Left Ventricular Mechanoenergetics under Altered Coronary Perfusion in Guinea Pig Hearts

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Abstract  Coronary perfusion pressure (CPP) is well known to affect left ventricular (LV) mechanoenergetics (Gregg’s phenomenon). The garden hose effect via the Frank-Starling mechanism caused by coronary distension has long been considered to be the underlying mechanism of this phenomenon. However, recent studies have revealed a close correlation between CPP and the excitation-contraction coupling in myocytes. The aim of this study was to investigate the mechanoenergetic aspects of Gregg’s phenomenon by the ventricular contractility ($E_{\text{max}}$) dependency of the myocardial oxygen consumption ($V_{O_2}$)-total mechanical energy (PVA, systolic pressure-volume area) relationship. Experiments were performed in the excised, cross-circulated guinea pig heart preparation. The protocol consisted of LV volume loading (VOL run), changing coronary perfusion pressure at a fixed LV volume (CPP run) and intracoronary calcium (Ca) infusion also at the same LV volume (Ca run). In all seven hearts, we obtained a linear $V_{O_2}$-PVA relation in VOL run. The $V_{O_2}$-PVA relations in CPP and Ca runs, which equally enhanced $E_{\text{max}}$, were highly linear and had no significant difference in their slopes, both significantly steeper than in VOL run. These findings suggest no significant difference in the oxygen cost of $E_{\text{max}}$ between CPP and Ca runs. The enhanced LV mechanoenergetics under increasing CPP is characterized by increases in the $V_{O_2}$ component primarily for the excitation-contraction coupling to a greater degree than expected from the mechanical (garden hose) effect.

Key words: coronary perfusion pressure, Gregg’s phenomenon, cardiac mechanoenergetics, $E_{\text{max}}$, pressure-volume area.

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Effects of coronary perfusion pressure and flow on cardiac mechanics and oxygen consumption have been reported by many investigators \cite{1-8}. The positive inotropic effect of increased coronary perfusion is called "Gregg's phenomenon" \cite{3}. The "garden hose effect" has been proposed as the underlying mechanism \cite{1}. Namely, coronary distension elicited by increasing intracoronary pressure stretches myocardial fibers which, in turn, increases fiber tension and enhances contractile performance via the Frank-Starling mechanism even at a constant ventricular chamber volume. On the other hand, recent studies have demonstrated a close correlation between the increases in transient intracellular free calcium (Ca) concentration and contractility enhanced with increased coronary perfusion pressure \cite{9,10}.

We therefore hypothesized that the increases in myocardial oxygen consumption with increased coronary perfusion pressure primarily involve increases in oxygen consumption for the excitation-contraction (E-C) coupling, though contribution of other mechanisms such as the garden hose effect via the Frank-Starling mechanism may also be included.

The aim of the present study was to investigate the energetic aspects of Gregg's phenomenon for a better understanding of the underlying mechanism, using the \(E_{\text{max}}\) (an index of contractility)-\(V_{\Omega_{2}}\) (myocardial oxygen consumption per beat)-PVA (end-systolic pressure-volume area, a measure of total mechanical energy) relationship. This relationship, which has been thoroughly reviewed by Suga \cite{11}, has been very useful for the analysis of the energetic effects of various inotropic interventions \cite{11-16}.

METHODS

Surgical preparation. The investigation conforms with the Guiding Principles for the Care and Use of Animals approved by the Council of the Physiological Society of Japan. Experiments were performed on seven excised, cross-circulated (blood-perfused) guinea pig heart preparations instituted after the conventional excised, cross-circulated canine heart preparation. In each experiment, three guinea pigs were anesthetized with urethane (1 mg/g, i.p.) and intubated. All guinea pigs were heparinized (1,000 U, i.v.). The largest guinea pig (body weight 907 ± 173 g) was used as a blood supplier to extract its blood for priming the cross-circulation tubing. The chest was opened midsternally and the blood was drained from an 18-gauge needle stabbed into the left ventricle (LV). The middle-size guinea pig (579 ± 83 g) was used as the metabolic supporter; the bilateral common carotid arteries and right external jugular vein were cannulated with the arterial and venous cross-circulation tubing, respectively. The chest of the smallest guinea pig (364 ± 25 g), as the heart donor, was opened midsternally under artificial ventilation. The brachiocephalic artery and the right ventricle (RV) via the superior vena cava were cannulated and connected to the arterial and venous cross-circulation tubing, respectively, from the support

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guinea pig. The heart-lung section was isolated from the systemic and pulmonary circulation by ligating the left common carotid artery, descending aorta, inferior vena cava, and pulmonary trunk in this order. The beating heart, supported by cross-circulation, was then excised from the chest. Coronary perfusion of the excised heart was never interrupted during the preparation.

In the excised, beating heart, the LV apex was punctured with an 18-gauge needle to drain the thebesian and aortic regurgitant blood. The left atrium was opened and all the LV chordae tendineae were cut. A thin latex balloon (unstressed volume, 0.4 ml) which had been attached to the end of a polyethylene tube was fitted into the LV. The balloon, primed with water, was connected to a pressure transducer (Life Kit DX-312, Nihon Kohden, Tokyo, Japan) and a 0.5 ml precision glass syringe with fine scales (minimum scale = 0.005 ml). LV pressure (LVP) was measured with this transducer. LV volume was changed by adjusting intraballoon water volume with the syringe in 0.025 ml steps between 0.05 and 0.23 ml and fixed constant by a three-way stopcock. LV epicardial electrocardiogram (ECG) was recorded with a pair of fine wire electrodes. The heart rate was fixed constant at 240 beats/min by left atrial pacing. The heart was then set into a thermostat chamber to maintain its temperature at 37°C throughout the experiment. Coronary perfusion pressure (CPP) was measured in the arterial perfusion tubing with a pressure transducer, and was controlled by adjusting coronary arterial cross-circulation flow with a roller pump. Systemic arterial blood pressure of the support guinea pig ranged between 80 and 100 mmHg throughout the experiment. Arterial pH, $P_{O_2}$ and $P_{CO_2}$ of the support guinea pig were maintained within their physiological ranges by using supplemental oxygen and intravenous sodium bicarbonate as needed. We used only isovolumic contractions throughout this study.

Oxygen consumption. Total coronary blood flow was measured with our custom-made drop-counter flowmeter placed in the middle of the coronary venous drainage tubing from the RV. Calibration of this flowmeter was performed by measuring blood volume per minute under different flow rates. We confirmed that the blood flow could be precisely measured by this flowmeter between 0.2 and 5 ml/min, wider than the measured range. We neglected the LV thebesian flow. The coronary arteriovenous $O_2$ content difference (AVO$_2$D) was continuously measured by passing all the arterial and venous cross-circulation blood through the two cuvettes of a custom-made oximeter (PWA-200S, SHOE TECHNICA Inc., Chiba, Japan) [17]. The oximeter was calibrated against a blood oxygen content analyzer (IL-382 CO-Oximeter, Instrumentation Laboratory Inc., USA) in each experiment.

Cardiac oxygen consumption was obtained as the product of coronary flow and AVO$_2$D. It was divided by heart rate (beats/min) to obtain $V_O_2$ per beat in steady state. This signal processing was performed on-line with a personal computer (PC-9801ES, NEC, Tokyo, Japan) and our laboratory-made signal-processing software. The RV was kept collapsed by continuous hydrostatic drainage of the coronary venous return, so that the RV PVA and hence PVA-
dependent \( V_{O_2} \) [11] (see Data analyses) were assumed to be negligible. The RV PVA-independent \( V_{O_2} \) (see Data analyses) was then calculated by multiplying biventricular PVA-independent \( V_{O_2} \) in each contractile state with the ratio of RV weight divided by the sum of RV and LV weights. The RV PVA-independent \( V_{O_2} \) was subtracted from the total \( V_{O_2} \) to yield LV \( V_{O_2} \). At the end of each experiment, the LV including the septum and the RV free wall were separately weighed. They were \( 0.79 \pm 0.08 \) and \( 0.32 \pm 0.07 \) g, respectively.

**Contractility (\( E_{max} \)).** LV contractility was assessed by \( E_{max} \). LV pressure \( P(t) \) and volume \( V(t) \) data were sampled at 2-ms intervals and processed with the personal computer. LV \( E_{max} \) of each sampled contraction was determined as the maximum ratio of \( P(t)/[V(t) - V_0] \) [16]. \( V_0 \) was obtained by extrapolating the line passing through peak isovolumic pressure \( (P) \)-volume \( (V) \) data points obtained in the volume loading run (see Experimental Protocol) to zero pressure and recognized as the volume at which peak isovolumic pressure and hence PVA would be zero. The \( E_{max} \) of isovolumic contractions at a constant volume was proportional to peak isovolumic pressure. \( E_{max} \) was normalized for \( 1 \) g LV and presented in mmHg · ml \(^{-1} \) · g \(^{-1} \).

**Pressure-volume area (PVA).** PVA of each beat was computed from the digitized \( P(t) \) and \( V(t) \) data as the area in the \( P-V \) diagram surrounded by the end-systolic \( P-V \) relation line, the end-diastolic \( P-V \) relation curve, and the isovolumic \( P-V \) trajectory line. PVA was normalized for \( 1 \) g LV and presented in mmHg · ml · beat \(^{-1} \) · g \(^{-1} \).

**Experimental protocol.** Experiments were performed in a total of seven hearts. The experimental protocol consisted of the following three categories. The first category was a volume loading run “VOL run” to obtain \( V_0 \) by extrapolation and a volume-loaded \( V_{O_2} \)-PVA relation of steady-state isovolumic contractions produced at 4–5 different LV volumes between 0.05 and 0.23 ml in 0.025-ml steps at a constant CPP of 60 mmHg.

The second category was “CPP run.” We increased mean CPP in steps every 3–5 min from 60 to 100 mmHg at a fixed LV volume (0.13 ± 0.02 ml). We measured peak LV pressure at each CPP level, and calculated \( E_{max} \) and PVA from this \( P-V \) data set and the extrapolated \( V_0 \), and obtained another \( V_{O_2} \)-PVA relation. The fixed LV volume in each heart corresponded to an intermediate level with an LV end-diastolic pressure of 1–5 mmHg at a constant mean CPP of 60 mmHg.

The third category was “Ca run.” CaCl\(_2\) (1%) was infused into the coronary perfusion tubing to gradually enhance contractility at the same fixed LV volume (0.13 ± 0.02 ml) and a constant CPP of 60 mmHg. The infusion rate of CaCl\(_2\) was increased in steps every 3–5 min, which was long enough for the contractility to reach a new stable level. We also measured peak LV pressure at each Ca infusion rate, calculated \( E_{max} \) and PVA from this peak \( P-V \) data set and the extrapolated \( V_0 \), and obtained a third \( V_{O_2} \)-PVA relation. The maximum infusion rate of CaCl\(_2\) was 2.75 ± 0.56 \( \mu \)mol/min. This corresponded to an increase in blood Ca\(^{2+}\) concentration by 2.42 ± 1.31 mmol/l at a coronary blood flow of 0.76–2.40 (1.40 ± 0.59 (SD))

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ml/min. In one heart, however, Ca run was not performed because of the artificial ventilation failure of the support guinea pig.

After ventricular pressure, coronary flow and AVO₂D all became stable, their measurements were started. In all of the three runs, $E_{\text{max}}$, $V_{O_2}$, PVA, and other data were measured and computed at least three times in each steady state, and these values were averaged to obtain a single set of mean data for each contraction condition.

Data analyses. Since $V_{O_2}$ and PVA are shown to be correlated linearly in canine hearts [13] and in rabbit hearts [4], we assume in the guinea pig heart that the $V_{O_2}$ and PVA data in each VOL run could be subjected to linear regression analysis. We, therefore, obtained a volume-loaded $V_{O_2}$-PVA relation: $V_{O_2} = a \text{PVA} + b$, where $a$ is the slope of the regression line and $b$ is the $V_{O_2}$ intercept. $a \text{PVA}$ corresponds to the PVA-dependent $V_{O_2}$ and $b$ to the PVA-independent $V_{O_2}$ [11]. The $V_{O_2}$ and PVA data in the CPP and Ca runs were also subjected to linear regression analysis to obtain the different types of $V_{O_2}$-PVA relations.

The PVA-independent $V_{O_2}$ for each $E_{\text{max}}$ level at a fixed LV volume during either the CPP or Ca run was calculated as $V_{O_2}$ minus PVA-dependent $V_{O_2}$ for the respective PVA [11]. This PVA-dependent $V_{O_2}$ was calculated as the product of the slope value $a$ and PVA of this contraction on the presumption that the slope $a$ was the same as the $a$ in the VOL run and was constant at each $E_{\text{max}}$ level in guinea pig hearts, as it is in canine hearts (see RESULTS) [11]. Thus, the PVA-independent $V_{O_2}$ at each $E_{\text{max}}$ level was calculated as LV $V_{O_2}$ minus $a \text{PVA}$ [11].

Statistics. Analysis of covariance (ANCOVA) was applied to compare the three regression lines of LV $V_{O_2}$ on PVA in each heart among the VOL, CPP, and Ca runs and to compare the two regression lines of LV PVA-independent $V_{O_2}$ on $E_{\text{max}}$ in each heart between CPP and Ca runs. Statistical significance of the differences in the slopes and elevations of the regression lines was tested by the F-test. Multiple comparison of paired individual values was performed by analysis of variance (ANOVA) and Bonferroni's t-test. Comparison of paired individual values was performed by paired t-test. A value of $p < 0.05$ was considered statistically significant. All data are expressed as mean±SD.

RESULTS

VOL run

Figure 1 shows highly linear relations between LV peak isovolumic (end-systolic) pressure (ESP) and LV volume in one heart under the two different $E_{\text{max}}$ levels: control and an increased $E_{\text{max}}$ by Ca loading at the maximal infusion rate. Similar relations were observed by increasing CPP. In every tested heart, the correlation coefficient between LV ESP and volume was very close to unity (0.984–0.999, 0.995±0.005, all $p < 0.05$). Their $E_{\text{max}}$ values were 666±58 mmHg·ml⁻¹·g in LV volume ranges of 0.095±0.013 and 0.195±0.013 ml in the seven hearts. In every heart, $V_{O_2}$ increased linearly with increases in PVA. Their correlation

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Fig. 1. A representative scatter diagram of left ventricular (LV) end-systolic pressure (ESP)-volume data points in VOL (volume loading) run obtained in one heart under the control $E_{\text{max}}$ level (solid squares) and an increased $E_{\text{max}}$ level by Ca loading at the maximal infusion rate (solid circles).

Fig. 2. Simultaneous tracings of mean coronary perfusion pressure (CPP), left ventricular isovolumic pressure (LVP), and left ventricular epicardial electrocardiogram (ECG) during CPP run. CPP was increased in steps of 10 mmHg from 60 to 100 mmHg.

coefficients were also close to unity ($0.872 \pm 0.999$, $0.973 \pm 0.043$, all $p < 0.05$). The slope $a$ and $V_{O_2}$ intercept $b$ of the $V_{O_2}$-PVA relation were $(8.39 \pm 3.36) \times 10^{-3} \mu l \ O_2 \cdot mmHg^{-1} \cdot ml^{-1}$ and $0.129 \pm 0.056 \mu l \ O_2 \cdot \text{beat}^{-1} \cdot g^{-1}$, respectively.

CPP run

Figure 2 shows a representative set of tracings of CPP, LVP, and ECG during
a CPP run in one heart. CPP was increased in steps of 10 mmHg from 60 to 100 mmHg. With increased CPP, LV ESP rose proportionally, but end-diastolic pressure (EDP) remained almost unchanged. Table 1 summarizes the changes in CPP, ESP, EDP, \( E_{\text{max}} \), PVA, AVO\(_2\)D, CF, and \( V_{O_2} \) per beat in all seven hearts. ESP, \( E_{\text{max}} \), and PVA increased with the stepwise increases in CPP. EDP at CPP of about 100 mmHg rose slightly but not significantly from the value at CPP of 60 mmHg. CF increased proportionally with increased CPP. Therefore, the coronary vascular tone was stable. In contrast to CF, AVO\(_2\)D at CPP of 100 mmHg slightly decreased but not significantly from the value at CPP of 60 mmHg. Therefore, \( V_{O_2} \) per beat increased proportionally from \( 0.233 \pm 0.091 \mu l \text{O}_2 \cdot \text{beat}^{-1} \cdot \text{g}^{-1} \) at CPP of 60 mmHg to \( 0.377 \pm 0.146 \mu l \text{O}_2 \cdot \text{beat}^{-1} \cdot \text{g}^{-1} \) at CPP of 100 mmHg.

**Ca run**

\( E_{\text{max}} \) and PVA increased proportionally with the stepwise increases in Ca infusion rate. \( E_{\text{max}} \) increased from \( 583 \pm 60 \) to \( 836 \pm 77 \text{mmHg} \cdot \text{ml}^{-1} \cdot \text{g} \) and PVA increased from \( 9.33 \pm 4.81 \) to \( 12.94 \pm 6.31 \text{mmHg} \cdot \text{ml} \cdot \text{beat}^{-1} \cdot \text{g}^{-1} \) at the maximum Ca infusion rate. CF also increased proportionally from \( 1.08 \pm 0.59 \) to \( 1.40 \pm 0.64 \) ml/min with the increases in Ca infusion rate.

<table>
<thead>
<tr>
<th>CPP (mmHg)</th>
<th>ESP (mmHg)</th>
<th>EDP (mmHg)</th>
<th>( E_{\text{max}} ) (mmHg · ml·beat(^{-1}) · g(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>59 ± 2</td>
<td>75 ± 25</td>
<td>5.0 ± 0.7</td>
<td>524 ± 113</td>
</tr>
<tr>
<td>70 ± 0*</td>
<td>85 ± 26*</td>
<td>6.0 ± 1.2</td>
<td>597 ± 113*</td>
</tr>
<tr>
<td>80 ± 0*</td>
<td>100 ± 21*</td>
<td>6.3 ± 1.2</td>
<td>721 ± 58*</td>
</tr>
<tr>
<td>90 ± 1*</td>
<td>110 ± 20*</td>
<td>6.7 ± 0.9</td>
<td>800 ± 74*</td>
</tr>
<tr>
<td>99 ± 1*</td>
<td>119 ± 19*</td>
<td>7.7 ± 1.2</td>
<td>870 ± 82*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PVA (mmHg · ml·beat(^{-1}) · g(^{-1}))</th>
<th>AVO(_2)D (vol%)</th>
<th>CF (ml·min(^{-1}) · g(^{-1}))</th>
<th>( V_{O_2} ) (( \mu l \cdot \text{beat}^{-1} \cdot \text{g}^{-1} ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.6 ± 4.6</td>
<td>4.96 ± 1.06</td>
<td>0.98 ± 0.27</td>
<td>0.233 ± 0.091</td>
</tr>
<tr>
<td>10.8 ± 5.1*</td>
<td>4.68 ± 0.97</td>
<td>1.20 ± 0.36*</td>
<td>0.271 ± 0.112</td>
</tr>
<tr>
<td>12.3 ± 5.1*</td>
<td>4.49 ± 0.95</td>
<td>1.46 ± 0.46*</td>
<td>0.311 ± 0.125*</td>
</tr>
<tr>
<td>13.5 ± 5.5*</td>
<td>4.09 ± 0.88</td>
<td>1.77 ± 0.59*</td>
<td>0.345 ± 0.144*</td>
</tr>
<tr>
<td>14.3 ± 5.6*</td>
<td>3.90 ± 1.01</td>
<td>2.12 ± 0.84*</td>
<td>0.377 ± 0.146*</td>
</tr>
</tbody>
</table>

Values are mean ± SD at a constant left ventricular end-diastolic volume of 0.13 ± 0.02 ml. CPP, coronary perfusion pressure; ESP, left ventricular peak isovolumic (end-systolic) pressure; EDP, left ventricular end-diastolic pressure; \( E_{\text{max}} \), slope of end-systolic pressure-volume relation line; PVA, systolic pressure-volume area; AVO\(_2\)D, coronary arteriovenous oxygen content difference; CF, coronary blood flow; \( V_{O_2} \), myocardial oxygen consumption. *\( p < 0.05 \) compared with the value at CPP of 60 mmHg; †\( p < 0.01 \) compared with the value at CPP of 60 mmHg.
**V_{O_2}-PVA relation**

Figure 3A shows the $V_{O_2}$-PVA relations obtained in VOL, CPP, and Ca runs in one heart. The $V_{O_2}$-PVA slopes in CPP and Ca runs were significantly steeper than that in VOL run ($p < 0.05$), but the former slopes were not different from each other by ANCOVA. All other hearts showed similar results to this heart. Figure 3B compares the mean slope values of the $V_{O_2}$-PVA regression lines in the VOL, CPP, and Ca runs in all seven hearts. The mean slopes in the VOL, CPP, and Ca runs were compared by ANOVA and Bonferroni's $t$-test. The mean slope in the CPP run was greater than that in the VOL run ($p < 0.001$). However, there was no significant difference in mean slopes between the two regression lines in the CPP and Ca runs.

**PVA-independent $V_{O_2}$-$E_{max}$ relations**

Figure 4A plots PVA-independent $V_{O_2}$ values against the corresponding $E_{max}$ values in the CPP and Ca runs in the same heart as shown in Fig. 3A. PVA-independent $V_{O_2}$ values for corresponding $E_{max}$ values were calculated by the method described in *Data analyses* on the assumption that the method for canine hearts [11] was applicable to guinea pig hearts. (In fact, we found a piece of evidence supportive of this assumption in one preliminary experiment. Figure 5

![Graph A](image)

**Fig. 3.** (A) shows a representative scatter diagram of $V_{O_2}$-PVA data points in VOL run (solid circle), CPP run (open square), and Ca run (open circle) and their regression lines of $V_{O_2}$ on PVA. The slope in CPP run and Ca run was significantly steeper than that in VOL run, but there were no significant differences in slope between CPP and Ca runs (ANCOVA). (B) compares the slopes (mean±SD) of the $V_{O_2}$-PVA regression lines in VOL, CPP, and Ca runs. The slope in CPP run was significantly larger than that in VOL run ($p < 0.001$). However, there was no significant difference in slopes between CPP and Ca runs.

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Fig. 4. (A) shows representative plots of the PVA-independent $V_{O_2}$ values against corresponding $E_{\text{max}}$ values in CPP and Ca runs of the same heart as shown in Fig. 4A. The slopes of the two regression lines were not significantly different (ANCOVA). (B) compares the slopes (mean±SD) of the PVA-independent $V_{O_2}$-$E_{\text{max}}$ regression lines in CPP and Ca runs. There was no significant difference in slope between CPP and Ca runs.

Fig. 5. Two $V_{O_2}$-PVA regression lines in VOL run at two different $E_{\text{max}}$ levels at 60 and 100 mmHg of CPP in one heart. The slopes of the two regression lines were not significantly different (ANCOVA).

shows two $V_{O_2}$-PVA regression lines in the VOL run at two different $E_{\text{max}}$ levels at 60 and 100 mmHg of CPP in one guinea pig heart. The slopes of the two regression lines were not significantly different (ANCOVA). Neither the slope nor the elevation was significantly different between these two regression lines.
(ANCOVA). All other hearts showed similar results to this heart. Figure 4B compares the mean slopes of PVA-independent \( V_{O_2} \)-\( E_{\text{max}} \) regression lines in the CPP and Ca runs. There was no significant difference in mean slopes between these two regression lines.

**DISCUSSION**

In the guinea pig excised, cross-circulated heart preparation, we for the first time obtained LV mechanoenergetic results substantially similar to those in the canine cross-circulated heart preparation, i.e., a reasonable \( E_{\text{max}} \) and linear \( V_{O_2} \)-PVA relation in the VOL run [13, 15, 16, 18, 19].

In the present study, we obtained obvious Gregg's phenomenon in that increases in CPP from 60 to 100 mmHg increased \( E_{\text{max}} \) significantly. The occurrence of Gregg's phenomenon per se has been reported in many studies [1, 2, 4–8, 14, 20–22], though Sunagawa et al. reported that the changes in CPP within the same range did not affect \( E_{\text{max}} \) in the isovolumic contracting canine heart [23]. However, its underlying mechanisms remain unknown.

Increases in intracoronary pressure have been speculated to enhance contractile performance by the resultant extension of the coronary vessels (garden hose effect) mediated via the Frank-Starling mechanism [1, 3, 4]. The Frank-Starling mechanism per se has not yet been completely explained [24]. In the Frank-Starling mechanism, the PVA-independent \( V_{O_2} \) can reasonably be assumed to be volume-independent [25, 26]. On the other hand, the increase in PVA-independent \( V_{O_2} \) would be expected considering an increased Ca sensitivity of myofilament with myocardial stretch as proposed by some investigators [24, 27–30]. We intended to investigate whether the underlying mechanisms of Gregg's phenomenon would involve primarily the Frank-Starling mechanism (garden hose effect) or any other mechanisms (such as augmentation of the excitation-contraction (E-C) coupling) or both.

The presently observed increase in PVA-independent \( V_{O_2} \) (which is considered to be almost equivalent to the increased energy utilization for the E-C coupling or primarily total Ca handling [11]) in the CPP run suggests that the increased contractile strength together with an increase in CPP was mainly due to an increase in total Ca handling as follows. In the VOL run, we assume that myocardial contractile strength increases with volume loading via the Frank-Starling mechanism. Based on the report by Yasumura et al. [26], the length-dependent increases in the PVA-independent \( V_{O_2} \) seem to be negligible. Thus, we assume that only PVA-dependent \( V_{O_2} \) increases with increasing contractile strength in the VOL run. In the Ca run, we assume that PVA-independent \( V_{O_2} \) increases, with a probable increase in Ca handling, and the resultant increases in PVA-dependent \( V_{O_2} \) for cross-bridge cycling occurs with increasing contractile strength.

The present study has revealed that the \( V_{O_2} \)-PVA regression line in the CPP run is almost identical to that in the Ca run at the same LV volume, but it is significantly
steeper than that in the VOL run; \( V_{O_2} \)-PVA data points in both CPP and Ca runs deviated upwards and to the right from the \( V_{O_2} \)-PVA relation in the VOL run. This indicates increases in PVA-independent \( V_{O_2} \) and the resultant increases in PVA-dependent \( V_{O_2} \) for cross-bridge cycling in the CPP run, as in the Ca run. Furthermore, the present study has revealed that the slope of the PVA-independent \( V_{O_2} - E_{max} \) regression line in the CPP run is not significantly different from that in the Ca run. This indicates that, in the CPP and Ca runs, increments in PVA-independent \( V_{O_2} \) for the same increment in \( E_{max} \) are not significantly different. On the basis of the proportionality between the amount of Ca handled in the E-C coupling and the Ca handling energy in the sarcoplasmic reticulum in normal hearts [11], we interpret the present result to indicate that the observed Gregg's phenomenon is mainly due to an increase in the amount of Ca handled in the E-C coupling. This interpretation could be supported by the postulate of Schouten et al. [22] whereby the perfusion-induced increase in contractile force in isolated papillary muscles is probably due to an increase in the amount of activator Ca. We cannot yet determine how the amount of Ca handled in the E-C coupling increases in the CPP run. However, we could speculate about at least the possibility of increases in the transsarcolemmal Ca influx and the releasable Ca from the sarcoplasmic reticulum.

In the present study, we varied CPP from 60 to 100 mmHg. We could not increase CPP above 100 mmHg because of severe aortic regurgitation; at CPP above 100 mmHg, blood leaked from the LV apical vent abruptly increased and the experiment could not be continued. Therefore, we started to increase CPP from 60 mmHg so that the range of CPP would be sufficient. In crystalloid-perfused ferret hearts at CPP below 60 mmHg, the concentrations of phosphorus-containing metabolites increased, lactate efflux occurred, and the developed pressure depended on CPP more steeply below 60 mmHg than above 60 mmHg [9]. In our study in blood-perfused guinea pig hearts, the dependence of LVP on CPP was linear between 60 and 100 mmHg. Therefore, it seems unlikely that significant ischemia existed in our preparation although we did not measure lactate efflux or intracellular pH. Furthermore, the observed linear dependence of LVP on CPP in the normal and subnormal coronary perfusion pressure range has characterized Gregg's phenomenon of both physiological and pathophysiological significance.

Cardiac energetic studies like our present one, which can fractionate myocardial oxygen consumption into PVA-dependent and PVA-independent fractions, are very useful to evaluate ventricular mechanical performance in relation to myocardial metabolism. Many recent mechanoenergetic studies have been performed by taking advantage of this \( V_{O_2} \)-PVA-\( E_{max} \) framework in canine cross-circulated heart preparations [11], and have given us many pieces of new information which could not have been obtained by other methods. However, alternative animal heart models have long been wanted for the canine cross-circulated heart preparation. Although the crystalloid-perfused heart preparations are popular in small animals [31], blood-perfused preparations are more preferable in terms of cardiac perform-
ance [4]. Blood perfusion seems to be much more physiological than crystallloid perfusion [4]. Our blood-perfused guinea pig heart preparation seems to be useful for studies of cardiac mechanoenergetics under physiological conditions.

We conclude that the increasing CPP enhances LV mechanoenergetics (E_{max}, PVA, and V_{O2}) mainly via increases in PVA-independent V_{O2} (probably total Ca handling energy in the E-C coupling) and the contractility-dependent increases in PVA-dependent V_{O2} (probably for cross-bridge cycling) in blood-perfused guinea pig hearts.

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