Changes in Free and Total Catecholamine Concentrations in Plasma in Patients Undergoing Coronary Artery Bypass Grafting under High-dose Fentanyl Anesthesia

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We measured free and total catecholamine in ten patients undergoing coronary artery-bypass grafting under high-dose fentanyl (93.9 ± 2.2 $\mu g \cdot kg^{-1}$, mean ± SE) anesthesia. Arterial blood samples were obtained: 1) before induction of anesthesia (control), 2) 1 min after intubation, 3) 1 min after skin ininsion, 4) 1 min after median sternotomy and, 5) just before termination of cardiopulmonary bypass (CPB). The concentrations of free and total catecholamine were measured by HPLC using fully automated analyzer, 8030-TOHSO.

Free and total catecholamine concentrations did not change significantly before CPB. At the termination of CPB, however, the levels in free dopamine, norepinephrine and epinephrine all increased several fold as compared with control. Similarly, total norepinephrine and epinephrine also increased at the end of PCB, while total dopamine did not change. Present results indicated that 1) the measurement of free CAs is more significant than the measurement of total CAs for the assessment of sympathoadrenal responses to surgical stimuli, and that 2) high-doses of fentanyl produce hemodynamic stability by suppressing sympathoadrenal responeses elicited by the usual surgical procedures. However, stress triggered by CPB could not be suppressed totally by fentanyl even with high dose. (Key words: catecholamine, surgery, fentanyl, cardiopulmonary bypass)

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Catecholamine (CA) in plasma exists partly in "free" active forms (free CA) and remaining amines are conjugated mostly by phenolsulforansferase in humans loosing their principal activities as neurohumoral transmitter. It is important to recognize that the levels of "conjugated" CA in plasma are 2 to 3 times as great as those of the free amine[1]. Furthermore, it was reported that physiological procedures which elevated levels of free CAs did not much influence the concentrations

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Table 1. Clinical characteristics of patients

Patient number	Sex	Age (yr)	Weight (kg)	Fentanyl used ($\mu g \cdot kg^{-1}$)	Duration (min) CPB	Duration (min) Aortic clamp	Preoperative cardiac medications
1	M	48	65	84.6	114	56	Nif, Iso, Ticl, Asp
2	F	61	58	86.2	70	28	Nif, Iso, Dilt
3	F	58	62	88.7	101	53	Nif, Iso, Dilt
4	M	51	60	100.0	123	43	Nif, Iso, Ticl, Asp
5	M	72	56	107.1	148	50	Nif, Iso, Dilt
6	M	69	50	100.1	100	40	Nif, Iso
7	M	47	67	89.6	113	52	Nif, Iso, Ticl
8	F	66	35	93.2	123	45	Nif, Iso, Dilt, Dipyr, Warf
9	F	56	56	98.0	110	50	Nif, Iso
10	M	56	59	91.3	107	49	Nif, Iso, Ticl, Asp, Propr
Mean		58.4	56.8	93.9	110.9	46.6	
SE		2.6	2.7	2.2	6.0	2.4	

CPB = Cardiopulmonary bypass, NIf = Nifedipine, Iso = Isosorbide dinitrate, Ticl = Ticlopidine, Asp = Aspirin, Dilt = Diltiazem, Dipyr = Dipyridamole, Warf = Warfarin, Propr = Propranolol

of the conjugates[1]. Therefore, when we assess the sympathoadrenal activity with CA in plasma, it is more straightfoward if the levels in free CA are measured. However, to our knowledge, CAs in plasma have been treated generally as a single "total" without distinctions among conjugates and their parents compounds. Takino and others[2] reported recently the changes in free CA as well as those in total CA before and after anesthetic induction and tracheal intubation. They pointed out the possibility of misinterpretation on the estimation of sympathoadrenal activity only by measuring the concentrations of total CA in plasma.

There has not been a study in which the changes in free CAs before and during cardiopulmonary bypass (CPB) were investigated. Therefore, this study was designed to clarify the changes in free and total CAs in plasma in patients undergoing coronary-artery bypass grafting (CABG) under high-dose fentanyl anesthesia.

Methods

Ten patients scheduled for elective CABG were studied. Written informed consent to perform the study was obtained from each patient. Chronically taken cardiac drugs were continued on the moring of operation. Clinical characteristics of patients are listed in table 1.

All patients were given oral diazepam, 5–10 mg, 90 min before the induction of anesthesia, followed 30 min later by intramuscular injection of scopolamine 0.3–0.5 mg and pethidine 35–70 mg. Before anesthesia patients breathed oxygen for 10 min and were given 1 mg of pancuronium to attenuate fentanyl induced muscle rigidity. Two minutes later, anesthesia and muscle relaxation were induced by infusing fentanyl 40 $\mu g \cdot kg^{-1}$ and pancuronium 3 mg iv over 10 min. Respiration were first assisted and then controlled using a face mask. Endotrachal intubation was performed upon termination of fentanyl infusion and lungs were ventilated by oxygen thereafter

Table 2. Changes in heart rate and blood pressure

	Control	1 min after		
		intubation	incision	sternotomy
HR (min^{-1})	70.2 ± 2.9	68.6 ± 3.0	69.8 ± 3.1	71.5 ± 2.5
SBP (mmHg)	123.1 ± 3.9	118.0 ± 4.8	116.6 ± 3.4	124.4 ± 4.7
DSP (mmHg)	71.3 ± 2.9	68.0 ± 2.5	70.0 ± 1.8	73.1 ± 2.3

HR = Heart rate, SBP = Systolic blood pressure, DSP = Diastolic blood pressure, means ± SE; n = 10.

throughout the course of anesthesia to maintain Pa_{CO_2} 35–40 mmHg. Fentanyl and nitroglycerine were then begun to infuse until the end of study at the rate of 10 and 0.5 $\mu g \cdot kg \cdot hr^{-1}$, respectively. Paralysis was maintained with 1–3 mg increment of pancuronium or vecuronium every 40–60 min. When blood pressure rised more than 20% above preanesthetic values, 0.5–1.0% of enflurane was supplementary inhaled. No patient given a positive or negative inotropic compound before and during CPB.

The heart was approached through a median sternotomy. After cannulation for CPB, a membrane oxygenator was used priming with 600 ml of Ringer's lactate, 500 ml of 5% dextrose and 200 ml of mannitol. The non-pulsatile flow during the extra corporeal support was about 70 $ml \cdot kg^{-1} \cdot min^{-1}$. Patients were cooled to 28°C during CPB and rewarmed 37°C at its conclusion.

Blood samples were collected from the intra arterial cathter at the following times: 1) before induction of anesthesia (control), 2) 1 min after intubation, 3) 1 min after skin incision, 4) 1 min after median sternotomy, and 5) 4–5 min before termination of CPB. A study sample was taken into a heparinized tube containing ethylenediamine-tetraacetic acid·disodium salt (EDTA·2Na) 10.5 mg. After mixing, the sample was placed in an ice-water bath immediately and then centrifugated at 25000g at 4°C for 10 min to separate plasma from cells. The plasma was removed and frozened until analysis.

Spectrofluometric determination with 1, 2-diethylenediamine by high performance liquid chromatography was used for the measurement of CAs[3] by fully automated catecholamine analyzer, HLC-8030, TOHSO[4], Japan.

The total and free CA values for each subject were processed within the same assay. Sensitivity levels for dopamine (DA), norepinephrine (NE) and epinephrine (EN) were 3, 10, and 3 $pg \cdot ml^{-1}$, respectively. The inter and intraasay variations for all of these amines were less than 7%.

All data are expressed as mean ± SE, and their statistical significance was determined one-way analysis of variance. Differences were assesed with the Student's t-test and $P < 0.05$ was considered significant.

Results

The induction of anesthesia and endotracheal intubation were performed smoothly without any episodes of tachycardia, hypertension and changes in ECG. Heart rates and blood pressure remained essentially unchanged thereafter until the initiation of CPB (table 2).

The changes in DA (table 3): Preanesthetic (control) levels of free and total DA were 0.013 ± 0.002 and 2.7 ±

Table 3. Changes in plasma catecholamine concentration ($ng \cdot ml^{-1}$)

	Control	1 min after			End of CPB	Normal range
		intubation	incision	sternotomy		
Depamine						
Free	0.013±0.002	0.013±0.002	0.012±0.002	0.013±0.002	0.046±0.008*	<0.02
Total	2.7 ±0.3	2.7 ±0.3	2.6 ±0.3	2.6 ±0.3	2.6 ±0.3	0.8–4.6
Norepinephrine						
Free	0.26 ±0.04	0.28 ±0.03	0.21 ±0.03	0.30 ±0.03	0.65 ±0.12*	0.17–0.53
Total	1.1 ±0.2	1.2 ±0.2	1.2 ±0.2	1.2 ±0.2	1.8 ±0.1*	0.06–0.45
Epinephrine						
Free	0.050±0.013	0.046±0.009	0.071±0.003	0.082±0.002	0.17 ±0.003*	<0.10
Total	0.11 ±0.02	0.11 ±0.02	0.14 ±0.03	0.15 ±0.03	0.36 ±0.05*	<0.12

Means ± SE; n = 10, *$P < 0.05$ versus control value.

0.3 $ng \cdot ml^{-1}$, respectively. These valeus were all within normal range. Total DA did not changed significantly throughout the study, whereas the level of free DA rose significantly to 0.046 ± 0.008 $ng \cdot ml^{-1}$ ($P < 0.05$) at the end of CPB.

The changes in NE (table 3): Control levels of free and total NE were 0.26 ± 0.04 and 1.1 ± 0.2 $ng \cdot ml^{-1}$, respectively. The former was in normal range, whereas the latter was higher than normal. These values did not change signidicantly until the initiation of CPB. However, both free and total NE increased during CPB reaching 0.65 ± 0.12 and 1.8 ± 0.1 $ng \cdot ml^{-1}$, respectively ($P < 0.05$).

The changes in EN (table 3): Control levels of free and total EN were 0.050 ± 0.013, and 0.11 ± 0.02 $ng \cdot ml^{-1}$, respectively. These values were all in normal range and did not change significantly until the initiation of CPB. However, both free and total EN increased at the end of CPB reaching 0.17 ± 0.003 and 0.36 ± 0.05 $ng \cdot ml^{-1}$, respectively ($P < 0.05$).

Discussion

It is well established that anesthesia with high dose of fentanyl suppresses the sympathoadrenal responses evoked by laryngoscopy, skin incision or sternotomy in patients undergoing coronary artery operation. Thus fentanyl in high dose is effective to blunt surgically induced stress response[5,6]. However, once CPB initiated, it was also demonstrated that fentanyl, even in high dose, could not prevent elevations in DA, NE, and DA suggesting stress response to CPB to be significantly greater than that before CPB[5]. Present results were similar to previous observation which showed the increase in CA concentrations in plasma during CPB[5]. What is new in this study is the employment of free CA in plasma as a indicator for sympathoadrenal activity. In former studies, conclusions were all based upon changes only in "total" CA which includes a lot of physiolgically inactive conjugates. Therefore, it is still unelucidated whether plasma levels in free CA actually rise or not in patients undergoing cardiac surgery.

Several points are worthy of comment. Surgical stress may increase total CAs concentration in plasma. However, the elevation in total CAs might not always associate with the increase in free CAs in plasma. As shown in this study, free NE levels prior to CPB

were all within normal range, whereas corresponding total NE levels were higher than normal. The measurement of total NE would have indicate the presence of sympathetic hyperactivity before and during entire surgery. Conversely, absence of increase in total CAs does not always indicate lack of the increase in free CAs, as observed in DA levels in this study. Therefore, as we have previously pointed out[2], so far as an assesment of sympatoadrenal response by CAs in plasma is concerned, the measurement of free CAs is mandatory. Present study also showed that, because free DA was extremely less than conjugated DA, the measurement of total DA without recognition of free DA in plasma might miss actual dopaminergic activity.

The absence of increase in free CAs levels until the onset of CPB suggests that "Mega opioid" anesthesia could suppress the secretion of CA and thus contribute to produce hemodynamic stability. On the other hand, the stimulation induced by CPB was so serious to totally ablate sympathetic response even when fentanyl given in high dose as evidenced by the elevated concentrations in free DA, NE and EN. Derbyshire and others[7] stated that sudden introduction of CPB would elicit profound sympathoadrenal responses mediated through different pathway from that of surgical stimulation. However, the levels of CAs during CPB in present study were much lower than those observed in a patient with asthmatic attack[8] in whom the levels in free NE and EN in plasma were extraordinary high, reaching 1.35 and 1.13 $ng \cdot ml^{-1}$, respectively. Somewhat higher concentrations in CAs might contribute to maintain circulatory homeostasis during CPB which has been likened to controlled shock.

In summary, this study revealed several points. Firstly, measurement of free CA in plasma was mandatory in an assessment of sympathoadrenal response ot physical stress, otherwise some incorrect conclusions might be introduced. Secondly, high dose fentanyl anesthesia can effectively suppress sympathetic response elicited by laryngoscopy, skin incision and sternotomy in patients undergoing CABG. Thirdly, although CAs secretion induced by CPB cannot be totally suppressed by this anesthetic technique, the observed increase in CA levels might be favorable to homeostasis counterbalancing unphysiological state of CPB.

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