolol administration or moderately lowered coronary perfusion pressure did not affect contractile efficiency either. In stunned myocardium, contractile efficiency was similar to that in sham group hearts, although it was $19\%$ lower than that before stunning (data not shown). During cardiac cooling, contractile efficiency remained constant despite a significant slowing of contraction evidenced by a $45\%$ increase in the time to $E_{\text{max}}$. Contractile efficiency in the pacing-induced failing heart calculated using the parabolic ESPVR analysis was $44\%$ on average (data not shown), which was similar to the value for the nonfailing dog heart ($35\% - 45\%$). In the normal rabbit heart, contractile efficiency was similar to that in the normal dog heart despite the difference in species. In contrast, contractile efficiency in the thyrotoxic rabbit heart ($27 \pm 6\%$) was significantly lower ($p < 0.01$) than that in the normal rabbit heart ($40 \pm 4\%$).

Oxygen Cost of Contractility

Fig. 3 depicts the relative changes in PVA-independent VO$_2$ plotted against the relative changes in $E_{\text{max}}$ during various interventions. Calcium and epinephrine produced proportional increases in $E_{\text{max}}$ and PVA-independent VO$_2$. On the other hand, propranolol and lowered coronary perfusion pressure resulted in proportional decreases in $E_{\text{max}}$ and PVA-independent VO$_2$. In stunned myocardium, $E_{\text{max}}$ decreased by $37 \pm 23\%$ whereas PVA-independent VO$_2$ was unchanged from the control value. When the decreased $E_{\text{max}}$ in stunned myocardium was enhanced with calcium to the control level, PVA-independent VO$_2$ exceeded the control value by $37 \pm 27\%$. In contrast, cardiac cooling resulted in a $46 \pm 13\%$ increase in $E_{\text{max}}$ while PVA-independent VO$_2$ was not significantly changed ($7 \pm 17\%$). These findings indicate that calcium, epinephrine, propranolol, and lowered coronary perfusion pressure proportionally alter LV contractility and VO$_2$ for E-C coupling. In contrast, myocar-
ity without changing VO₂ for E-C coupling. Thus, the oxygen cost of contractility is increased in stunned myocardium and decreased during cardiac cooling. In the thyrotoxic rabbit heart, PVA-independent VO₂ was 27% higher than that in the normal heart despite unchanged Eₘₐₓ, suggesting an increased oxygen cost of contractility.

DISCUSSION

Contractile efficiency
PVA theoretically represents the total mechanical energy generated by a ventricular contraction. Therefore, the reciprocal of the slope of the linear VO₂-PVA relation, i.e., contractile efficiency, implies the output/input ratio of energy used exclusively for mechanical activities. Contractile efficiency is the product of VO₂-to-ATP (oxidative phosphorylation) efficiency and ATP-to-PVA (crossbridge) efficiency. The fact that all the inotropic drugs examined (calcium, epinephrine, OPC-8212, and propranolol) and low perfusion pressure did not change contractile efficiency indicates that a change in intracellular calcium ([Ca²⁺]₅₅) inase does not significantly affect either of the oxidative phosphorylation or crossbridge efficiency. Also, the fact that thyrotoxicosis (accelerating crossbridge cycling) decreased contractile efficiency suggests that a change in myosin ATPase activity or crossbridge cycling rate is responsible for a change in contractile efficiency. However, contractile efficiency was unchanged during cardiac cooling which decreases myosin ATPase activity? This suggests that other factors such as myosin isoform transition from V₃ to V₁, rather than a simple increase in the crossbridge cycling rate, could be responsible for the change in contractile efficiency. Further, the unchanged contractile efficiency in the pacing-induced failing heart suggests that the pathogenesis of contractile dysfunction in this model originates from the sites other than crossbridges.

Oxygen cost of contractility
Oxygen cost of contractility reflects energy cost of nonmechanical activities from VO₂ to Eₘₐₓ, i.e., energy costs of oxidative phosphorylation (VO₂-to-ATP) and E-C coupling (ATP-to-Eₘₐₓ). Energy cost of ATP-to-Eₘₐₓ consists of the cost of Ca²⁺ transportation in sarcoplasmic reticulum (coupling ratio of Ca²⁺ to ATP) and the responsiveness of myofilament to Ca²⁺. Because normal oxidative phosphorylation has been reported in stunned myocardium, the increased oxygen cost of contractility in stunned myocardium indicates either a decreased Ca²⁺/ATP coupling ratio in sarcoplasmic reticulum or a decreased responsiveness of myofilament to Ca²⁺. In contrast, increased oxygen cost of contractility in the thyrotoxic rabbit heart may result from either an increased cost of Ca²⁺ transportation in sarcoplasmic reticulum or an uncoupling of oxidative phosphorylation, because unimpaired Ca²⁺ responsiveness of skinned muscles has been reported in the thyrotoxic rabbit heart.

In conclusion, using the frameworks of Eₘₐₓ and PVA, we can interconnect cardiac mechanics and energetics by dividing VO₂ into mechanical and nonmechanical portions. Further, using the concepts of contractile efficiency and oxygen cost of contractility, we can analyze the energetic consequences of various inotropic interventions, and gain insight into the pathogenesis of variously altered contractile conditions.

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