Effects of Intracoronary Fentanyl on Left Ventricular Mechanoenergetics in the Excised Cross-circulated Canine Heart (Revised Publication)

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Background: It is still unclear whether fentanyl directly alters left ventricular (LV) contractility and oxygen consumption. This is because of the difficulty in defining and evaluating contractility and energy use independently of ventricular loading conditions and heart rate in beating whole hearts.

Methods: This study was conducted to clarify the mechanoenergetic effects of intracoronary fentanyl in six excised cross-circulated canine hearts. The authors used the framework of the $E_{max}$ (a contractility index)—PVA (systolic pressure—volume area, a measure of total mechanical energy)—VO$_2$ (myocardial oxygen consumption per beat) relationship practically independent of ventricular loading conditions. The authors measured LV pressure, volume, coronary flow, and arteriogenous oxygen content difference to calculate $E_{max}$, PVA, and VO$_2$. They first obtained the VO$_2$—PVA relationship for varied LV volumes at control $E_{max}$. The authors then obtained the VO$_2$—PVA relationship at a constant LV volume, whereas coronary blood fentanyl concentration was increased in steps up to 240 ng/ml. Finally, they obtained the VO$_2$—PVA relationship for varied LV volumes at the final dose of fentanyl.

Results: Fentanyl at any concentrations did not significantly change $E_{max}$, PVA, and VO$_2$ from the control. The linear end-systolic pressure—volume relations and their slopes were virtually the same between the control and fentanyl volume loading in each heart. Further, either the slope (oxygen cost of PVA) or the VO$_2$ intercept (unloaded VO$_2$) of the linear VO$_2$—PVA relationship remained unchanged by fentanyl.

Conclusions: These results indicate that intracoronary fentanyl produces virtually no effects on LV mechanoenergetics for a wide range of its blood concentration. (Key words: Analgesics: narcotic; fentanyl. Heart: contractility; $E_{max}$: total mechanical energy; pressure—volume area. Myocardial oxygen consumption: oxygen cost of PVA, unloaded VO$_2$.)

In recent clinical anesthesia, the high-dose fentanyl anesthesia technique is adopted to avoid noxious stimuli for the patients either undergoing cardiac surgery or with poor left ventricular (LV) function. In these patients, anesthetic should produce no adverse effects on cardiac mechanoenergetics for a wide safety range of blood anesthetic concentration.

Most clinical and laboratory studies indicated little change in cardiac function after administration of fentanyl (10–160 μg/kg) alone. Some laboratory studies using isolated myocardium preparations indicated a marked negative inotropic effect of fentanyl at much higher concentrations than those achieved in clinical practice. Thus, it is still controversial whether fentanyl depresses cardiac contractile function (contractility).

In contrast to numerous studies on the effects on cardiac function, few studies have reported on the effects of fentanyl on cardiac energetics. Fentanyl did not affect cardiac energetics and blood flow distribution in dogs. Fentanyl was devoid of major direct effects on coronary circulation and myocardial metabolism in dogs, pigs, and rats. However, fentanyl markedly reduced coronary sinus blood flow and cardiac oxygen consumption per minute accompanied by bradycardia.
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whereas blood pressure and the maximal rate of increase of LV pressure (LV dp/dt) remained unchanged in dogs. Thus, it is not yet clear whether and to what extent fentanyl alters cardiac energetics and coronary circulation.

These contradictions may derive from the difficulty in defining and evaluating LV contractility and energy use in beating whole hearts independently of ventricular loading conditions and heart rate. We performed the present study to investigate whether intracoronary fentanyl produces any direct effects on LV mechanism energetics in the excised (denervated) cross-circulated (blood-perfused) canine heart. To evaluate the cardiac inotropic effect of fentanyl, we used a reliable contractility index, E\textsubscript{max}, practically independent of ventricular loading conditions. To assess the effects of fentanyl on cardiac energetics, we used the relationship between VO\textsubscript{2} (myocardial oxygen consumption per beat) and PVA (systolic pressure-volume area, a measure of total mechanical energy) of the LV.

**Methods and Materials**

*Theoretical Background*

The framework of the E\textsubscript{max}-PVA-VO\textsubscript{2} relationship has the following physiologic significance. E\textsubscript{max} is the maximal value of time-varying elastance and is determined as the maximal ratio of P(t)/[V(t)-V\textsubscript{t}]. P(t) means instantaneous LV pressure, V(t) means instantaneous LV volume, and V\textsubscript{t} means the volume at which LV peak isovolumic pressure is zero. E\textsubscript{max} is alternatively defined as the slope (E\textsubscript{sa}) of the end-systolic pressure-volume relationship (ESPVR) in a stable contractile condition (fig. 1A).\textsuperscript{23} E\textsubscript{max} sensitively reflects LV contractility, practically independent of ventricular pre- and afterloading conditions within their physiologic ranges.\textsuperscript{20-24}

Systolic pressure-volume area is a measure of total mechanical energy generated by an LV contraction.\textsuperscript{20-22,25-31} In an isovolumic contraction, PVA is composed only of potential energy and is quantified by the area in the pressure-volume (PV) diagram that is bounded by the ESPVR line, the end-diastolic PV relationship curve, and the systolic PV trajectory (fig. 1A). LV PVA closely and linearly correlates with LV VO\textsubscript{2} in a load-independent manner in a stable contractile state with a constant E\textsubscript{max} (fig. 1B).\textsuperscript{25-27} The slope (a) of the VO\textsubscript{2}-PVA relationship means the oxygen cost of PVA.\textsuperscript{20-22,27,29} VO\textsubscript{2} can be divided into the PVA-dependent and the PVA-independent VO\textsubscript{2} (unloaded VO\textsubscript{2}) components at the VO\textsubscript{2} intercept (b) of the VO\textsubscript{2}-PVA relationship. The PVA-dependent VO\textsubscript{2} corresponds to the energy use for crossbridge cycling, and the PVA-independent VO\textsubscript{2} corresponds to the energy use for total calcium handling in the excitation-contraction (E-C) coupling and for basal metabolism.\textsuperscript{20-22,27,29}

The VO\textsubscript{2}-PVA relationship usually shifts upward or downward in a parallel manner with an increase or decrease in E\textsubscript{max}, respectively (fig. 1C).\textsuperscript{25-27} When E\textsubscript{max} increases or decreases at a constant LV volume, a VO\textsubscript{2}-PVA point deviates upward or downward from the baseline VO\textsubscript{2}-PVA relationship and forms a new steeper VO\textsubscript{2}-PVA relationship, which traverses multiple parallel VO\textsubscript{2}-PVA relationships for different contractilities (E\textsubscript{max}). We called this steeper relationship the composite VO\textsubscript{2}-PVA relationship.\textsuperscript{20-22,29} In this relationship, the PVA-independent VO\textsubscript{2} of the data point increases or decreases in proportion to an increase or decrease in E\textsubscript{max}, respectively. The slope (c) of the relation between PVA-independent VO\textsubscript{2} and E\textsubscript{max} means the oxygen cost of E\textsubscript{max}, and the intercept (d) of this relationship indicates the PVA-independent VO\textsubscript{2} extrapolated to zero E\textsubscript{max} (fig. 1D).\textsuperscript{20-22,29} These features of the framework of the E\textsubscript{max}-PVA-VO\textsubscript{2} relationship have been thoroughly reviewed.\textsuperscript{20-22} We for the first time applied this mechanoenergetic framework to fentanyl.

*Surgical Preparation*

All procedures in this study conformed to US Institutional and National Institutes of Health animal care guidelines. Experiments were performed in six LVs of the excised cross-circulated canine heart preparation that have consistently been used in our laboratory.\textsuperscript{31} The surgical procedure has been described in detail elsewhere.\textsuperscript{25-27} Briefly, a pair of mongrel dogs (6-25 kg) were anesthetized with pentobarbital (30 mg/kg, intravenous) after the premedication with ketamine (10 mg/kg, intramuscular) and atropine (0.25 mg per dog, intramuscular), intubated, and ventilated artificially with room air. Anesthesia was stably maintained throughout the experiment. If necessary, we administered additional pentobarbital (< 5 mg/kg, intravenous) and had an enough interval for data acquisition (see Discussion section). The blood of each dog was heparinized (at least 10,000 IU per dog).

In each experiment, the larger dog was used as the metabolic supporter for the excised heart from the smaller dog. The chest of the donor (smaller) dog was opened mid sternally during artificial ventilation. Cross-circulation tubes were cannulated into the bilateral common carotid arteries and unilateral jugular vein of

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the support dog and connected to the left subclavian artery and the right ventricle (RV) via the right auricle of the donor dog, respectively. The donor heart was isolated from the systemic and pulmonary circulation by ligating the descending aorta, inferior vena cava,azygos vein, brachiocephalic artery, superior vena cava, and bilateral pulmonary hilus in this order. The heart was excised without interruption of coronary perfusion.

The left atrium of the excised heart was widely opened, and all LV chordae tendineae were cut. A thin rubber balloon (an unstressed volume, 50 ml) was fitted into the LV. The excised heart was placed in a box, and temperature of the heart was monitored and maintained at 35–37°C by warming the arterial tube and heating this box. The balloon was connected to our custom-made volume servo pump system (Air-Brown, Tokyo, Japan) and filled with water. This servo-pump system enabled us to control precisely and measure accurately LV volume. LV pressure was measured with a miniature pressure gauge (model P-7, Konigsberg Instruments, Pasadena, CA) placed inside the apical end of the balloon. LV volume and pressure signals were recorded on a strip-chart recorder and stored and processed with a signal-processing computer (7T18, NEC San-ei, Tokyo, Japan). LV epicardial electrocardiogram (ECG) was recorded by a pair of screw-in electrodes to trigger volume control with the servo pump and data acquisition with the processor. The left atrium was paced by a pair of clip electrodes to keep heart rate constant throughout each experiment (136 ± 15 beats/min; mean ± SD), approximately 20% above a spontaneous sinus rate to avoid arrhythmia.

Mean systemic arterial blood pressure of the support dog (112.0 ± 4.4 mmHg), which served as mean coronary perfusion pressure of the excised heart, was monitored in the arterial tube from the bilateral common carotid arteries. We maintained the perfusion pressure above 80 mmHg by primarily transusing whole blood from the donor dog and additionally hydroxyethyl starch solution (Hesperan®), 6%, as needed.

Arterial blood gases were repeatedly analyzed with
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a blood gas analyzer (ABL 350 Acid-Base Laboratory, Radiometer, Copenhagen, Denmark). At the beginning of data sampling, arterial blood gases were adjusted as follows: pH = 7.41 ± 0.02; PO₂ = 129.9 ± 19.1 mmHg; PCO₂ = 36.4 ± 3.3 mmHg; and base excess = −1.1 ± 1.9 mm). They were maintained within their physiologic ranges by adjusting artificial ventilation of the support dog and intravenous administrations of sodium bicarbonate as needed.

At the end of every experiment, we measured the weight of LV (54.2 ± 17.0 g), including the septum, and RV free wall (23.8 ± 6.6 g). The ratio of the RV weight to the biventricular weight was 30.7 ± 4.0%. These LV and RV weights were used to normalize $E_{max}$, PVA, and $VO_2$ for 100-g LV weight and to normalize coronary flow (CF) and coronary vascular resistance (CVR) for 100-g biventricular weight, as usual.20

Data Samplings and Analyses

We used isovolumic contractions (shown as arrows in fig. 1A) throughout this study. We considered that the contraction mode did not substantially affect the present results because the $VO_2$-PVA relationship is largely independent of the mode of contraction within physiologic loading conditions.27

Mechanics. We assessed LV contractility by $E_{max}$, P(t) and V(t) data were obtained at 2-ms intervals with the signal processor. In the inotropism run (See Experiment Protocol), we computed $E_{max}$ of isovolumic contractions simultaneously at data sampling with the predetermined $V_0$.23 In each volume loading run (See Experiment Protocol), we determined $E_0$ as the slope of the ESPVR regression line obtained from isovolumic contractions at 4–7 different LV volumes, including $V_0$ (fig. 1A).24 LV volume, $E_{max}$, and $E_0$ were normalized for 100-g LV weight and presented in ml/100 g and mmHg·ml·beat⁻¹·100 g⁻¹, respectively. Note that 100 g, not 100 g⁻¹, appears in the unit of $E_{max}$ and $E_0$. In addition, $T_{max}$ was determined as the time to $E_{max}$ from the onset of the R wave of ECG and served as a measure of the duration of systole.20,23

Energetics. Pressure–volume Area. We calculated PVA of each LV isovolumic contraction from the digitized P(t) and V(t) data in the same way as before (fig. 1A).20–22,25–27 PVA was normalized for 100-g LV and was presented in mmHg·ml·beat⁻¹·100 g⁻¹.

$VO_2$. We continuously measured coronary arteriovenous oxygen content difference ($AVO_2$) with a custom-made oximeter (PWA-2008, Shoe Technica Inc., Chiba, Japan). Blood hemoglobin concentration (10.0 ± 1.6 g/dl) was occasionally measured with a blood $O_2$ content analyzer (IL-382 CO-oximeter, Instrumentation Laboratory Inc., Lexington, MA, USA) and was kept high enough (5.0 g/dl) to measure accurate $AVO_2$.20–35 CF was also continuously measured with an electromagnetic flow meter (MVF-3200, Nihon Kohden, Tokyo, Japan) placed in the coronary venous drainage tube from the RV (fig. 2). We neglected LV Thebesian flow because of its very small fraction (< 3%) in CF.20

Myocardial oxygen consumption of the excited heart per minute was obtained as the product of CF and coronary $AVO_2$. It was divided by the heart rate to obtain biventricular myocardial oxygen consumption per beat, $VO_2$. RV $VO_2$ was minimized by collapsing the RV by continuous hydrostatic drainage of the coronary venous return throughout the experiment and was considered to be constant, regardless of changes in LV PVA. The collapsed RV was assumed to have virtually zero PVA and, hence, no PVA-dependent $VO_2$ and biventricular PVA-independent $VO_2$ (mechanically unloaded $VO_2$) could be measured at $V_0$. Then, RV PVA-independent $VO_2$ was calculated as the product of the biventricular $VO_2$ at $V_0$ and the ratio of RV weight to the biventricular weight, and this value was subtracted from the total $VO_2$ to yield LV $VO_2$. Finally, LV $VO_2$ was normalized for 100-g LV and was presented in milliliters of $O_2$·beat⁻¹·100 g⁻¹.27

$VO_2$–pressure–volume area relationship. In the volume loading run, LV $VO_2$ and PVA data were subjected to linear regression analysis to obtain a volume loading $VO_2$–PVA relationship (fig. 1B). The equation of the linear

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VO2-PVA relationship, represented as \( \text{VO}_2 = a \text{ PVA} + b \), has the following meaningful interpretation: \( a \) is the slope of this relationship that represents the oxygen cost of PVA (in milliliters of \( \text{O}_2 \cdot \text{mmHg}^{-1} \cdot \text{ml}^{-1} \)), \( a \) PVA represents the PVA-dependent \( \text{VO}_2 \), and \( b \) is the \( \text{VO}_2 \) intercept that represents the PVA-independent \( \text{VO}_2 \) (unloaded \( \text{VO}_2 \)).

In the inotropism run, the oxygen cost of \( E_{\text{max}} \) of fentanyl could be obtained from the composite VO2-PVA relationship if LV contractility (\( E_{\text{max}} \)) changes in a dose-dependent manner (fig. 1C, 1D).

**Coronary Circulation.** Coronary flow was regarded as total biventricular perfusion flow and normalized for 100-g biventricular weight. Coronary perfusion pressure was divided by the normalized CF to yield CVR. CF was presented in ml · min⁻¹ · 100 g⁻¹, and CVR was presented in mmHg · ml⁻¹ · min⁻¹ · 100 g.

**Experimental Protocol**

The experimental protocol consisted of three runs to be described. \( E_{\text{max}} \), PVA, \( \text{VO}_2 \), and other data were repeatedly measured at least three times to obtain a single set of mean data for each loading and inotropic condition.

1) **Control volume loading run**: Stable isovolumetric contractions were produced at 4–7 different LV volumes including \( V_0 \) between 8.0–44.0 ml/100 g. Peak isovolumic pressure ranged between 0 (at \( V_{\text{bo}} \)) and 189 mmHg.

2) **Fentanyl inotropism run**: Fentanyl solution (50 \( \mu \)g/ml) was diluted to 20 \( \mu \)g/ml with 1.5% NaCl to have physiologic osmolarity (0.9% NaCl). Fentanyl was infused into the coronary artery via the cross-circulation tubes through the left subclavian artery with an infusion pump (STC-521, Terumo, Tokyo, Japan; see fig. 2). In two preliminary experiments, we confirmed that intracoronary infusion of saline alone did not affect \( E_{\text{max}} \), PVA, and \( \text{VO}_2 \) data at the maximal infusion rate of the pump (2.5 ml/min).

We fixed LV volume at an intermediate level (27.5 ± 6.1 ml/100 g) where peak isovolumic pressure was 96.1 ± 22.8 mmHg. The coronary blood fentanyl concentration was increased in steps from 0 (control) to 20, 40, and to 240 ng/ml by increasing the infusion rate. We calculated these concentrations simply by dividing the administration dose by concomitant CF at data sampling and neglected the redistributed fentanyl in these calculations as in our previous studies.

3) **Fentanyl volume loading run**: When the fentanyl concentration reached 240 ng/ml at the end of fentanyl inotropism run, we finally obtained a set of data at 4–7 different LV volumes in the same way as in the control volume loading run.

**Statistics**

The VO2-PVA linear relationships of the control and fentanyl volume runs were compared by analysis of covariance (ANCOVA) in each heart. The significance of the differences in their slopes and elevations was tested by F test. Comparison of control mean values paired with those of fentanyl was performed by Student’s paired t test. A value of \( P < 0.05 \) was considered statistically significant. All data are presented as mean ± SD.

**Results**

In two preliminary experiments, we confirmed that neither \( E_{\text{max}} \) nor the VO2-PVA relationship changed for more than 5 h without any intervention after the onset of cross-circulation, except for transusions and administration of bicarbonate. Therefore, we performed each experiment within 5 h after the onset of cross-circulation.

Table 1 shows the data of mechanoeffectics and coronary circulation in the six hearts during the fentanyl inotropism run. None of them were significantly changed by fentanyl at any coronary blood concentrations.

Table 2 compares a pair of regression lines in the control and fentanyl (240 ng/ml) volume loading runs in each heart; the slope (\( E_{\text{max}} \)) of the ESPVR, the slope and the VO2-axis intercept of the VO2-PVA relationship, and correlation coefficient (\( r \)) are shown. All ESPVRs and VO2-PVA relationships in the control and fentanyl volume loading runs had high and linear correlation; correlation coefficient was always nearly equal to 1.000.

**Mechanics**

In the fentanyl inotropism run, \( E_{\text{max}} \) never decreased significantly at any concentrations at least up to 240 ng/ml in any heart (table 1).

Between the control and fentanyl volume loading runs in each heart, the ESPVR and its slope were the same (table 2). Figure 3A shows representative data of ESPVRs (experiment 6). These ESPVRs are virtually superimpos-
Table 1. Effects of Fentanyl on Left Ventricular Mechanoenergetics and Coronary Circulation in Fentanyl Inotropism Run

<table>
<thead>
<tr>
<th></th>
<th>HR (beat.min⁻¹)</th>
<th>LVP (mmHg)</th>
<th>Eₘₐₓ (mmHg. ml⁻¹. 100 g⁻¹)</th>
<th>Tₘₐₓ (min)</th>
<th>PVA</th>
<th>V̇O₂ (ml.min⁻¹. 100 g⁻¹)</th>
<th>CF</th>
<th>AVO₂.D (vol %)</th>
<th>CVR (mmHg. ml⁻¹. 100 g⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>136 ± 16</td>
<td>98.1 ± 22.8</td>
<td>6.9 ± 3.2</td>
<td>178 ± 36</td>
<td>689 ± 94</td>
<td>0.036 ± 0.010</td>
<td>70 ± 18</td>
<td>6.4 ± 1.8</td>
<td>1.82 ± 0.51</td>
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<tr>
<td>Fentanyl</td>
<td>20 ng ml⁻¹</td>
<td>136 ± 16</td>
<td>94.8 ± 20.3</td>
<td>6.8 ± 3.0</td>
<td>177 ± 36</td>
<td>681 ± 95</td>
<td>0.036 ± 0.010</td>
<td>70 ± 18</td>
<td>6.4 ± 1.9</td>
</tr>
<tr>
<td></td>
<td>40 ng ml⁻¹</td>
<td>136 ± 16</td>
<td>95.8 ± 19.4</td>
<td>6.9 ± 3.0</td>
<td>179 ± 37</td>
<td>686 ± 96</td>
<td>0.036 ± 0.011</td>
<td>68 ± 22</td>
<td>6.4 ± 1.9</td>
</tr>
<tr>
<td></td>
<td>240 ng ml⁻¹</td>
<td>136 ± 16</td>
<td>95.5 ± 19.5</td>
<td>6.9 ± 3.0</td>
<td>179 ± 37</td>
<td>686 ± 87</td>
<td>0.034 ± 0.010</td>
<td>66 ± 22</td>
<td>6.3 ± 1.9</td>
</tr>
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</table>

Each value (mean ± SD) was obtained from the data in the fentanyl inotropism run at a constant intermediate left ventricular (LV) volume (27.3 ± 6.1 ml. 100 g⁻¹) in the six experiments. There is no significant difference of any variable between control and fentanyl at any concentration by Student’s paired t test (n = 6).

HR = heart rate (beat.min⁻¹); LVP = LV pressure (mmHg); Eₘₐₓ = a contractility index (mmHg. ml⁻¹. 100 g⁻¹); Tₘₐₓ = time from the onset of contraction to Eₘₐₓ (min); PVA = systolic pressure-volume area, a measure of total mechanical energy (mmHg. ml⁻¹. 100 g⁻¹); V̇O₂ = oxygen consumption per beat (ml O₂. beat⁻¹. 100 g⁻¹); CF = coronary flow (ml.min⁻¹. 100 g⁻¹); AVO₂.D = coronary arteriovenous oxygen content difference (vol %); CVR = coronary vascular resistance (mmHg. ml⁻¹. 100 g⁻¹).

Table 2. Effects of Fentanyl on Left Ventricular Mechanoenergetics in Volume Loading Run

<table>
<thead>
<tr>
<th>Experiment No.</th>
<th>Run</th>
<th>HR (beat.min⁻¹)</th>
<th>Eₘₐₓ (mmHg. ml⁻¹. 100 g⁻¹)</th>
<th>Tₘₐₓ (min)</th>
<th>VO₂ (ml.min⁻¹. 100 g⁻¹)</th>
<th>O₂ Cost of PVA</th>
<th>Unloaded VO₂</th>
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<tr>
<td>1</td>
<td>120</td>
<td>0.996</td>
<td>4.0</td>
<td>229</td>
<td>0.997</td>
<td>2.03</td>
<td>0.023</td>
</tr>
<tr>
<td>2</td>
<td>120</td>
<td>0.999</td>
<td>4.1</td>
<td>229</td>
<td>0.994</td>
<td>1.79</td>
<td>0.022</td>
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<tr>
<td>3</td>
<td>120</td>
<td>0.997</td>
<td>4.3</td>
<td>213</td>
<td>0.994</td>
<td>1.36</td>
<td>0.018</td>
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<tr>
<td>4</td>
<td>162</td>
<td>0.984</td>
<td>4.2</td>
<td>214</td>
<td>0.910</td>
<td>1.30</td>
<td>0.021</td>
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<tr>
<td>5</td>
<td>162</td>
<td>0.989</td>
<td>7.0</td>
<td>140</td>
<td>0.956</td>
<td>1.30</td>
<td>0.026</td>
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<tr>
<td>6</td>
<td>139</td>
<td>0.999</td>
<td>4.5</td>
<td>165</td>
<td>0.928</td>
<td>1.44</td>
<td>0.023</td>
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<td></td>
<td>139</td>
<td>0.994</td>
<td>4.5</td>
<td>167</td>
<td>0.977</td>
<td>1.16</td>
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<td>136</td>
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<td>153</td>
<td>0.998</td>
<td>1.35</td>
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<td>136</td>
<td>0.980</td>
<td>8.7</td>
<td>153</td>
<td>0.993</td>
<td>2.29</td>
<td>0.023</td>
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<tr>
<td></td>
<td>139</td>
<td>0.905</td>
<td>10.4</td>
<td>166</td>
<td>0.987</td>
<td>1.94</td>
<td>0.036</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>136 ± 16</td>
<td>0.996 ± 0.004</td>
<td>6.5 ± 2.7</td>
<td>178 ± 35</td>
<td>0.988 ± 0.016</td>
<td>1.71 ± 0.43</td>
<td>0.024 ± 0.007</td>
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<tr>
<td>VO₂-PVA Relation</td>
<td></td>
<td>r</td>
<td></td>
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<tr>
<td></td>
<td>0.961 ± 0.035</td>
<td>6.2 ± 2.4</td>
<td>179 ± 35</td>
<td>0.961 ± 0.035</td>
<td>6.4 ± 0.42</td>
<td>0.023 ± 0.007</td>
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</table>

These results were calculated from the data in control and fentanyl (240 ng/ml) volume loading runs. Analysis of covariance (ANCOVA) was applied to comparisons of the slope and the VO₂-axis intercept of the VO₂-PVA regression lines in each heart (F test was used for the comparisons), and the differences of mean value were tested by Student’s paired t test (n = 6).

ESPVR = the end-systolic pressure-volume relation; NS = statistically not significant; O₂ cost of PVA = slope of the VO₂-PVA relation (10⁻³ ml O₂. mmHg⁻¹. ml⁻¹); Unloaded VO₂ = the VO₂-axis intercept of the VO₂-PVA relation, virtually equal to VO₂ for unloaded contraction with zero PVA (ml O₂. beat⁻¹. 100 g⁻¹).

* Statistically significant at P < 0.05.

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Energetics

Between the control and fentanyl volume loading runs in each heart, neither the slope nor the VO₂ intercept of the VO₂-PVA relationships showed any significant differences by ANCOVA, except the VO₂-PVA intercept in experiment 4 (table 2). Figure 3B shows a representative set of the VO₂-PVA relationships (experiment 6). Both VO₂-PVA relationships are superimposable. In any of the six hearts, the mean values of neither the slope nor the

able. In any of the six hearts, the mean values of Eₘₐₓ showed no significant difference by Student’s t test (table 2). These results indicate that fentanyl at 240 ng/ml concentrations produced virtually no direct inotropic effect on LV in the excised cross-circulated canine heart.

Fentanyl did not significantly change Tₘₐₓ as shown in tables 1 and 2, indicating that fentanyl did not affect the duration of systole.
The VO₂ intercept of the VO₂–PVA relationships showed any significant differences by Student's t test (table 2). These results indicate that fentanyl did not affect the oxygen cost of PVA and unloaded VO₂ (fig. 1B).

In the fentanyl inotropic run, the VO₂–PVA points never deviated from the control point at any concentrations, corresponding to a constant Eₘₐₓ. Therefore, we could not obtain any composite VO₂–PVA relationship for fentanyl. Consequently, the oxygen cost of Eₘₐₓ was not applicable to fentanyl (fig. 1C, 1D).

Coronary Circulation

In the fentanyl inotropic run, AVO₂,D, CF, and CVR remained unchanged at any concentrations (table 1). These results indicate that intracoronary fentanyl did not interfere with the coronary circulation.

Discussion

This is the first study to have assessed the direct effects of fentanyl on LV mechanoenergetics using the framework of the Eₘₐₓ–PVA–VO₂ relationship. The present results indicate that intracoronary fentanyl has no effects on LV mechanoenergetics. These results are reliable because this mechanoenergetic relationship is practically independent of ventricular loading conditions.20–22 In contrast to conventional myocardial contractility indexes, such as LV dp/dtₘₐₓ and maximal unloaded shortening velocity (Vₘₐₓ), Eₘₐₓ and Eₙₛ are considered to be less dependent on ventricular loading conditions.14,20 Although the effects of fentanyl on cardiac mechanics were previously analyzed by using LV dp/dtₘₐₓ, this index depends on preload, afterload, and heart rate.12,13,16

To evaluate LV mechanoenergetics, we adopted the excised cross-circulated (blood-perfused) canine heart preparation. For clinical relevance, the intact in situ whole heart preparation is the most ideal. However, the in situ beating heart includes many complicating factors because it is hardly possible to control various ventricular loading conditions and exclude any extracardiac inotropic interventions other than intracoronary fentanyl. In the present preparation, we could control LV volume directly and measure LV pressure–volume data and myocardial oxygen consumption precisely.23–35

Blood Fentanyl Concentration

The blood maximal fentanyl concentration we used in the present study (240 ng/ml) is relatively higher than that in the usual clinical and experimental dose. During the induction of clinical anesthesia with a bolus injection of fentanyl (30 µg/kg, 60 µg/kg,9 and 75 µg/kg10), mean blood fentanyl concentrations ranged within 20–160 ng/ml. During the maintenance of fentanyl action, 10–40 ng/ml of fentanyl was required to avoid noxious stimuli sufficiently.8,9,11 Further, in dogs and humans, 30 ng/ml of fentanyl was reported to be sufficient for saturating the general opiate receptors and reaching the maximal effects.15 However, there was another study reporting that the requirements as an analgesic in the dog vary enormously (25–760 ng/ml) and are extremely high in some animals.34

Experimental Implications

In recent cardiac studies, conscious animals are frequently used to avoid any interference of general anesthetics with experimental data. However, certain preparations require general anesthesia for technical and ethical reasons. The present results indicate that the cardiac mechanoenergetic data during fentanyl treatment are highly favorable. We previously reported that pentobar-
bital widely used in animal studies initially had positive and then negative inotropism over 25 \( \mu g/ml \) of coronary blood concentration, suggesting a narrow safety range of blood concentration in terms of the interference with LV mechanoenergetics.\(^{31} \) Therefore, we consider that fentanyl is more beneficial than pentobarbital for the excised cross-circulated heart preparation to obtain cardiac mechanoenergetic data.

**Clinical Implications**

The present results indicate no direct effects of fentanyl on LV mechanoenergetics up to a much higher concentration than the usual clinical dose. In laboratory studies using isolated myocardiad preparations, some investigators have reported a marked direct negative inotropic effect of fentanyl.\(^{16,17} \) However, these studies are often performed during unphysiologic conditions such as crystalloid-perfusate, low-temperature, and insufficient oxygen supply. Our preparation is blood-perfused, normothermic, and sufficient oxygen supply, but subject is denervated. Therefore, our present results may not be simply applicable to clinical practice. Further, fentanyl is an analgesic and does not provide reliable unconsciousness. Consequently, it should not be used as a solitary anesthetic in animals or in humans without supplementary hypnotic drugs.

**Methodologic Considerations**

Certain methodologic issues in the present study should be discussed. First, the heart preparation required general anesthesia, and any cardiac effects of the general anesthesia with pentobarbital may have affected the present data. A bolus injection of pentobarbital (30 mg/kg) in dogs has been reported to depress LV contractility only for the first 15–30 min\(^{32} \) and thereafter it maintains a satisfactory anesthetic level with a constant blood concentration between 1–4 h without depressing LV contractility.\(^{36} \) We administered 30 mg/kg of pentobarbital as used in these studies and started the data acquisition at least 1 h after the surgical procedures. If we observed hypertension or spontaneous movement of the support dog as a sign of inadequate anesthesia, we administered additional pentobarbital with an infusion pump by an intravenous slow injection (50–100 mg over 5 min) and had a sufficient interval (at least 15 min) before the next data acquisition not to affect LV contractility of the excised heart. Consequently, we considered that we could anesthetize the support dogs sufficiently and stably throughout the experiment and could avoid any interference by pentobarbital to the excised hearts.

Second, the possibility that the accumulated fentanyl in the support dog may have produced any indirect effects on the excised heart should be discussed.\(^{5,6,8} \) We infused fentanyl cumulatively less than 300 \( \mu g \) (\(< 20 \mu g/kg \) of the support dog) over 1 h in each experiment. We considered that such slowly infused fentanyl was fully diluted and ineffective for the support dogs. We measured blood catecholamine concentration of the support dog during the fentanyl inotropism, which was run in six preliminary experiments. The coronary arteriolar blood concentration of epinephrine (control, 0.318 ± 0.335 ng/ml) remained unchanged (\( P > 0.05 \)) at 20 ng/ml (0.168 ± 0.176 ng/ml) and 240 ng/ml (0.078 ± 0.052 ng/ml) of intracoronary fentanyl. The concentration of norepinephrine (control, 0.688 ± 0.661 ng/ml) also remained unchanged (\( P > 0.05 \)) at 20 ng/ml (1.443 ± 1.646 ng/ml) and 240 ng/ml (1.356 ± 1.622 ng/ml). Therefore, we exclude the possibility that any indirect effects of fentanyl mediated via the support dog’s catecholamine may have affected our present data.

**Conclusions**

We have clarified the effects of intracoronary fentanyl on LV mechanoenergetics in the excised cross-circulated (blood-perfused) canine hearts using the framework of the \( E_{max} - PVA - VO_2 \) relationship. The present results indicate that intracoronary fentanyl produces no effects on LV mechanoenergetics for a wide range of blood concentration, which suggests that fentanyl is a better management choice for experimental animals’ general anesthesia required in cardiac studies such as the present mechanoenergetic study. Further, we could suggest that fentanyl anesthesia is suitable for the patients whose LV contractility and energy use have little reserve.

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