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Fentanyl Is Devoid of Major Effects on Coronary Vasoreactivity and Myocardial Metabolism in Experimental Animals

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Experiments were designed to determine the effects of fentanyl on coronary vascular tone and energetic state of the heart. Both arterial and arteriolar responses were assessed; particular attention was directed to epicardial vessels. Four experimental methods and three animal species were used. Isolated canine coronary artery rings with and without endothelium were suspended in organ chambers, and changes in their tension were measured. Fentanyl (100 ng/ml) had no effect on resting tension of unstimulated rings on a contraction evoked by serotonin 10^{-8} to 10^{-4} M. In rings with endothelium, the opioid had a minimal depressant effect on the contractile response to phenylephrine. Tension of vessels precontracted with serotonin (3×10^{-7} M), or phenylephrine (10^{-5} M) was unchanged following fentanyl at 10, 30, 70, or 150 ng/ml. Computerized quantitative angiography was used in intact pigs anesthetized with ketamine to determine the effects of fentanyl on coronary artery diameters of vessels with or without endothelium. Intravenous fentanyl 50 and 250 μg/kg had no effect on vessel diameters. Isolated perfused rat hearts were used to assess fentanyl effects upon coronary flow and arteriolar tone and upon myocardial energy state. Coronary blood flow was not altered by fentanyl (100 ng/ml) and was unchanged following washout of the drug. The heart maintained a normal energy status prior to and following fentanyl treatment. These data demonstrate that, under the conditions tested, fentanyl is devoid of major effects on the coronary circulation and upon myocardial metabolism. (Key words: Anesthetics, intravenous: fentanyl. Arteries: coronary. Heart: blood flow.)

FENTANYL is a potent and useful synthetic opioid. Effects of the drug on cardiovascular function, myocardial oxygen consumption, and coronary blood flow have been described in animals and in human beings.[1–5] However, little is known concerning the direct effect of fentanyl on coronary arteries and coronary arterioles. The purpose of these experiments was to determine the effect of the opioid on coronary vascular tone. Four experimental methods and three animal species were used. Effects of the drug on isolated vessels were studied using canine coronary artery rings suspended in organ chambers. Responses of coronary arteries in intact animals were investigated using computerized quantitative angiography in pigs anesthetized with ketamine.

An isolated rat heart preparation was used to assess coronary flow and arteriolar tone. In this preparation myocardial oxygen consumption remains relatively constant; therefore, any changes in coronary flow would reflect direct effects of fentanyl on coronary arterioles. The energy state of the heart was measured to determine whether potential vascular changes were associated with derangement of high-energy metabolite content of the myocardium.

Methods

Institutional Animal Care Committee approval was obtained and experiments performed under humane conditions using dogs, pigs, and rats. Rings of the left anterior descending and circumflex coronary arteries were obtained from 11 mongrel dogs anesthetized with intravenous (iv) pentobarbital 30 mg/kg. They were suspended in organ chambers filled with aerated (95% O_2–5% CO_2) modified Krebs-Ringer bicarbonate solution, the composition (mM) of which was NaCl 118.3, KCl 4.7, $CaCl_2$ 2.5, $MgSO_4$ 1.2, KH_2PO_4 1.2, $NaHCO_3$ 25, and glucose 11.1. The endothelium was removed in some rings by placing the bent tips of watchmakers forceps in the lumen and gently rolling the preparation on saline wetted filter paper. Acetylcholine 10^{-6} M was used to test for the presence or absence of endothelium. (Acetylcholine is an endothelium-dependent vasodilator of canine coronary arteries. In the absence of endothelium, acetylcholine evokes contraction. Acetylcholine can therefore be used to test for the presence or absence of endothelium.[6]) Each ring was stretched to the optimal point on its length–tension curve (10–11 g) using repeated doses of 2×10^{-2} M KCl and then maintained at this tension. The maximal tension developed following a standard challenge of 4×10^{-2} M KCl was used as a reference contraction for comparison of contractile responses obtained during the experimental period.

The effect of fentanyl upon quiescent ring tension and upon contractile responses to phenylephrine and serotonin was investigated. Fifty-six coronary rings, with or without endothelium, from seven dogs were studied. One-half were treated with fentanyl; the others served as control. Fentanyl 100 ng/ml was used in the organ chambers because this concentration corresponds to plasma con-

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centrations occurring in patients anesthetized with fentanyl for major surgery.[7] (However, in human beings a certain proportion would be bound to proteins in blood and actual free fentanyl concentration would be less than 100 ng/ml.) Contractile responses were next measured following addition of sequentially increasing cumulative concentrations of either serotonin or phenylephrine. (Contraction evoked by serotonin is biphasic. At higher serotonin concentrations, low-affinity smooth muscle receptors are stimulated with resultant relaxation.[8])

The effect of fentanyl on tension of rings precontracted to obtain maximum plateau contraction with either serotonin 3×10^{-7} M or phenylephrine 10^{-5} M was measured. Thirty-two preparations with or without endothelium from four dogs were studied. One-half were treated with fentanyl in sequentially increasing cumulative concentrations of 10, 30, 70, or 150 ng/ml. The other rings served as control.

Computer-assisted quantitative coronary angiography[9,10] was used to measure epicardial coronary artery diameters before and after fentanyl administration. Eleven 40-kg pigs received preanesthetic premedication consisting of 1 g intramuscular ketamine and were anesthetized with an iv infusion of ketamine (40–50 mg/kg) supplemented with a single bolus of 80 mg thiopental. They received heparin ($125 \text{ units} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$). Their lungs were mechanically ventilated, and the adequacy of ventilation was tested with repeated arterial blood gas measurements. Following an iv bolus dose of 50 mg lidocaine and 50 mg esmolol to prevent arrhythmias, a 2.5-mm diameter coronary artery guide catheter was advanced using fluoroscopy from the carotid artery to the ostium of the left main coronary artery. This catheter was used to inject radiopaque dye. Coronary artery pressure was measured using the coronary catheter and systemic pressure measured *via* the carotid artery introducer catheter, and both were continuously displayed.

Five pigs with normal coronary arteries were studied, and in the other six pigs the endothelium was damaged by passing a 2.0-Fr coronary angioplasty catheter (Gruntzig Dilaca USCI) into the left anterior descending coronary artery *via* the guide catheter and gently withdrawing it five times. This technique has been shown to remove endothelium without damaging the underlying vascular smooth muscle.[11] (Endothelial damage but absence of smooth muscle damage was confirmed in two animals by histologic examination of the arteries at postmortem using light and scanning electron microscopy.)

Coronary angiograms were obtained during the injection of 6 ml of 10% xaglate meglumine, 10% xaglate sodium (Hexabrix, Mallinckrodt), a nonionic low osmolar contrast medium that has little effect on coronary artery tone. Exposures, 110 kV, 300 mA for 6 ms were gated to mid-diastole. The opacified edges of the coronary artery lumens were manually traced and digitized using a PDP 11/34 computer (Digital Equipment Corporation). The program calculated luminal diameter at 1-mm intervals.[10] Coronary and carotid arterial pressures and heart rate were displayed and recorded and coronary angiograms were obtained in triplicate during a 20-min period prior to fentanyl infusion. Intravenous fentanyl 50 μg/kg was administered, and 30 min later fentanyl 250 μg/kg was injected and on each occasion measurements made. (The initial dose was chosen to reflect that used in anesthetizing human beings for major surgery. However, this dose has little effect on consciousness in pigs; therefore, effects of a second larger dose was also assessed.)

Rat hearts were studied using the methods originally described by Langendorff and subsequently modified and summarized by Doring and Dehnert.[12] In each experiment a 350–450 g Sprague-Dawley rat was anesthetized with intraperitoneal phenobarbital, a thoracotomy performed, the heart exposed and freed of pericardium, and the aorta freed of connective tissue. The surgical area was flooded with ice-cold saline solution to cool the heart and slow its rate and to prevent the entrapment of air. The pulmonary artery was incised, the ascending aorta was incised as far cranially as possible, the cannula inserted, and perfusion begun. Care was taken to avoid interference with aortic valve function or cause occlusion of the coronary ostia. Oxygenated modified Krebs-Ringer solution of the following composition (mM): NaCl 118.3, KCl 4.7, $CaCl_2$ 2.5, $MgSO_4$ 1.2, KH_2PO_4 1.2, $NaHCO_3$ 25, glucose 11.1; and insulin 5 units/l. The heart was excised and perfused *in vitro* in a Langendorff apparatus maintained at 37° C. The coronary perfusion pressure was maintained constant at 85 cmH_2O, and the hearts were paced electrically at 250 beats/min. Coronary flow was measured by collecting the perfusate draining out of the right atrium into a graduated cylinder.

Measurements of coronary flow were made every 2 min for 16 min. Fentanyl (final concentration 100 ng/ml) was added to the perfusion solution. Coronary flow measurements were repeated every 2 min for 16 min. Fentanyl was allowed to wash out, control period conditions reestablished, and measurements of coronary flow repeated. Integrity of vasodilator responsiveness was tested by infusing adenosine 10^{-4} M, a direct acting coronary arteriolar dilator, and then measuring changes in flow.[13] In a separate experiment appropriate vasoconstriction responses were confirmed by observing a decrease in coronary flow following the administration of ergonovine, a direct acting coronary constrictor (data not shown).

The effects of fentanyl on the metabolic state of the heart were examined using isolated rat hearts. They were obtained and perfused as described. Four hearts were perfused with modified Krebs-Ringer solution containing

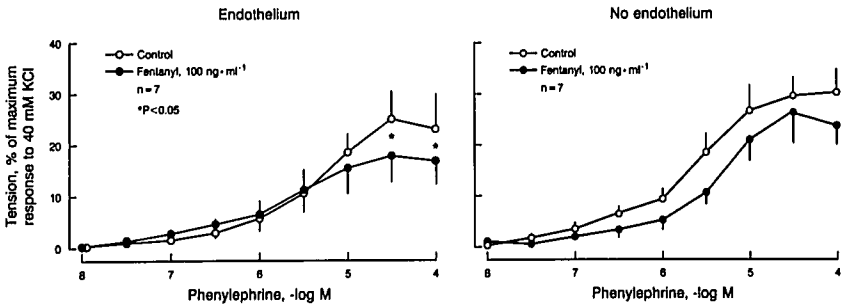

FIG. 1. Cumulative concentration response relationships of canine coronary rings both with and without endothelium exposed to increasing concentrations of phenylephrine. Response of control rings and rings suspended in Krebs-Ringer solution containing 100 ng/ml fentanyl are shown. Contractions are expressed as a percentage of the maximum response to a standard 4×10^{-2} M KCl challenge. Phenylephrine evoked concentration-dependent contractions. In rings with endothelium, fentanyl attenuated the contractile response to higher concentrations of phenylephrine ($P < 0.05$). No effect was observed in rings without endothelium. Data are mean ± SEM.

100 ng/ml fentanyl, and three hearts were untreated and served as controls. The beating hearts were then immersed in cold isopentane at the temperature of liquid nitrogen. The hearts, kept at −70° C until analysis, were then pulverized and thawed in 4 ml/g wet weight ice-cold 10% perchloric acid (PCA). The PCA extract was centrifuged, and the clear supernatant was neutralized with potassium hydroxide solution and used for the various measurements. Adenosine-5'triphosphate (ATP),[14] diphosphate (ADP),[15] monophosphate (AMP),[15] inoganic phosphate (Pi),[16] pyrophosphate,[17] creatine phosphate,[18] lactate,[19] pyruvate,[20] and glucose[21] were measured with specific enzymatic methods. A sample of each extract was also passed through a 0.45-μm Millex filter and analyzed using high-performance liquid chromotography to quantify the concentrations of adenosine, xanthine, and hypoxanthine in the tissue.

The sum of nucleotides (ATP + ADP + AMP), the sum of tissue phosphates (3ATP + 2ADP + AMP + Pi + creatine phosphate), the energy charge [½(2 ATP + ADP)/(ATP + ADP + AMP)], and the lactate/pyruvate ratio were calculated.

In another experiment the sensitivity of the experimental model and biochemical assays to adverse stimuli was tested by examining hearts that had been inadequately perfused or had been made hypoxic (positive control). The expected decrease in high-energy phosphates and energy charge was observed (data not shown).[22]

The following pharmacologic agents were used: serotonin creatinine sulphate, phenylephrine hydrochloride, adenosine, (Sigma Chemical Company, St Louis, Missouri), and fentanyl citrate (Janssens Pharmaceuticals). Drugs were dissolved in distilled water.

STATISTICAL ANALYSIS

Isolated paired coronary artery rings from the same artery of the same animal were studied in parallel. Contractile responses in the presence and absence of fentanyl were compared using paired Student's t test. Paired t test was also used to analyze coronary artery cross-section dimensions. Coronary flow data were evaluated using analysis of variance (ANOVA) and Tukey multiple comparison tests on real numbers. The effect of fentanyl treatment on tissue metabolite concentration was analyzed using an ANOVA for multiple comparisons. $P < 0.05$ was considered significant in all statistical analyses.

Results

Fentanyl had no effect on unstimulated rings, with or without endothelium, maintained at their optimal tension (data not shown). Phenylephrine induced a typical contractile response (fig. 1). Fentanyl induced a small but statistically significant attenuation of contraction in rings with endothelium but not in those without endothelium. Serotonin evoked a typical biphasic contractile response, which was not modified by fentanyl in rings either with or without endothelium (fig. 2). Fentanyl had no effect

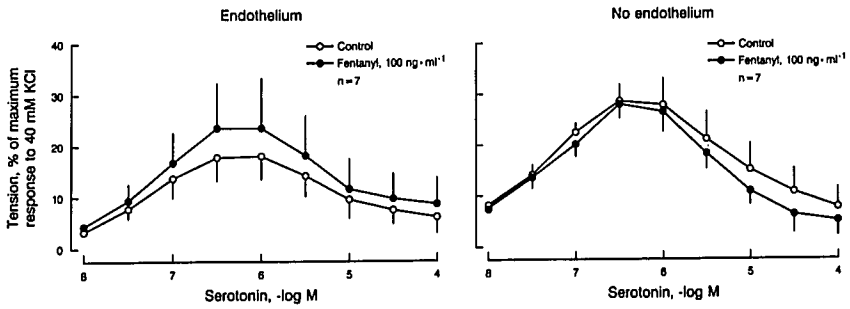

FIG. 2. Cumulative concentration response relationships of canine coronary rings with and without endothelium exposed to increasing concentrations of serotonin. Response of control rings and rings suspended in Krebs-Ringer solution containing 100 ng/ml fentanyl are shown. Contractions are expressed as a percentage of the maximum response to a standard 4×10^{-2} M KCl challenge. Serotonin evoked a biphasic contractile response. Fentanyl had no effect on the response. Data are mean ± SEM.

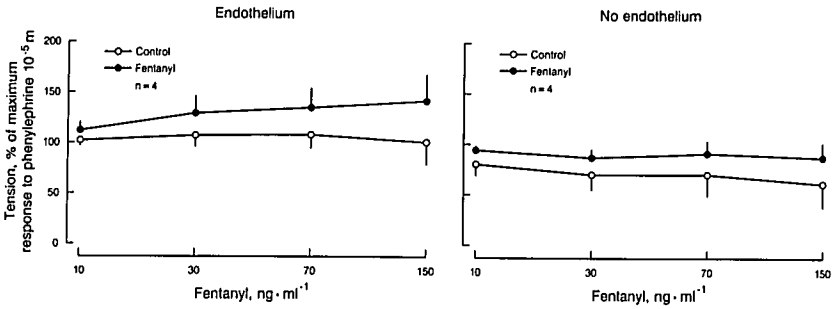

FIG. 3. Canine coronary artery rings with and without endothelium were precontracted with phenylephrine 10^{-5} M and then either treated with cumulative increasing concentrations of fentanyl or left untreated (control). Fentanyl had no effect on contraction. Data are mean ± SEM.

on the tension of rings with or without endothelium precontracted with phenylephrine or serotonin (figs. 3 and 4).

Fentanyl had no effect on the diameters of normal left anterior descending coronary arteries or on vessels denuded of endothelium (fig. 5). Fentanyl had little effect on hemodynamics; arterial pressure remaining constant while heart rate decreased slightly (99 ± 5 to 86 ± 3 beats/min $P < 0.05$).

Fentanyl had no effect on coronary flow (fig. 6). Flow remained unchanged following the administration of fentanyl and remained unchanged following washout of the opioid. The integrity of arteriolar responsiveness was tested with adenosine and an increase in flow was observed ($P < 0.05$).

The biochemical parameters measured indicate that both untreated hearts and hearts treated with fentanyl had a normal balance of high-energy phosphates (table 1). The concentration of lactate and pyruvate remained below 1 and 0.1 μM/g, respectively, in the tissue during both conditions. The lactate/pyruvate ratio was calculated at 15, indicating a normal cytoplasmic redox state. The ATP concentration did not differ between the control and that measured in the hearts exposed to fentanyl. However, a small ($P < 0.05$) increase in ADP occurred in the fentanyl-perfused hearts, resulting in a reduction in the calculated energy charge values ($P < 0.05$). The sum of adenylates was unchanged and the creatine phosphate levels were normal. The xanthine concentration was comparable in treated and untreated hearts. Adenosine concentrations remained below that required for detection (0.003 μM/g wet weight).

Discussion

The purpose of the study was to determine the effect of fentanyl on the coronary circulation and upon the energy state of the heart. The results demonstrate that fentanyl had no effect on coronary arteries in intact pigs. It had no effect on unstimulated isolated canine coronary arteries and no effect on contractions evoked by serotonin. In rings with endothelium, fentanyl had a limited inhibitory effect on the contractile response to increasing concentrations of phenylephrine but no effect on sustained contraction evoked by phenylephrine. Rat coronary arteriolar tone remained unchanged by fentanyl, and fentanyl did not disturb the myocardial energy state of isolated perfused rat hearts.

Opioids can have marked effects upon the circulation in animals, and these effects can be mediated by either alterations in autonomic nervous system activity or by direct actions on blood vessels.[23] It is not known if opiate receptors exist in coronary vessels; however, opioids do have direct actions on conductance vessels, such as the cerebral arteries of the dog[24] and cat[25,26] and aorta of the rabbit.[27] It is perhaps surprising, therefore, that in the experiments reported here, fentanyl had little effect on the coronary vessels of dogs, pigs, or rats. However, opioids are a diverse group of compounds, and their actions are mediated by a family of receptors that may recognize different opiates and opioid peptides in different ways to yield variable, sometimes opposing cardiovascular effects.

No clear pattern of opioid effect on conductance vessels has emerged. Enkephalins, peptides the pharmacologic

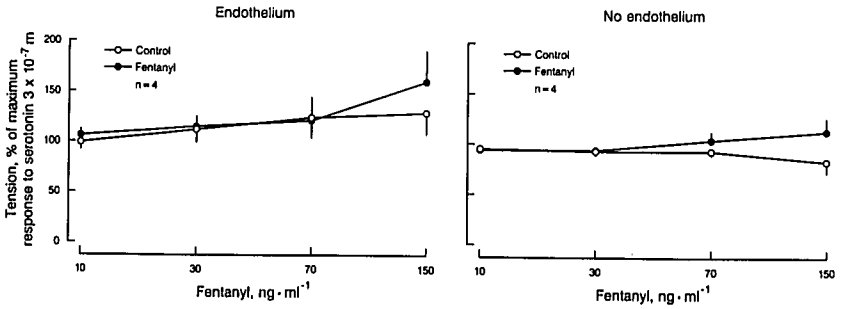

FIG. 4. Canine coronary artery rings with and without endothelium were precontracted with serotonin 3×10^{-7} M and then either treated with cumulative increasing concentrations of fentanyl or left untreated (control). Fentanyl had no effect on contraction. Data are mean ± SEM.

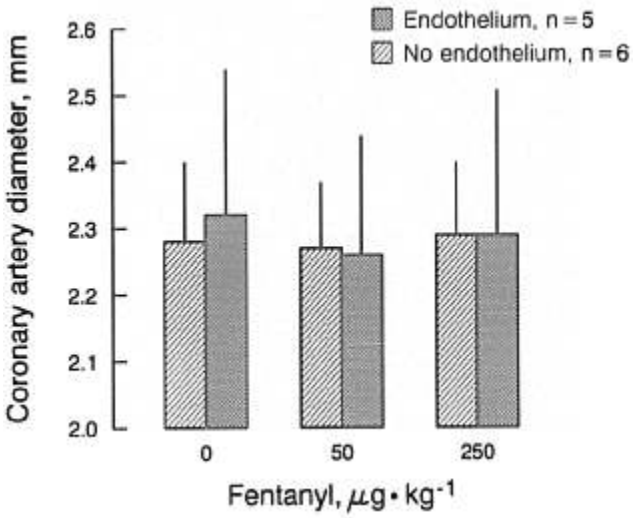

FIG. 5. Effects of two iv doses of fentanyl on the diameters of the left anterior descending coronary arteries of intact pigs. Diameters were measured every 1 mm along the vessel using computer-assisted quantitative angiography. Diameters of normal vessels and vessels denuded of endothelium are shown. Fentanyl had no effect on vessel diameter. Data are mean of actual diameters ± SEM.

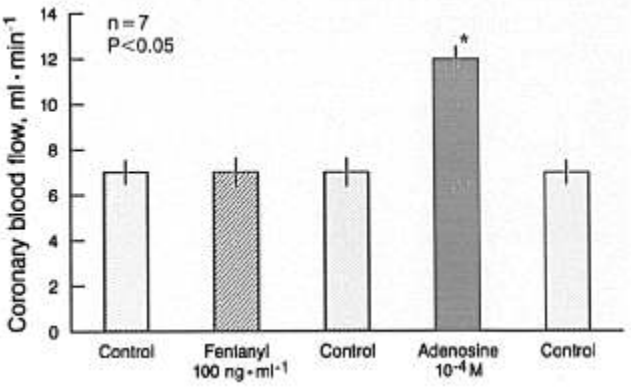

FIG. 6. Effects of fentanyl on coronary blood flow in isolated perfused rat hearts. Perfusion with Krebs-Ringer solution containing 100 ng/ml fentanyl had no effect on coronary blood flow. Adenosine 10^{-4} M increased blood flow, indicating preservation of the response to vasodilator stimuli. Data are mean ± SEM.

properties of which are similar to those of morphine, have been shown to contract cerebral vessels in the dog *in vitro*, perhaps by an action on opiate κ receptors.[24] However, enkephalins also relax canine cerebral vessels precontracted with prostaglandin $F_{2\alpha}$, perhaps by an opiate κ receptor-mediated effect.[24] In the cat pial arteries have been shown to relax in response to enkephalins,[26] and middle cerebral vessels have been reported to be hyperpolarized and relaxed by morphine.[25] Fentanyl, in contrast, is principally a μ receptor agonist with lesser action on other opiate receptors.[28] Absence of fentanyl effects might imply that μ receptors are not of great importance in regulating coronary vascular tone.

Fentanyl 10^{-6} to 10^{-5} M (corresponding to approximately 35–350 ng/ml) has previously been shown to attenuate norepinephrine-evoked contraction of rabbit aortic helical strips but not those evoked by serotonin.[27] Alpha$_1$-adrenergic receptor antagonism was proposed as the mechanism of this effect. Integrity of the endothelium was not verified in these experiments because at the time the important role of the endothelium in modifying vascular smooth muscle tone had not been established. However, it is difficult to maintain intact endothelium in helical strips; thus, it is likely that preparations denuded of endothelium were examined. Results from current experiments suggest that in canine coronary arteries the effect of fentanyl on α_1-adrenergic activity is small.

Ketamine was used as a background anesthetic. However, it is possible that ketamine may have an independent effect on coronary artery tone, such as by stimulation of the sympathetic nervous system. The problem was partially addressed in two separate pilot experiments. Ketamine had no effect on coronary artery diameters in three intact pigs anesthetized with etomidate and fentanyl (results not shown). Ketamine had little effect on isolated coronary arteries of five pigs precontracted with prostaglandin $F_{2\alpha}$ when concentrations corresponding to those used in anesthetizing pigs were tested (results not shown).

The effect of drugs on coronary arteriolar caliber is difficult to investigate because resistance vessels are extremely small. Arteriolar responses were studied because

TABLE 1. Effects of Fentanyl on Metabolites and Nucleotides in Perfused Rat Hearts

	Measured Metabolites (μM/g wet weight)											Calculated Parameters			
	ATP	ADP	AMP	Creatinine Phosphate	Pi	PPi	Lactate	Pyruvate	Glucose	Xanthine	Adenosine	Sum of Nucleotides	Energy Charge	Phosphate Potential	Lactate/ Pyruvate
Control	2.50	0.46	0.062	3.82	6.05	0.600	0.900	0.060	9.50	0.64	<0.003	3.00	0.903	0.916	15.0
(n = 4)	± 0.24	± 0.05	± 0.006	± 0.28	± 0.29	± 0.130	± 0.310	± 0.014	± 0.18	± 0.02		± 0.14	± 0.003	± 0.080	± 1.15
Fentanyl	2.54	0.67	0.093	3.69	6.73	0.710	0.670	0.041	9.97	0.68	<0.003	3.30	0.871	0.58	16.7
(n = 3)	± 0.15	± 0.04	± 0.013	± 0.46	± 0.51	± 0.009	± 0.290	± 0.011	± 0.12	± 0.10		± 0.10	± 0.004	± 0.06	± 3.20
Significance	NS	$P < 0.05$	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	$P < 0.01$	$P < 0.05$	NS

Data are mean ± SEM.

effects of drugs on arterioles may be entirely different and even opposite to effects on epicardial vessels.[29] Providing myocardial oxygen consumption remains constant, changes in coronary blood flow reflect the direct effect of drugs on resistance vessels. In human beings and intact animals, changes in coronary blood flow do not necessarily reflect direct drug effects on coronary vascular tone because most anesthetic drugs simultaneously alter loading conditions of the heart, heart rate, or myocardial contractility and therefore change myocardial oxygen consumption. In contrast, by using the electrically paced isolated perfused heart, myocardial oxygen consumption can be held relatively constant. Changes in coronary flow reflect changes in arteriolar tone. However, in the current experiment actual myocardial oxygen consumption was not measured, but because fentanyl does not have major effects on cardiac contractility, it was assumed that myocardial oxygen consumption remained relatively constant. In the current experiment fentanyl did not alter coronary flow, indicating the absence of effect on coronary arterioles.

Drugs that induce profound coronary arteriolar dilatation may, in the presence of coronary artery stenoses or left ventricular hypertrophy, impair autoregulation of coronary blood flow.[30] Flow may be distributed away from underperfused regions to better perfused regions. It is noteworthy that under the current experimental conditions, fentanyl had no major effect on coronary arteriolar tone. However, the effect of fentanyl on human coronary arterioles was not investigated.

Energy state studies[31] indicate that myocardial metabolism was not altered by fentanyl. Fentanyl induced a small increase in ADP concentration with a modest reduction in energy charge. Coronary flow was not altered by fentanyl; therefore, reduction in delivery of exogenous metabolic substrate or oxygen does not explain this observation. The small decrease of lactate and pyruvate concentrations in the tissues may indicate that fentanyl stimulates endogenous fatty acid oxidation. However, this effect was extremely modest and is of doubtful metabolic significance. Thus, fentanyl is neutral in its effects on myocardial energy balance.

The results demonstrate that fentanyl is an anesthetic devoid of major effects on the coronary circulation and myocardial metabolism. Because fentanyl lacks an action on coronary arteries and arterioles, it may be an appropriate anesthetic agent for animals used in the study of coronary vasomotion. However, it must be remembered that the fentanyl dose required to anesthetize laboratory animals may far exceed that needed for human beings.[32] If an opioid-based system has a role in regulating coronary artery and arteriolar tone, then it does not appear to be sensitive to fentanyl.

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