

## Effects of Intracoronary Fentanyl on Left Ventricular Mechanoenergetics in the Excised Cross-circulated Canine Heart

Kunihisa Kohno, M.D.,\* Miyako Takaki, Ph.D.,† Kazunari Ishioka, M.D.,‡ Yasunori Nakayama, M.D.,§ Shunsuke Suzuki, M.D.,§ Junichi Araki, M.D.,|| Taketoshi Namba, M.D.,# Hiroyuki Suga, M.D., DMSc.\*\*

**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 arteriovenous 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.<sup>1-11</sup> In these patients, an 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  $\mu\text{g/kg}$ ) alone.<sup>1-7,12-15</sup> 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.<sup>16,17</sup> 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.<sup>12,18</sup> Fentanyl was devoid of major direct effects on coronary circulation and myocardial metabolism in dogs, pigs, and rats.<sup>19</sup> However, fentanyl markedly reduced coronary sinus blood flow and cardiac oxygen consumption per minute accompanied by bradycardia,

\* Postdoctoral Fellow, Department of Anesthesiology and Resuscitology.

† Professor, Department of Physiology II, Nara Medical University.

‡ Senior Research Fellow, Department of Anesthesiology and Resuscitology.

§ Postdoctoral Fellow, Department of Physiology II.

|| Assistant Professor, Department of Physiology II.

# Assistant Professor, Department of Anesthesiology and Resuscitology.

\*\* Professor and Chairman, Department of Physiology II.

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Address reprint requests to Dr. Takaki: Professor, Department of Physiology II, Nara Medical University, 840 Shijo-cho, Kashihara 634, Japan.



whereas blood pressure and the maximal rate of increase of LV pressure ( $LV\ dp/dt_{max}$ ) remained unchanged in dogs.<sup>13</sup> 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.<sup>14</sup>

We performed the present study to investigate whether intracoronary fentanyl produces any direct effects on LV mechanoenergetics in the excised (denervated) cross-circulated (blood-perfused) canine heart. To evaluate the cardiac inotropic effect of fentanyl, we used a reliable contractility index,  $E_{max}$ , practically independent of ventricular loading conditions.<sup>20-24</sup> To assess the effects of fentanyl on cardiac energetics, we used the relationship between  $VO_2$  (myocardial oxygen consumption per beat) and PVA (systolic pressure-volume area, a measure of total mechanical energy) of the LV.<sup>20-22,25-29</sup>

## Methods and Materials

### Theoretical Background

The framework of the  $E_{max}$ -PVA- $VO_2$  relationship has the following physiologic significance.  $E_{max}$  is the maximal value of time-varying elastance and is determined as the maximal ratio of  $P(t)/[V(t)-V_0]$ .<sup>23</sup>  $P(t)$  means instantaneous LV pressure;  $V(t)$  means instantaneous LV volume, and  $V_0$  means the volume at which LV peak isovolumic pressure is zero.  $E_{max}$  is alternatively defined as the slope ( $E_{es}$ ) of the end-systolic pressure-volume relationship (ESPVR) in a stable contractile condition (fig. 1A).<sup>24</sup>  $E_{max}$  sensitively reflects LV contractility, practically independent of ventricular pre- and afterloading conditions within their physiologic ranges.<sup>20-24</sup>

Systolic pressure-volume area is a measure of total mechanical energy generated by an LV contraction.<sup>20-22,25-31</sup> In an isovolumic contraction, PVA is composed only of potential energy and is quantified by the area in the pressure-volume (P-V) diagram that is bounded by the ESPVR line, the end-diastolic P-V relationship curve, and the systolic P-V trajectory (fig. 1A). LV PVA closely and linearly correlates with LV  $VO_2$  in a load-independent manner in a stable contractile state with a constant  $E_{max}$  (fig. 1B).<sup>25-27</sup> The slope (a) of the  $VO_2$ -PVA relationship means the oxygen cost of PVA.<sup>20-22,27,29</sup>  $VO_2$  can be divided into the PVA-dependent and the PVA-independent  $VO_2$  (unloaded  $VO_2$ ) components at the  $VO_2$  intercept (b) of the  $VO_2$ -PVA rela-

tionship. The PVA-dependent  $VO_2$  corresponds to the energy use for crossbridge cycling, and the PVA-independent  $VO_2$  corresponds to the energy use for total calcium handling in the excitation-contraction (E-C) coupling and for basal metabolism.<sup>20-22,27,29</sup>

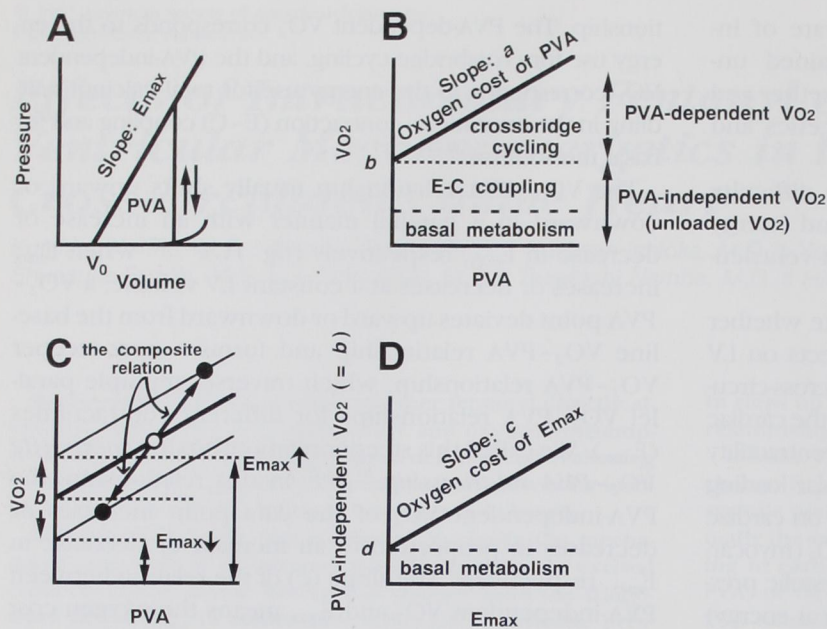
The  $VO_2$ -PVA relationship usually shifts upward or downward in a parallel manner with an increase or decrease in  $E_{max}$ , respectively (fig. 1C).<sup>25-27</sup> When  $E_{max}$  increases or decreases at a constant LV volume, a  $VO_2$ -PVA point deviates upward or downward from the baseline  $VO_2$ -PVA relationship and forms a new steeper  $VO_2$ -PVA relationship, which traverses multiple parallel  $VO_2$ -PVA relationships for different contractilities ( $E_{max}$ ). We called this steeper relationship *the composite  $VO_2$ -PVA relationship*.<sup>20-22,29</sup> In this relationship, the PVA-independent  $VO_2$  of the data point increases or decreases in proportion to an increase or decrease in  $E_{max}$ , respectively. The slope (c) of the relation between PVA-independent  $VO_2$  and  $E_{max}$  means the oxygen cost of  $E_{max}$ , and the intercept (d) of this relationship indicates the PVA-independent  $VO_2$  extrapolated to zero  $E_{max}$  (fig. 1D).<sup>20-22,29</sup> These features of the framework of the  $E_{max}$ -PVA- $VO_2$  relationship have been thoroughly reviewed.<sup>20-22</sup> 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.<sup>31</sup> The surgical procedure has been described in detail elsewhere.<sup>25-27</sup> 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 U 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 midsternally during artificial ventilation. Cross-circulation tubes were cannulated into the bilateral common carotid arteries and unilateral jugular vein of





loaded  $\text{VO}_2$ ) corresponding to the energy use for the total calcium handling in the excitation-contraction (E-C) coupling and for basal metabolism. *C*, Three volume loading  $\text{VO}_2$ -PVA relationships in the baseline contractility (*thick solid line*) and in two altered contractilities (*thin solid lines*). They usually are parallel to each other, having the same oxygen cost of PVA (slope *a*). Only the PVA-independent  $\text{VO}_2$  (*b*, indicated by arrows) increases or decreases as  $E_{\max}$  increases or decreases, respectively. In an inotropism run at a constant LV volume,  $\text{VO}_2$ -PVA data point (*filled circle*) deviating from a baseline data (*empty circle*) with changes in  $E_{\max}$  forms a new steeper relationship. This steeper  $\text{VO}_2$ -PVA relationship is the composite  $\text{VO}_2$ -PVA relationship (upward and downward relationships are shown as *thick solid lines with arrow heads*). *D*, The relationship between the PVA-independent  $\text{VO}_2$  and  $E_{\max}$ . The slope *c* of this relationship represents the oxygen cost of  $E_{\max}$ , and the PVA-independent  $\text{VO}_2$  intercept *d* indicates the PVA-independent  $\text{VO}_2$  at zero  $E_{\max}$  nearly equal to basal metabolism.

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 hilli 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,  $\sim 50$  ml) was fitted into the LV. The excised heart was placed in a box, and temperature of the heart was monitored and maintained at  $35$ - $37^\circ\text{C}$  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 In-

struments, 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 ( $136 \pm 15$  beats/min; mean  $\pm$  SD), approximately 20% above a spontaneous sinus rate to avoid arrhythmia.

Mean systemic arterial blood pressure of the support dog ( $112.0 \pm 4.4$  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 transfusing whole blood from the donor dog and additionally hydroxyethyl starch solution (Hespan<sup>®</sup>), 6%, as needed.

Arterial blood gases were repeatedly analyzed with

Fig. 1. Schematic illustrations of the framework of the  $E_{\max}$  (a contractility index)-PVA (systolic pressure volume area, a measure of total mechanical energy)- $\text{VO}_2$  (myocardial oxygen consumption per beat) relationship fully used in this study. *A*,  $E_{\max}$  and PVA in the left ventricular (LV) pressure-volume (P-V) diagram.  $E_{\max}$  is the slope of the line connecting the end-systolic P-V point and  $V_0$  (see below).  $E_{\max}$  is alternatively defined as the slope ( $E_{\text{cs}}$ ) of the end-systolic pressure-volume relation (ESPVR) in a stable contractile state. PVA is the area surrounded by the ESPVR line, the end-diastolic P-V relation curve, and the systolic P-V trajectory.  $V_0$  is a volume at which LV isovolumic peak pressure and, hence, PVA are zero. In an isovolumic contraction, P-V data points move up and down on the vertical systolic P-V trajectory as indicated by arrows, and PVA is composed only of potential energy. *B*, The linear  $\text{VO}_2$ -PVA relationship in a volume loading run (see text) in a stable contractile state (*thick solid line*). The slope *a* of this relationship represents the oxygen cost of PVA.  $\text{VO}_2$  consists of two components at the  $\text{VO}_2$  intercept *b* of this relation: the PVA-dependent  $\text{VO}_2$  corresponding to the energy use for crossbridge cycling, and the PVA-independent  $\text{VO}_2$  (unloaded  $\text{VO}_2$ )







$\text{VO}_2$ -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  $\text{VO}_2$ ).<sup>20-22,25-27</sup>

In the inotropism run, the oxygen cost of  $E_{\text{max}}$  of fentanyl could be obtained from the composite  $\text{VO}_2$ -PVA relationship if LV contractility ( $E_{\text{max}}$ ) changes in a dose-dependent manner (fig. 1C, 1D).<sup>20-22,28-30</sup>

**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  $\text{ml} \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}$ , and CVR was presented in  $\text{mmHg} \cdot \text{ml}^{-1} \cdot \text{min} \cdot 100 \text{ g}$ .

#### 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 isovolumic 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  $V_0$ ) and 189 mmHg.
- 2) Fentanyl inotropism run: Fentanyl solution (50  $\mu\text{g}$ /ml) was diluted to 20  $\mu\text{g}$ /ml with 1.5% NaCl to have physiologic osmolality (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 ( $27.3 \pm 6.1 \text{ ml}/100 \text{ g}$ ) where peak isovolumic pressure was  $96.1 \pm 22.8 \text{ mmHg}$ . 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.<sup>22,31</sup>

- 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  $\text{VO}_2$ -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  $\pm$  SD.

#### Results

In two preliminary experiments, we confirmed that neither  $E_{\text{max}}$  nor the  $\text{VO}_2$ -PVA relationship changed for more than 5 h without any intervention after the onset of cross-circulation, except for transfusions and administration of bicarbonate. Therefore, we performed each experiment within 5 h after the onset of cross-circulation.

Table 1 shows the data of mechanoenergetics 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 ( $E_{\text{cs}}$ ) of the ESPVR, the slope and the  $\text{VO}_2$ -axis intercept of the  $\text{VO}_2$ -PVA relationship, and correlation coefficient ( $r$ ) are shown. All ESPVRs and  $\text{VO}_2$ -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 superimposed.



## FENTANYL AND CARDIAC MECHANOENERGETICS

**Table 1. Effects of Fentanyl on Left Ventricular Mechanoenergetics and Coronary Circulation in Fentanyl Inotropism Run**

	HR	LVP	E <sub>max</sub>	T <sub>max</sub>	PVA	VO <sub>2</sub>	CF	AVO <sub>2</sub> D	CVR
Control	136 ± 16	96.1 ± 22.8	6.9 ± 3.2	178 ± 36	689 ± 94	0.036 ± 0.010	70 ± 18	6.4 ± 1.8	1.82 ± 0.51
Fentanyl									
20 ng · ml <sup>-1</sup>	136 ± 16	94.8 ± 20.3	6.8 ± 3.0	177 ± 36	681 ± 95	0.036 ± 0.010	70 ± 18	6.4 ± 1.9	1.81 ± 0.53
40 ng · ml <sup>-1</sup>	136 ± 16	95.8 ± 19.4	6.9 ± 3.0	179 ± 37	689 ± 96	0.036 ± 0.011	68 ± 22	6.4 ± 1.9	1.98 ± 0.68
240 ng · ml <sup>-1</sup>	136 ± 16	95.5 ± 19.5	6.9 ± 3.0	179 ± 37	686 ± 87	0.034 ± 0.010	66 ± 22	6.3 ± 1.9	1.99 ± 0.66

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<sup>-1</sup>) 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 (paced beat · min<sup>-1</sup>); LVP = LV pressure (mmHg); E<sub>max</sub> = a contractility index (mmHg · ml<sup>-1</sup> · 100 g); T<sub>max</sub> = time from the onset of contraction to E<sub>max</sub> (ms); PVA = systolic pressure-volume area, a measure of total mechanical energy (mmHg · ml · beat<sup>-1</sup> · 100 g<sup>-1</sup>); VO<sub>2</sub> = oxygen consumption per beat (ml O<sub>2</sub> · beat<sup>-1</sup> · 100 g<sup>-1</sup>); CF = coronary flow (ml · min<sup>-1</sup> · 100 g<sup>-1</sup>); AVO<sub>2</sub>D = coronary arteriovenous oxygen content difference (vol %); CVR = coronary vascular resistance (mmHg · ml<sup>-1</sup> · min · 100 g).

able. In any of all the six hearts, the mean values of E<sub>cs</sub> showed no significant difference by Student's *t* test (table 2). These results indicate that fentanyl at any concentrations produced virtually no direct inotropic effect on LV in the excised cross-circulated canine heart.

Fentanyl did not significantly change T<sub>max</sub> as shown in tables 1 and 2, indicating that fentanyl did not affect the duration of systole.

**Energetics**

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

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

Experiment No.	Run	HR	ESPVR			VO <sub>2</sub> -PVA Relation		
			<i>r</i>	EES	T <sub>max</sub>	<i>r</i>	O <sub>2</sub> Cost of PVA	Unloaded VO <sub>2</sub>
1	Control	120	0.996	4.0	229	0.997	2.03	0.023
	Fentanyl	120	0.999	4.1	229	0.994	1.79	0.022
2	Control	120	0.997	4.3	213	0.994	1.36	0.018
	Fentanyl	120	0.984	4.2	214	0.910	1.30	0.021
3	Control	162	0.989	7.0	140	0.956	1.30	0.026
	Fentanyl	162	0.994	6.5	142	0.928	1.44	0.023
4	Control	139	0.999	4.5	165	0.998	1.35	0.016
	Fentanyl	139	0.994	4.5	167	0.977	1.16	0.013*
5	Control	136	0.999	9.1	153	0.998	2.30	0.022
	Fentanyl	136	0.980	8.7	153	0.992	2.29	0.023
6	Control	139	0.995	10.4	166	0.987	1.94	0.036
	Fentanyl	139	0.984	9.4	171	0.967	1.84	0.036
Mean ± SD	Control	136 ± 16	0.996 ± 0.004	6.5 ± 2.7	178 ± 35	0.988 ± 0.016	1.71 ± 0.43	0.024 ± 0.007
	Fentanyl	136 ± 16	0.990 ± 0.008	6.2 ± 2.4	179 ± 35	0.961 ± 0.035	1.64 ± 0.42	0.023 ± 0.007
Paired <i>t</i> test		NS	NS	NS	NS	NS	NS	NS

These results were calculated from the data in control and fentanyl (240 ng · ml<sup>-1</sup>) volume loading runs. Analysis of covariance (ANCOVA) was applied to comparisons of the slope and the VO<sub>2</sub>-axis intercept of the VO<sub>2</sub>-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; O<sub>2</sub> cost of PVA = slope of the VO<sub>2</sub>-PVA relation (10<sup>-5</sup> ml O<sub>2</sub> · mmHg<sup>-1</sup> · ml<sup>-1</sup>); Unloaded VO<sub>2</sub> = the VO<sub>2</sub>-axis intercept of the VO<sub>2</sub>-PVA relation, virtually equal to VO<sub>2</sub> for unloaded contraction with zero PVA (ml O<sub>2</sub> · beat<sup>-1</sup> · 100 g<sup>-1</sup>).

\* Statistically significant at *P* < 0.05.



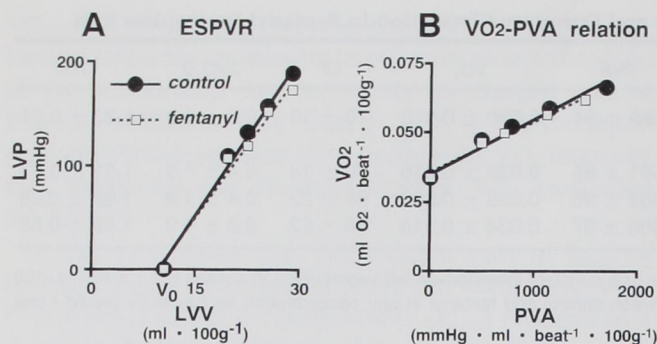


Fig. 3. A representative set of data from experiment 6. The thick solid lines (connecting closed circles) and the dashed lines (connecting open squares) indicate the regression lines during the control and fentanyl (240 ng/ml) volume loading runs, respectively. All end-systolic pressure-volume relations (ESPVR) and  $\text{VO}_2$  (oxygen consumption per beat)–PVA (pressure volume area) relationships in the control and fentanyl volume loading runs have high and linear correlation. A pair of ESPVRs (A) and a corresponding pair of  $\text{VO}_2$ –PVA relations (B) are virtually superimposable, respectively. A, Left ventricular ESPVRs in the pressure–volume diagram. The slopes ( $E_{\text{es}}$ ) of ESPVRs in the control and fentanyl volume loading runs were 10.4 and 9.4 mmHg  $\cdot$  ml $^{-1}$   $\cdot$  100 g, respectively. LVP = left ventricular pressure (mmHg); LVV = left ventricular volume (ml/100 g);  $V_0$  = a left ventricular volume at which isovolumic peak pressure was zero (ml/100 g). LV contractility was not changed by fentanyl. B, Left ventricular  $\text{VO}_2$ –PVA relationships. The slope and the  $\text{VO}_2$  intercept of the  $\text{VO}_2$ –PVA relationships in the control and fentanyl volume loading runs were 1.94 and  $1.84 \times 10^{-5}$  ml O $_2$   $\cdot$  mmHg $^{-1}$   $\cdot$  ml $^{-1}$ , and 0.036 and 0.036 ml O $_2$   $\cdot$  beat $^{-1}$   $\cdot$  100 g $^{-1}$ , respectively. Neither O $_2$  cost of PVA nor unloaded  $\text{VO}_2$  was changed by fentanyl.

six hearts, the mean values of neither the slope nor the  $\text{VO}_2$  intercept of the  $\text{VO}_2$ –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  $\text{VO}_2$  (fig. 1B).

In the fentanyl inotropism run, the  $\text{VO}_2$ –PVA points never deviated from the control point at any concentrations, correspondingly to a constant  $E_{\text{max}}$ . Therefore, we could not obtain any composite  $\text{VO}_2$ –PVA relationship for fentanyl. Consequently, the oxygen cost of  $E_{\text{max}}$  was not applicable to fentanyl (fig. 1C, 1D).

#### Coronary Circulation

In the fentanyl inotropism run,  $\text{AVO}_2\text{D}$ , 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  $E_{\text{max}}$ –PVA– $\text{VO}_2$  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.<sup>20–22</sup> In contrast to conventional myocardial contractility indexes, such as LV  $\text{dp/dt}_{\text{max}}$  and maximal unloaded shortening velocity ( $V_{\text{max}}$ ),  $E_{\text{max}}$  and  $E_{\text{es}}$  are considered to be less dependent on ventricular loading conditions.<sup>14,20</sup> Although the effects of fentanyl on cardiac mechanics were previously analyzed by using LV  $\text{dp/dt}_{\text{max}}$ , this index depends on preload, afterload, and heart rate.<sup>12,13,18</sup>

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.<sup>23–33</sup>

#### 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  $\mu\text{g/kg}$ ,<sup>7</sup> 60  $\mu\text{g/kg}$ ,<sup>9</sup> and 75  $\mu\text{g/kg}$ <sup>3,10</sup>), mean blood fentanyl concentrations range within 20–160 ng/ml. During the maintenance of fentanyl action, 10–40 ng/ml of fentanyl was required to avoid noxious stimuli sufficiently.<sup>3,7,9–11</sup> 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.<sup>15</sup> However, there was another study reporting that the requirements as an analgesic in the dog vary enormously (25–60 ng/ml) and are extremely high in some animals.<sup>34</sup>

#### 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  $\mu\text{g/ml}$  of coronary blood concentration, suggesting a narrow safety range of blood concentration in terms of the interference with LV mechanoenergetics.<sup>31</sup> 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 myocardial preparations, some investigators have reported a marked direct negative inotropic effect of fentanyl.<sup>16,17</sup> However, these studies are often performed during physiologic 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 consciousness. 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  $\text{mg} \cdot \text{kg}^{-1}$   $\text{ng} \cdot \text{ml}^{-1}$ ) remained unchanged ( $P > 0.05$ ) at 20  $\text{ng/ml}$  ( $0.168 \pm 0.176$   $\text{ng/ml}$ ) and 240  $\text{ng/ml}$  ( $0.078 \pm 0.052$   $\text{ng/ml}$ ) of intracoronary fentanyl. The concentration of norepinephrine (control,  $0.688 \pm 0.661$   $\text{ng/ml}$ ) also remained unchanged ( $P > 0.05$ ) at 20  $\text{ng/ml}$  ( $1.443 \pm 1.646$   $\text{ng/ml}$ ) and 240  $\text{ng/ml}$  ( $1.356 \pm 1.622$   $\text{ng/ml}$ ). 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  $E_{\text{max}}$ -PVA- $\text{VO}_2$  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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