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Myocardial Blood Flow and Oxygen Consumption during High-dose Fentanyl Anesthesia in Patients with Coronary Artery Disease

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The effects of high-dose fentanyl–oxygen anesthesia (100 μg/kg) on myocardial blood flow (argon washin), myocardial oxygen consumption, myocardial lactate balance, and cardiovascular dynamics were studied in nine patients undergoing three-vessel coronary artery bypass operations. All patients had been on maintenance doses of a beta-receptor blocker (pindolol). Except for pindolol all medication had been discontinued 48 hours prior to the study. Measurements were performed in the awake state, after 10 μg/kg fentanyl, after 100 μg/kg fentanyl, and during sternotomy. Moderate doses of fentanyl (10 μg/kg) produced minimal changes in myocardial blood flow, myocardial oxygen consumption, and cardiovascular dynamics; myocardial oxygen balance was well maintained. Large doses of fentanyl (100 μg/kg) produced a 16 per cent decrease in mean aortic pressure, cardiac index did not change significantly, while stroke volume index decreased by 23 per cent. Myocardial oxygen consumption decreased by 14 per cent and myocardial blood flow by 10 per cent. Myocardial lactate production was observed in five patients, indicating myocardial ischemia. During sternotomy arterial pressure and heart rate increased 8 per cent and 29 per cent, respectively, resulting in an increase in myocardial work, as reflected by a 38 per cent increase in myocardial oxygen consumption and by a 54 per cent increase in myocardial blood flow. Myocardial lactate production was observed in seven of nine patients. Our data demonstrate that in patients on maintenance doses of beta-receptor blockers, large doses of fentanyl as the sole "anesthetic" produce incomplete anesthesia and fail to protect the myocardium from ischemia due to noxious stimuli during coronary artery surgery. (Key words: Analgesics: fentanyl. Anesthesia: cardiovascular. Anesthetics, intravenous: fentanyl. Heart: blood flow, myocardial; lactate production; oxygen consumption.)

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ANESTHESIA for coronary artery surgery requires control of those factors known to adversely affect myocardial oxygen balance. Therefore, anesthetics are employed which provide sufficient anesthesia to eliminate awareness and sympathetic reflex response to noxious stimuli while causing minimal impairment of cardiovascular function. At present, no single anesthetic is available which accomplishes these requirements in an ideal manner. Rather, most anesthetics have to be supplemented by various pharmacologic agents, *e.g.*, vasodilators, β-blockers, vasopressors, or inotropic drugs to protect the myocardium from ischemia at critical phases during anesthesia, surgery, and recovery.

High-dose fentanyl–oxygen anesthesia (50–100 μg/kg) has been reported to produce minimal changes in cardiovascular dynamics in patients with coronary artery disease and has been suggested as an alternative to morphine or halothane anesthesia in patients undergoing coronary artery bypass operations.[1–3]

We have observed a marked degree of cardiovascular instability with this anesthetic technique during aorto-coronary bypass surgery. This study was designed to investigate in detail the effects of high-dose fentanyl–oxygen anesthesia on myocardial blood flow, oxygen consumption, and oxygen balance in patients undergoing coronary artery bypass operations during major anesthetic and surgical manipulations.

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Methods

Nine patients with stable angina scheduled for three-vessel coronary artery bypass surgery, ranging in age from 43–61 years and in weight from 62–83 kg, were studied. The study was approved by the Göttingen University Human Subjects Review Committee. Each patient signed an informed consent at the time of the preoperative visit. Seven patients had a history of one previous myocardial infarction. No patient had a history of congestive heart failure or valvular heart disease, and none demonstrated angiographic evidence of pathologic left ventricular wall motion. In all patients the ejection fraction was greater than 55 per cent and the pre-angiogram left ventricular end-diastolic pressure was less than 12 mmHg. All patients were on maintenance doses of the beta-receptor antagonist pindolol§ (15 mg per day). All medication, with the exception of pindolol, had been discontinued 48 h prior to operation. The last dose of pindolol (5 mg) was administered at 10:00 P.M. the night prior to surgery. All patients were premedicated with diazepam, 10 mg orally, 90 min before the operation. Upon arrival in the induction room at 7:45 A.M., ECG leads (including V_5) were attached and the following catheters were placed under local anesthesia: a Goodale-Lubin catheter (7-F, USCI) into the coronary sinus via the right internal jugular vein (Seldinger technique) for measurement of myocardial blood flow and withdrawal of blood samples; a Goodale-Lubin catheter (7-F, USCI) into the left radial artery (arterial cut-down) for monitoring arterial blood pressure and for blood sampling (the argon technique requires two gas-tight catheters of same dead space); a Swan-Ganz catheter (Edwards quadruple thermodilution model no. 93 A 131-7F) into the pulmonary artery via a left antecubital vein for measurement of pulmonary artery pressure, pulmonary capillary wedge pressure, right atrial pressure, and cardiac output; and a polyethylene catheter into the superior vena cava for infusion of drugs. The position of all catheters was confirmed by image-intensification fluoroscopy. Body temperature was monitored with the thermistor of the Swan-Ganz catheter. ECG and all pressures were monitored continuously and recorded simultaneously on a 10-channel strip chart recorder (Hellige, Freiburg). After a rest period of 20 min, 10 μg/kg fentanyl was administered at a rate of 200 μg/min. Patients were breathing 100 per cent oxygen, with respirations assisted using a face mask to maintain Pa_{CO_2} at 36 to 40 mmHg, as confirmed by arterial blood-gas analyses. After 10 μg/kg fentanyl all patients received 0.3 mg/kg etomidate, and 4–6 mg pancuronium. Following endotracheal intubation controlled ventilation with 100 per cent O_2 was instituted using a volume constant respirator (Engström ER 300). Administration of fentanyl at a rate of 300 μg/min was then continued until each patient had received 100 μg/kg. Thirty minutes after completion of fentanyl administration the surgical procedure began. Muscular paralysis was maintained during the operation with 2-mg increments of pancuronium every 45–60 min. Additional fentanyl was administered at a rate of 200 μg/min whenever blood pressure and/or heart rate increased more than 15 per cent above control values. Severe hypertension, when unresponsive to additional fentanyl, was controlled with intravenous nitroglycerin. Apparent awareness during the operation was also treated with additional fentanyl. Patients who opened their eyes during the operative procedure also received 5–10 mg increments of etomidate when fentanyl did not succeed in producing unconsciousness. Measurements were recorded and blood samples were taken while the patients were awake (I), after 10 μg/kg of fentanyl before administration of etomidate and pancuronium and endotracheal intubation (II), after 100 μg/kg of fentanyl before the operation (III), and during sternotomy (IV). No pancuronium and etomidate or any other drug was administered 15 min before and during the period of data collection.

Measurements in this study included: myocardial blood flow (MBF), using the argon–washin technique[4] (coefficient of variation ± 5.1 per cent) with sampling from the coronary sinus after inhalation of a standard concentration of argon, cardiac output (CO) by thermodilution using the pulmonary artery catheter and a cardiac output computer (Fischer BN 7206), mean arterial pressure (MAP), mean pulmonary arterial pressure (MPAP), pulmonary capillary wedge pressure (PCWP) and right atrial pressure (RAP) (Statham P 23 Db). Immediately before and after each measurement of myocardial blood flow samples were drawn from the coronary sinus and the radial artery. Samples were analyzed for hemoglobin concentration and oxygen saturation (CO-Oximeter, 282 Instrumentation Lab.), blood gases (standard electrodes, Radiometer Copenhagen), lactate (enzymatically, as described by Bergmeyer[5]; coefficient of variation ± 3.9 per cent), and electrolyte concentrations (by atom absorption spectrophotometry, Perkin Elmer 303).

Derived variables were calculated as follows: coronary vascular resistance (CVR) as $mmHg/(ml \cdot min^{-1} \cdot 100\ g^{-1})$

$$CVR = \frac{MDAP - PCWP}{MBF}$$

where MDAP = mean diastolic arterial pressure.

Cardiac index (CI) was calculated by dividing cardiac output by the body surface area, and stroke volume index

§ For details of the pharmacokinetics of pindolol see reference 15.

(SVI) by dividing cardiac index by heart rate. The heart rate-pressure product was obtained by multiplication of heart rate by systolic pressure. Heart rate (HR) was obtained from the electrocardiogram. Myocardial oxygen uptake ($M\dot{V}O_2$) was calculated by multiplication of arterial-coronary sinus blood oxygen content difference by myocardial blood flow. Blood O_2 contents were calculated from measurements of hemoglobin concentration, O_2 saturation, and O_2 tension. Lactate uptake and production, respectively, were calculated by multiplication of arterial-coronary sinus blood lactate difference by myocardial blood flow.

Statistical analysis of the obtained data was performed using the Kruskal-Wallis test.[6] $P < 0.05$ was assigned statistical significance.

Results

Table 1 presents single and mean values of myocardial variables for all patients. Fentanyl, 10 μg/kg, produced a slight increase in myocardial blood flow and myocardial oxygen uptake ($P < 0.01$), while coronary vascular resistance decreased ($P < 0.01$). Coronary sinus blood oxygen saturation did not change. Lactate uptake decreased ($P < 0.01$).

With additional fentanyl myocardial blood flow and myocardial oxygen uptake decreased to below control values ($P < 0.01$), while coronary vascular resistance increased almost up to control levels ($P < 0.01$). At the same time small amounts of lactate were produced by the myocardium in five patients ($P < 0.01$).

During sternotomy there was a marked increase in myocardial blood flow and myocardial oxygen uptake ($P < 0.01$) and a marked decrease in coronary vascular resistance ($P < 0.01$), while coronary sinus blood oxygen saturation essentially remained unchanged. Myocardial lactate production was observed in seven patients ($P < 0.01$).

Mean values of hemodynamic variables and blood gases are presented in table 2. Fentanyl, 10 μg/kg, produced a minimal increase in heart rate ($P < 0.01$) and a significant reduction in arterial pressure ($P < 0.01$). Cardiac index did not change significantly, while stroke volume index was reduced ($P < 0.01$).

With 100 μg/kg fentanyl changes in mean arterial pressure and stroke volume index became more pronounced ($P < 0.01$), while heart rate and cardiac index essentially remained unchanged. During sternotomy there was a marked increase in heart rate and mean arterial pressure ($P < 0.01$). Four patients developed severe hypertension with systolic peak pressures of more than 200 mmHg, necessitating infusion of nitroglycerin. Cardiac index did not change significantly, while stroke volume was further decreased ($P < 0.01$).

TABLE 1. Myocardial Variables during High-dose Fentanyl-anesthesia (Single Values of Nine Patients and Mean Values ± SEM)

Patient	MBF [ml·min⁻¹·100 g⁻¹]				CVR [mmHg/(ml·min⁻¹·100 g⁻¹)]				O_2-Sat.cor.ven. [Per Cent]				$M\dot{V}O_2$ [ml·min⁻¹·100 g⁻¹]				Lactate [μmol·min⁻¹·100 g⁻¹]			
	I	II	III	IV	I	II	III	IV	I	II	III	IV	I	II	III	IV	I	II	III	IV
1	92	123	88	141	0.86	0.64	0.84	0.65	47.8	48.9	39.6	42.5	9.25	12.38	10.61	13.49	14.0	10.5	12.8	2.2
2	118	98	62	126	0.77	0.74	1.18	0.55	28.5	33.6	31.0	42.6	15.41	11.85	7.71	8.83	0.8	−1.3	−1.5	−2.1
3	68	109	95	129	1.28	0.70	0.79	0.62	34.4	41.0	35.1	33.3	7.79	10.85	10.36	14.29	9.2	−5.9	−1.0	−1.8
4	89	144	100	138	0.90	0.59	0.76	0.57	43.2	36.9	43.1	35.0	9.17	17.32	10.30	16.52	8.0	1.6	±0	−2.8
5	101	100	87	130	0.85	0.74	0.84	0.60	35.8	38.5	42.8	40.2	12.32	11.47	9.20	13.65	−10.3	1.1	±0	−1.9
6	97	117	91	198	1.00	0.71	0.79	0.50	36.3	23.4	38.6	40.8	12.65	17.56	9.92	20.88	8.5	2.2	−1.8	−1.1
7	118	82	80	165	0.68	0.81	0.79	0.47	37.0	38.2	35.5	46.2	13.03	8.55	8.63	14.91	16.1	1.2	1.1	±0
8	103	108	96	186	0.74	0.71	0.74	0.45	35.8	26.6	29.2	32.6	11.87	14.34	11.57	22.04	10.3	±0	−9.6	−0.7
9	86	88	80	141	0.99	0.87	0.90	0.59	24.9	37.1	27.6	30.8	11.86	10.50	11.07	18.89	5.6	12.3	−8.0	−2.8
MEAN	97	108*	87*	150*	0.90	0.72*	0.85*	0.56*	35.8	36.0†	35.8†	38.2†	11.5	12.7*	9.9*	15.9*	6.9	2.4*	−0.9*	−1.2*
SEM	5	6	4	9	0.06	0.03	0.04	0.02	2.2	2.5	1.9	1.8	0.8	1.0	0.4	1.4	2.6	1.9	2.1	0.4

* $P < 0.01$. † $P < 0.05$ *vs.* awake and between all values.
MBF = myocardial blood flow; CVR = coronary vascular resistance; O_2-Sat.cor.ven. = myocardial uptake or release (−).
I = awake; II = 10 μg/kg fentanyl; III = 100 μg/kg fentanyl; and IV = sternotomy.
= coronary sinus oxygen saturation; $M\dot{V}O_2$ = myocardial oxygen consumption; Lactate

TABLE 2. Hemodynamic Variables and Blood Gases during High-dose Fentanyl Anesthesia (Mean Values ± SEM)

	I	II	III	IV
HR [min^{-1}]	76 3	81* 5	82* 5	98* 5
P_{syst} [mmHg]	141 4	135* 7	124* 6	152* 7
MAP [mmHg]	103 3	91* 5	87* 4	106* 3
MDAP [mmHg]	91 3	84* 2	79* 1	91* 3
MPAP [mmHg]	13.7 0.6	14.9 0.9	15.2 0.7	15.0 1.0
PCWP [mmHg]	11.2 0.7	12.3 0.8	11.8 0.6	12.8 0.7
CI [$l \cdot min^{-1} \cdot m^{-2}$]	3.89 0.21	3.62 0.23	3.09 0.29	3.58 0.29
SVI [ml/m^2]	48 3	43* 3	37* 3	34* 3
$P_{syst} \cdot HR$ [$(mmHg \cdot min^{-1}) \cdot 10^{-3}$]	11.3 0.6	11.3 0.8	10.4 0.8	15.2 1.1
Hb [g/dl]	14.2 0.2	14.1 0.3	13.7 0.3	13.2 0.2
$P_{O_2 \text{ cor. ven.}}$ [mmHg]	21.5 1.1	23.3 1.2	22.7 1.0	20.4 0.7
Pa_{O_2} [mmHg]	84.7 4.5	118.4* 15.7	128.8* 14.6	170.9* 11.1
Pa_{CO_2} [mmHg]	37.2 0.9	39.4 1.3	37.9 1.7	38.2 0.7
pH_a	7.39	7.37	7.38	7.37

n = 9.

* $P < 0.01$ *vs.* awake and between all values.

HR = heart rate; P_{syst} = systolic pressure; MAP = mean arterial pressure; MDAP = mean diastolic arterial pressure; MPAP = mean pulmonary arterial pressure; PCWP = pulmonary capillary wedge pressure; CI = cardiac index; SVI = stroke volume index; $P_{syst} \cdot HR$ = heart rate pressure product; (pH = H^+ activity 40.8 ± 1.1, 42.6 ± 1.8, 41.7 ± 1.2, and 42.7 ± 1.1).

During the entire study period mean diastolic arterial pressure, a major factor that affects coronary blood flow, changed in parallel with the mean arterial pressure. Hemoglobin, blood gases, pH, and body temperature remained within the normal range throughout the whole procedure. All patients needed additional fentanyl during the operation; the average total dose for the entire operation was 127 ± 7 μg/kg fentanyl. Four patients showed signs of apparent awareness (obeying verbal commands of the anesthesiologist) during the operative procedure, three of them opened their eyes spontaneously during sternotomy and required 5 to 10 mg etomidate to produce hypnosis. The average total dose of pancuronium administered was 14 mg. The duration of operation averaged 285 ± 39 min. No patient remembered any aspect of the operative procedure. All patients required mechanical ventilation after operation for periods of 4 to 10 h.

Discussion

In all patients adjustment of coronary blood flow to the requirements of the heart was maintained in the awake state at rest, with the exception of patient 5, who sustained an anginal attack due to anxiety and apprehension, and who developed signs of myocardial ischemia (myocardial lactate production), which necessitated the administration of nitroglycerin.

Our data demonstrate that moderate doses of fentanyl (10 μg/kg) *per se* result in minimal changes in cardiovascular dynamics, myocardial blood flow, and myocardial oxygen consumption in patients with severe coronary artery disease. Heart rate only slightly increased ($P < 0.01$), probably due to anesthetic manipulations (*i.e.*, assisted ventilation via face mask) during infusion of the drug. Myocardial oxygen consumption and coronary blood flow increased in proportion, indicating that normal metabolic control of coronary blood flow was maintained with moderate doses of fentanyl. These results are consistent with data from a previous investigation by our group[7] concerned with the effects of fentanyl and sufentanil on general and coronary hemodynamics and myocardial metabolism in unpremedicated ASA class I patients. The hemodynamic effects reported here also are in accordance with the findings of other investigators in patients with coronary artery disease.[2,3,8]

Moderate doses of fentanyl caused skeletal muscular rigidity in all patients but did not produce unconsciousness consistently. Most patients remained responsive to verbal commands. Large doses of fentanyl (100 μg/kg) produced small changes in cardiovascular dynamics. Mean aortic pressure, cardiac index, and stroke volume index were decreased slightly, while heart rate remained unchanged. Myocardial oxygen consumption and coronary blood flow decreased in proportion. These observations essentially agree with the findings of other investigators,[2,3,9] and taken alone would suggest that cardiovascular stability is maintained in patients with severe coronary artery disease. However, this was not the case for the majority of patients. Rather, myocardial production of lactate was observed in five patients, indicating myocardial ischemia even in the absence of surgical stimuli. Presumably large doses of fentanyl produced redistribution of coronary blood flow, perhaps due to a reduction in coronary perfusion pressure, resulting in local myocardial ischemia in these patients. It has been shown that decreased local coronary blood flow with no change in total coronary blood flow is not uncommon in patients with coronary artery disease.[10] Therefore, it has

to be emphasized that measurements of total coronary blood flow alone usually will not reflect local myocardial oxygen balance in these patients.

In this study high doses of fentanyl failed to block autonomic sympathetic responses to noxious stimuli. During sternotomy marked increases in arterial pressure and heart rate resulted in an increase in myocardial work as reflected by an increase in myocardial oxygen consumption together with an increase in myocardial blood flow. During this phase myocardial lactate production was observed in seven of nine patients, indicating regional or global myocardial ischemia.

There is little doubt that fentanyl produces profound analgesia; however, it has been shown that even with large doses, loss of consciousness does not occur consistently.[11] In addition, it is well-known that opioids do not reliably block sympathetic responses to noxious stimuli in patients with coronary artery disease.[8,12-14] This is probably due to the fact that opioids, in contrast to true anesthetics, selectively bind to specific receptors unevenly distributed throughout the CNS without producing true anesthesia. It is therefore misleading to refer to opioids as anesthetics.

Contrary to the results reported by Stanley and coworkers,[1-3] large doses of fentanyl in this study failed to produce deep anesthesia during coronary artery bypass operations and in addition, did not protect the myocardium from ischemia during hemodynamic stress produced by major surgical stimuli. It is noteworthy, that even though all patients were on maintenance doses of beta-receptor blockers to within 12 h of surgery, these severe hemodynamic reactions were not prevented. Supported by data summarized by Frishman,[15] it would seem unlikely that the withdrawal of beta-receptor blocker 12 h previous could have caused these reactions since there is no evidence of a correlation between plasma levels and therapeutic effect of beta blockers. In addition it has to be pointed out that the period of withdrawal was very short. Furthermore, it has been shown in patients with coronary artery disease that abrupt propranolol withdrawal does not produce an enhanced sensitivity to sympathetic stimulation up to more than 48 h of withdrawal.[16] It seems important to mention at this point that the vast majority of patients of Stanley and coworker received no beta blockers at all. It seems very unlikely that the administration of etomidate exercised any substantial influence on our results. In a previous study[17] we could demonstrate that this drug produces no significant changes of general and coronary hemodynamics, myocardial function, and oxygen consumption of the heart in humans. Furthermore, the actions of etomidate are of short duration and cumulation does not occur with clinical doses.

The measurement of coronary blood flow and myocardial oxygen consumption is difficult in humans and cannot be employed in daily clinical practice. Therefore, several investigators have attempted to estimate myocardial oxygen consumption by taking into consideration the close relationship between hemodynamic parameters and myocardial oxygen consumption. Good correlation has been demonstrated in healthy volunteers and in patients with coronary artery disease during exercise between heart rate-systolic blood pressure product and measured myocardial oxygen consumption.[18,19] Consequently, the relationship has been introduced to anesthetic practice as an intraoperative guide to myocardial oxygen demand in patients with coronary artery disease,[20] although few data exist regarding correlation in humans during anesthesia. In our study there was poor correlation between the rate pressure product and myocardial oxygen consumption (fig. 1). There was also no close relationship between rate-pressure product and signs of myocardial ischemia (lactate production). Similar results have been obtained in a previous investigation by our group in healthy patients during halothane anesthesia.[21] These data indicate that the rate-pressure product is of limited practical value for computation of myocardial oxygen demand and prediction of myocardial ischemia during high-dose fentanyl–oxygen anesthesia in patients with severe coronary artery disease.

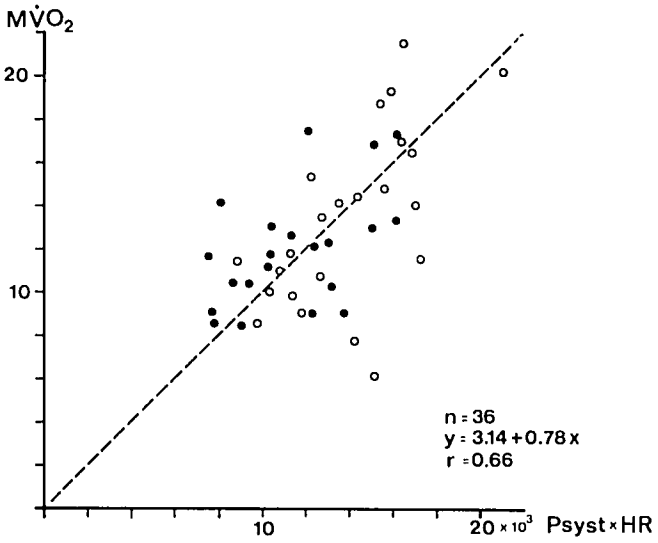

FIG. 1. Correlation between myocardial oxygen consumption and heart rate-systolic pressure product. $M\dot{V}O_2$ = myocardial oxygen consumption; $P_{syst} \cdot HR$ = heart rate-systolic pressure product. ● = Patients without lactate release. ○ = Patients with lactate release.

In conclusion, our findings demonstrate that large doses of fentanyl as the sole anesthetic, produce incomplete anesthesia and fail to protect the myocardium from ischemia due to noxious stimuli during coronary artery bypass operations in patients on maintenance doses of beta-receptor blockers.

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