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Endocrine responses to total intravenous anesthesia with droperidol, fentanyl, and ketamine in cardiac patients

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Abstract: Ketamine-induced sympathetic stimulation can be inhibited by administration of sedatives such as benzodiazepines, droperidol, or opioids. We have developed total intravenous anesthesia with ketamine in combination with droperidol and fentanyl (DFK) and have used this anesthetic method in more than 4000 surgical cases. In this study, we compared DFK in cardiac surgery with isoflurane-fentanyl anesthesia (AOI-F). Fourteen patients undergoing aortocoronary artery bypass graft surgery were randomly assigned to the DFK or AOI-F groups. The endocrine responses of the patients were evaluated from the plasma levels of cortisol, antidiuretic hormone (ADH), atrial natriuretic peptide (ANP), and aldosterone. In both groups, anesthesia per se did not induce any significant changes in the hormones. Although cortisol and ADH increased during surgery, ANP and aldosterone did not change appreciably. All hormones were significantly elevated after the end of cardiopulmonary bypass. There were no significant differences in any of the hormones, blood pressure, and heart rate measured at different points in both groups. These results showed that DFK anesthesia as a total intravenous anesthesia deserves to be studied in more depth.

Key words: Endocrine responses, Cardiopulmonary bypass, Total intravenous anesthesia, Ketamine

Introduction

As ketamine-induced cardiostimulatory effects result primarily from ketamine's direct action on the central nervous system, the administration of central nervous system depressants such as benzodiazepines and droperidol prior to ketamine can minimize cardiostimulation [1]. A continuous infusion of ketamine can also cause less cardiovascular stimulation than the bolus injection [2].

We have already applied ketamine total intravenous anesthesia (TIVA) in combination with droperidol and fentanyl (DFK) to more than 4000 surgical patients for various types of surgery and reported its advantages [3–6] such as an increase in urine volume [4] and good hemodynamic stability in cardiac patients [5]. Previous reports indicated [7–10] that plasma levels of stress hormones such as catecholamines, cortisol, antidiuretic hormone (ADH), and aldosterone increase during cardiopulmonary bypass (CPB). Plasma levels of diuresis-related hormones such as ADH, atrial natriuretic peptide (ANP) aldosterone, and renin have also been reported to be elevated during and/or after CPB [7–10].

Tuman et al. [11] reported that TIVA with ketamine and diazepam as compared with high-dose fentanyl anesthesia could reduce postoperative positive cumulative fluid balance despite less frequent use of postoperative diuretics. However, the reasons for this were not clear.

In this study, we evaluated endocrine responses from the plasma levels of stress and diuresis-related hormones to CPB in cardiac patients who received either DFK or isoflurane-fentanyl anesthesia (AOI-F).

Patients and methods

Subjects

After the approval of our study by the institutional ethical committee, 14 patients scheduled to undergo elective aortocoronary artery bypass surgery were randomly assigned to either the DFK group ($n = 7$) or the AOI-F group ($n = 7$). Informed consent was obtained from all patients.

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Anesthesia

All patients were premedicated with oral diazepam 10 mg and roxatidine 75 mg 90 min before their arrival in the operating room and with morphine 5 mg i.m. 30 min before the arrival.

In the DFK group, anesthesia was induced with divided doses of fentanyl 5–10 $\mu g \cdot kg^{-1}$ and ketamine 1.5 $mg \cdot kg^{-1}$, and maintained with a continuous infusion of ketamine at 2 $mg \cdot kg^{-1} \cdot h^{-1}$. Total doses were 30 $\mu g \cdot kg^{-1}$ for fentanyl and 0.25 $mg \cdot kg^{-1}$ for droperidol.

In the AOI-F group, anesthesia was induced with thiopental 3 $mg \cdot kg^{-1}$ and fentanyl 5–10 $\mu g \cdot kg^{-1}$ in divided dose and maintained with inhalation of isoflurane (0.25%–1.0%) in oxygen and air, and fentanyl in a total dose of 30 $\mu g \cdot kg^{-1}$ was given.

Tracheal intubation was facilitated with intravenous vecuronium 0.1 $mg \cdot kg^{-1}$ in both groups. Ventilation with oxygen in air was controlled to maintain Pao_2 at 100–200 mmHg. Intraoperative muscle relaxation was achieved with vecuronium. At the end of surgery, either ketamine infusion or inhalation of isoflurane was terminated.

Prostaglandin E_1 was continuously infused at 10–20 $ng \cdot kg^{-1} \cdot min^{-1}$ to decrease peripheral resistance. Isosorbide dinitrate as a coronary dilator was also continuously administered at 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Urinastatin 300 000 U and methylprednisolone 1.5 g were given during CPB. Catecholamines were infused if necessary.

Blood sampling and measurement of hormones

Arterial blood samples (5 ml) were collected to measure plasma concentrations of cortisol, aldosterone, ADH and ANP at the following times: before and at 1 h after the induction of anesthesia, before and at 1 h after the initiation of CPB, before and at 1 h after the end of CPB, and before and at 1 h after the end of surgery. The blood samples were immediately centrifuged with an anticoagulant and the plasma was stored at −20°C until analysis.

Plasma levels of aldosterone, ADH, and ANP were determined by radioimmunoassay.

Table 1. Patient profile

	DFK	AOI-F
Number of patients	7	7
Age (years)	65.1 ± 2.5	59.6 ± 4.6
Body weight (kg)	58.9 ± 2.7	56.0 ± 4.5
Height (cm)	159.9 ± 2.4	155.7 ± 3.6
Duration of: Operation (min)	305.1 ± 32.0	403.6 ± 62.6
CPB (min)	131.1 ± 16.0	194.1 ± 32.6
Cross-clamping (min)	76.6 ± 9.2	82.1 ± 14.1
Urine output ($ml \cdot kg^{-1} \cdot min^{-1}$):		
Before CPB	3.2 ± 1.0	4.0 ± 0.9
During CPB	6.4 ± 0.7	11.2 ± 2.3
After CPB	8.4 ± 1.2	10.6 ± 2.7

Mean ± SEM.
DFK, total intravenous anesthesia with ketamine in combination with droperidol and fentanyl; AOI-F, isoflurane-fentanyl anesthesia; CPB, cardiopulmonary bypass.

Statistics

Intergroup statistical comparison was analyzed by an unpaired *t*-test and intragroup analysis was performed by repeated measures analysis of variance (ANOVA) followed by Fisher's least significant difference test. *P* values less than 0.05 were considered significant.

Results

Demographic data

Table 1 shows no significant difference between the two groups in the patients' demography concerning age; height; weight; durations of surgery, CPB, and aorta cross-clamping; and urine output.

Hemodynamic data

Although ketamine was used as the main anesthetic in the DFK group, neither heart rate nor arterial blood pressure in the DFK group was significantly different from those in the AOI-F group (Table 2).

Endocrine responses

Plasma cortisol levels were not increased by anesthesia alone in both groups; they increased after the start of surgery, particularly during CPB. After the end of CPB, they remained significantly higher than the preanesthetic concentrations in both groups (Fig. 1A). Although the plasma concentrations of ADH were not changed by anesthesia alone, they increased significantly during CPB (Fig. 1B).

Plasma ANP levels remained unchanged until the end of total CPB when it increased significantly in both groups (Fig. 2A). The plasma levels of aldosterone increased significantly after the end of CPB in both groups (Fig. 2B).

Discussion

The endocrine and hemodynamic data in this study suggest the DFK may not stimulate sympathetic activity in cardiac patients because their blood pressures, heart rates, and any stress hormones such as cortisol, ADH,

Table 2. Hemodynamics during anesthesia and surgical procedures

		Pre-Anes	Post-IT	Anes30′	Anes60′	PreCPB	CPB30′	CPB60′	CPBoff	PCPB30′	PCPB60′	End-Op
HR	DFK	64.7 ± 5.3	59.9 ± 2.5	65.6 ± 6.5	76.1 ± 5.4	81.7 ± 5.9	/	/		HR was fixed at 100 bpm		
	AOI-F	72.3 ± 6.1	68.3 ± 4.3	65.7 ± 4.1	72.1 ± 6.1	92.9 ± 8.0	/	/		by pacemaker after CPB.		
SBP	DFK	135.0 ± 7.5	112.0 ± 6.5	123.7 ± 10.8	92.3 ± 5.4	96.0 ± 4.5	/	/	124.6 ± 8.8	139.0 ± 9.0	124.7 ± 6.3	127.9 ± 8.3
	AOI-F	137.4 ± 8.2	129.1 ± 5.9	113.1 ± 6.9	111.6 ± 7.6	107.0 ± 5.0	/	/	125.7 ± 8.1	123.7 ± 9.6	133.0 ± 9.3	135.4 ± 8.1
MBP	DFK	92.7 ± 5.3	80.0 ± 5.2	85.3 ± 8.1	71.4 ± 7.4	65.1 ± 3.8	58.4 ± 4.4	58.2 ± 6.0	76.4 ± 3.0	77.1 ± 3.9	82.7 ± 4.9	84.3 ± 6.3
	AOI-F	92.1 ± 6.0	87.1 ± 4.8	82.6 ± 6.3	78.6 ± 6.6	75.4 ± 3.9	65.3 ± 3.6	65.4 ± 4.9	69.6 ± 3.7	72.9 ± 6.5	74.9 ± 4.2	75.1 ± 2.5
DBP	DFK	68.0 ± 3.9	60.3 ± 3.3	60.0 ± 4.0	53.7 ± 2.6	55.1 ± 3.0	/	/	58.3 ± 1.6	58.7 ± 4.4	56.4 ± 3.2	58.7 ± 3.8
	AOI-F	66.7 ± 4.0	67.0 ± 4.3	64.9 ± 4.6	64.4 ± 4.8	63.0 ± 3.4	/	/	53.4 ± 2.4	53.4 ± 4.3	59.7 ± 4.2	57.7 ± 3.2
CVP	DFK	/	/	5.6 ± 0.6	5.4 ± 1.1	5.7 ± 1.2	4.4 ± 1.7	3.6 ± 1.4	8.1 ± 0.8	7.3 ± 0.6	7.6 ± 0.8	6.7 ± 1.0
	AOI-F	/	/	6.4 ± 0.9	6.7 ± 1.0	7.1 ± 1.0	8.3 ± 2.0	7.1 ± 1.8	8.4 ± 1.1	8.7 ± 0.9	8.7 ± 0.5	7.6 ± 1.0
TEMP	DFK	/	−0.3 ± 0.2	−0.3 ± 0.2	−0.2 ± 0.2	−0.2 ± 0.3	−5.3 ± 0.7	−1.6 ± 0.4	1.0 ± 0.4	−0.1 ± 0.2	−0.3 ± 0.2	−0.6 ± 0.2
	AOI-F	/	−0.2 ± 0.1	−0.2 ± 0.1	−0.2 ± 0.1	−0.5 ± 0.5	−4.7 ± 0.6	−1.9 ± 0.5	1.1 ± 0.4	−0.3 ± 0.2	−0.6 ± 0.3	−0.4 ± 0.2

Mean ± SEM.
Anes: anesthesia, IT: tracheal intubation, CPB: cardiopulmonary bypass, PCPB: post CPB, HR: heart rate (bpm), SBP: systolic blood pressure (mmHg), MBP: mean blood pressure (mmHg), DBP: diastolic blood pressure (mmHg), CVP: central venous pressure (mmHg), TEMP: esophageal temperature—rectal temperature (°C).

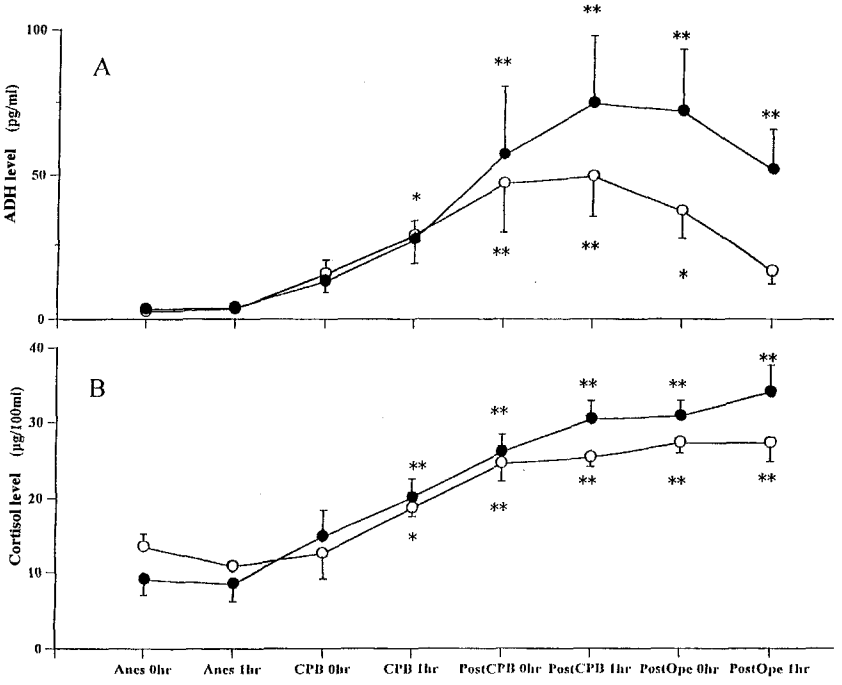

Fig. 1A,B. Changes in plasma levels of antidiuretic hormone (**A**) and cortisol (**B**). All values are expressed as mean ± SEM. *Open circles*, DFK group; *closed circles*, AOI-F group; Anes 0 hr, start of anesthesia; Anes 1 hr, 1 h after start of anesthesia; CPB 0 hr, start of cardiopulmonary bypass; CPB 1 hr, 1 h after start of cardiopulmonary bypass; PostCPB 0 hr, end of cardiopulmonary bypass; PostCPB 1 hr, 1 h after end of cardiopulmonary bypass; PostOpe 0 hr, end of operation; PostOpe 1 hr, 1 h after end of operation. $*P < 0.05$, $**P < 0.01$ versus Anes 0 hr

and aldosterone were not increased by the anesthesia alone. Ketamine, however, is well known to increase blood pressure, heart rate, and stress hormones [12,13]. Our previous reports [6,14] also indicate that the combination of droperidol and fentanyl can attenuate ketamine-induced excessive central sympathetic stimulation. We observed that ketamine following the administration of droperidol and fentanyl did not cause any appreciable elevation in heart rate, blood pressure, and epidural pressure, which is an index of cerebrospinal fluid pressure [15,16].

Tuman et al. [11] found that TIVA using ketamine and diazepam could reduce postoperative excessive fluid accumulation with less postoperative diuretic use in patients who underwent heart valve or coronary artery bypass surgery, as compared to high-dose fentanyl anesthesia. In the present study, we did not find any differences in diuresis-related hormone levels and urine output between both groups.

Lehtinen et al. [17] reported an increase in plasma ADH following fentanyl administration. However, we did not observe any increase in plasma ADH after the administration of fentanyl 30 $\mu g \cdot kg^{-1}$ in either group. An appreciable increase was observed only during the surgical procedures.

Iida et al. [18] and Murakawa et al. [19] reported that plasma ANP was not increased by inhalation anesthesia or by surgical stress. However, the response of ANP to fentanyl remains controversial. Vollmar et al. [20] reported that fentanyl increased ANP secretion in the rat,

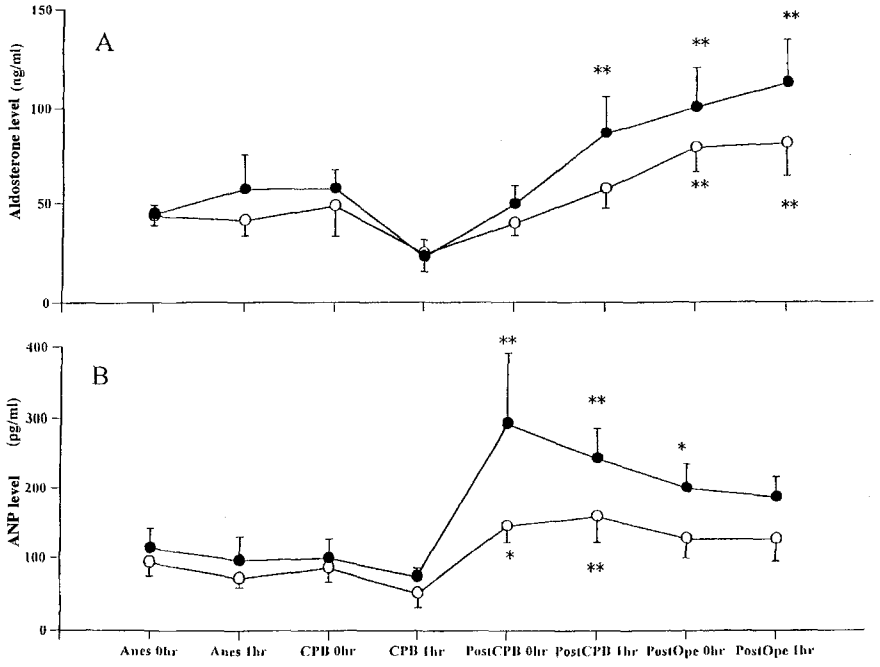

Fig. 2A,B. Changes in plasma levels of aldosterone (**A**) and atrial natriuretic peptide (*ANP*) (**B**). All values are expressed as mean ± SEM. *Open circles*, DFK group; *closed circles*, AOI-F group; Anes 0 hr, start of anesthesia; Anes 1 hr, 1 h after start of anesthesia; CPB 0 hr, start of cardiopulmonary bypass; CPB 1 hr, 1 h after start of cardiopulmonary bypass; PostCPB 0 hr, end of cardiopulmonary bypass; PostCPB 1 hr, 1 h after end of cardiopulmonary bypass; PostOpe 0 hr, end of operation; PostOpe 1 hr, 1 h after end of operation. $*P < 0.05$, $**P < 0.01$ versus Anes 0 hr

while Hoffman et al. [21] observed no change in the plasma level. Thus, there are no definite clinical reports of fentanyl increasing plasma ANP. Our study also showed that ANP levels in both groups did not change after fentanyl administration.

Oyama et al. [9] reported that ANP could be decreased during total CPB by hemodilution and by blockage of blood flow from the atria to the systemic circulation. In our study, plasma ANP decreased by about 30% with no significance in either group during total CPB.

Contrary to previous reports [7,9,10], plasma levels of aldosterone were not increased during the surgical procedures before or during CPB in either group. Methylprednisolone given during CPB might depress the plasma aldosterone level although plasma cortisol increased significantly.

In conclusion, we observed similar and stable endocrine responses and hemodynamics in cardiac patients during DFK as compared with those during AOI-F.

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