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Responses of Vasopressin Release in Patients with Cardiopulmonary Bypass Anesthetized with Enflurane and Morphine

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Changes in plasma level of arginine vasoprepssin (AVP), arterial pressure, and urine flow were studied before, during and after cardiopulmonary bypass (CPB) in 11 patients with congenital heart disease. Anesthesia was induced with thiopental sodium (3-5 mg/kg) and was maintained with enflurane (1.0-1.5%), 50% N_2O in O_2 and morphine (0.5 mg/kg). Concentration of plasma AVP Increased slightly from 3.8±1.5 pg/ml after induction and increased 3-fold after sternotomy. Plasma AVP level increased to 132±26 pg/ml and 218±54 pg/ml after 5 and 60 min on CPB, respectively. When the circulation returned to normal, plasma AVP level decreased gradually but was still significantly higher at 24 hr (13.4±2.5 pg/ml). Marked osmolar diuresis was induced with mannitcl in the priming solution used during the CPB: increases in urine flow, Na excretion and osmolar clearance. Possible mechanisms of marked increase in AVP release and differences of AVP responses during CPB reported by other investigators are discussed.

Key words: *Arginine vasopressin, enflurane anesthesia, cardiopulmonary bypass*

INTRODUCTION

Marked elevation of plasma level of arginine vasopressin (AVP; antidiuretic hormone) has been reported during a surgery using cardiopulmonary bypass (CPB) in man (Philbin & Coggins, 1978 a, b; Wu et al., 1980; de Lange et al., 1982; Viinamaki et al., 1986). Thus, renal functions in patients undergoing the CPB has long been investigated. The incidence of renal failure in these patients is relatively low, whereas the mortality rate from this complication is unacceptably high (Abel et al., 1976). Furthermore, AVP at high plasma level is a strong vasoconstrictor (Heyndrickx et al., 1976) and may result deleterious hemodynamic effects in CPB patients (Philbin et al., 1979). Reported peak AVP levels during the CPB surgery are variable among different investigators and it seems to be related to the anesthetics used. Plasma AVP level was more than three times higher in CPB patients anesthetized with halothane (Philbin & Coggins, 1978a) than in those anesthetized with fentanyl (Stanley et al., 1978; Viinamaki et al., 1986). Recently in the Western countries, opioid drugs like fentanyl, sufentanil or alfentanil (de Lange et al., 1982) were used for anesthesia in CPB because they were known to suppress the endocrine and hemodymanic responses observed during halothane anesthesia. However, there is no report on the effect of enflurane anesthesia on the AVP response to the cardiac surgery. Enflurane is routinely used in our university hospital. Therefore, We measured the plasma AVP level during CPB in patients anesthetized with enflurane to compare with values reported by Western investigators used different anesthetics.

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MATERIALS & METHODS

Eleven patients scheduled for elective open-heart operations were selected for study. Ages ranged from 4 to 24 years (11.1±5.4). The main disease was congenital heart disease including ventricular septal defect (7 cases) and atrial septal defect (4 cases). None had evidence of significant hepatic, renal, pulmonary or central nervous system pathology. All patients belonged to NYHA functional class I or II.

All patients were premedicated with morphine (0.1-0.2 mg/kg i.m.) 60 minutes before induction of anesthesia. Prior to anesthesia an intravenous line was established. And a radial artery catheter was inserted percutaneously which was attached to an arterial pressure transducer for arterial pressure monitoring. An indwelling urinary catheter was inserted. Anesthesia was induced with thiopental sodium (3-5 mg/kg) and endotracheal tube was inserted under succinylcholine-induced (1.0 mg/kg) paralysis. Maintenance of anesthesia was achieved with enflurane (1.0-1.5%), N_2O in O_2 and morphine (0.5 mg/kg). Pancuronium bromide was used intravenously as muscle relaxant. After induction of anesthesia a central venous pressure catheter was placed percutaneously in the right atrium through the internal jugular vein, and an esophageal thermister probe was inserted into the nasopharynx.

For high-flow cardiopulmonary bypass (2.4 l/min/m^2 of body surface), a Shiley bubble oxygenator primed with Hartmann's solution (1300-1700 ml) containing albumin (25 g), mannitol (12.5 g) and heparin (3 mg/kg), and Sarns roller pump were used with moderate hypothermia at 26-28°C rectally. The osmolality of the priming solution was 375 mOsm/kg. The blood cardioplegia and topical cooling with ice-slushed cold saline were used for global myocardial protection. The perfusion time was 68.5±15.8 min (range 55-105).

Postoperatively, all patients were assisted with artificial respirator until the return of consciousness. 500 ml/m^2 of 5% glucose in water was given intravenously on the day of operation, and whole blood, plasma, potassium and sodium were added as needed. Fluid administration was 750 ml/m^2 on the second postoperative day.

Blood and urine samples were taken as follows; before and after induction of anesthesia, after sternotomy, 5, 30 and 60 min after the beginning of CPB and 1, 6, 12 and 24 hrs after the operation. Plasma samples separated from the heparinized blood were stored at −20°C until plasma AVP assay. Plasma AVP was extracted by using Sep-Pak C_{18} and determined by radioimmunoassay (Lee et al. 1987). Plasma and urine osmolalities were determined by the osmometer (Advanced Inc.) using freezing point depression. Na and K were determined by the flame photometer (Beckman). Osmolar clearance (Cosm) and free water clearance (C_{H_2O}) were calculated according to the following formulas:

$$Cosm=\frac{Uosm\ V}{Posm},\quad C_{H_2O}=V-Cosm$$

(Uosm=urine osmolarity, V=urine flow rate, Posm=plasma osmolarity)

RESULTS

Changes in plasma AVP concentration, right atrial pressure, mean arterial pressure and plasma osmolality during the study period are shown in Fig. 1. Plasma AVP concentration increased slightly from 3.8±0.9 to 5.4±1.5 pg/ml after induction and increased three-fold after sternotomy. Plasma AVP concentration level increased sharply to 132±26 pg/ml 5 min after

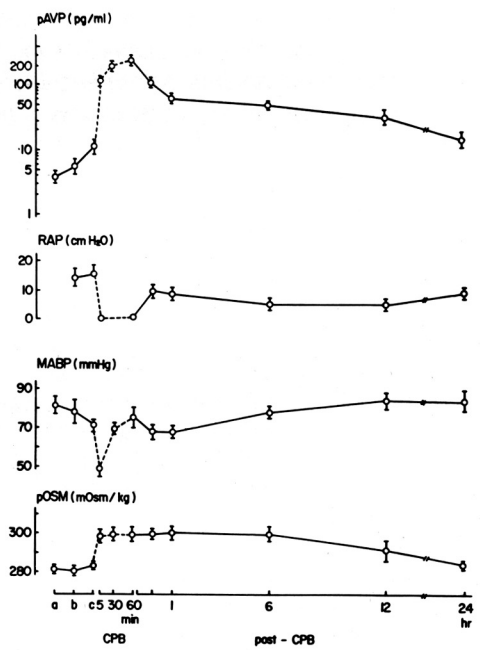

Fig. 1 Changes in plasma AVP concentration (pAVP), right atrial pressure (RAP), mean arterial blood pressure (MABP) and plasma osmolality (pOsm) pre-, during- and post-cardiopulmonary bypass (CPB) in 11 patients with congenital heart disease.
a: pre-induction, b: post-induction, c: post-sternotomy.

Table 1. Changes in urinary excretion of solutes, and osmolar and free water clearances (Cosm. C_{H_2O}) during cardiopulmonary bypass (CPB)

	Pre-CPB	During CPB		Post-CPB		
		0.5	1	1	6	24 Hr
V, ml/min	0.31	0.75	1.22	2.84	1.86	0.71
UosmV, μOsm/min	196	408	458	925	420	312
UNaV, μEq/min	47.2	96.7	167.3	355.3	293	249
UkV, μEq/min	55.8	37.3	35	118.5	97	92
Cosm, ml/min	0.72	1.37	1.62	3.63	1.41	1.07
C_{H_2O}, ml/min	−0.42	−0.67	−0.35	−0.79	−0.41	−0.36

Values are means of 4 subjects.

CPB and increased further to 218±54 pg/ml at 60 min of CPB. When the heart started pumping after weaning from CPB and normal circulation began, plasma AVP level dereased continuously but was still significantly higher at 24-hr (13.4±2.5 pg/ml) than the pre-induction period (3.8±0.9 pg/ml).

Right atrial pressure was 15.8 cm H_2O before CPB, dropped to zero during CPB, then increased to 9.6 cm H_2O immediately after the heart started pumping and maintained approximately 7 cm H_2O thereafter. Mean arterial pressure was 71 mmHg before CPB and dropped to 49 mmHg at 5 min of CPB. Then, arterial pressure returned to normal level throughout the study period. Plasma osmolality was 280 mOsm/kg before CPB, but increased to 300 mOsm/kg during CPB because of hypertonicity of the priming solution infused. Plasma osmolality remained high even 6 hrs after the surgery, then decreased gradually to 282 mOsm/Kg at 24 hr. Plasma concentrations of Na and K were not changed significantly throughout the study period. Body temperature was maintained at 27.9°C during CPB and raised to 37°C after heart started pumping.

Urine data are summarized in Table 1. During CPB, there was a marked osmolar diuresis; increases in urine flow, Na excretion and osmolar clearance. Urine flow decreased gradually and returned to the normal range 12 hrs after the operation.

DISCUSSION

In general, plasma AVP level did not change significantly after anesthesia, but increased after surgical incision and increased further during the cardiopulmonary bypass (CPB, Philbin & Coggins, 1978a; Staniey et al., 1979; Viinamaki et al., 1986). Responses of AVP release to surgical operations were remarkably variouse in different reports. Reasons for the different AVP responses during the surgery are not clear, but it seems to be primarily due to the anesthetics used.

Table 2 summarizes the AVP responses during surgical procedure of CPB in patients anesthetized with different drugs. Plasma AVP level was slightly increased after anesthesia with enflurane or halothane, but was not changed after anesthesia with opioid drugs like fentanyl, alfentanil or sufentanil. After surgical incision plasma AVP level was increased to above 100 pg/ml in halothane anesthetized patients, but was moderately increased in morphine or enflurane anesthetized patients. Anesthesia with high-dose of fentanyl, alfentanil or sufentanil. completely blocked the increase in AVP release during surgical incision. Immediately after the beginning of the CPB, plasma AVP level increased abruptly. Peak AVP levels during the CPB were remarkably different among patients anesthetized with different drugs: enflurane (264 pg/ml), halothane (174 pg/ml), halothane-fentanyl (120 pg/ml), and fentanyl (47 pg/ml). Fentanyl-O_2 anesthesia blocked the increase in plasma AVP level which occured during cardiac surgery before CPB but partially blocked that occured during CPB. Unlike fentanyl, however, alfentanil and sufentanil blocked the AVP responses both before and during CPB.

A high dose of an opioid drug fentanyl (50-100 μg/kg) plus oxygen is often used for anesthesia in CPB in the Western countries. Fentanyl blunts the responses of the increase in plasma levels of AVP, cortisol, growth hormone and glucose observed during halothane anesthesia (Hall et al., 1978; Stanley and Webster, 1978; Viinamaki et al., 1986). Furthermore, alfentaril and sufentanil seems to be more effective than fentanyl in blocking AVP responses and stabilizing cardiovascular dynamics during CPB (de Lange et al., 1982). Mechanisim of AVP response to different anesthetics during the surgery is unknown. Philbin and Coggins (1978b) observed that increase in depth of anesthesia that occur with high doses of morphine suppressed AVP responses to surgical stimulation. However, it was not true in fentanyl-like drugs: enormous doses of fentanyl did not prevent the increase

Table 2. Comparison of plasma AVP levels during surgical procedure of cardiopulmonary bypass (CPB) in patients anesthetized with different drugs

(pg/ml)

Anesthetics	Control	Anesthesia	After incision & sternotomy	During CPB	Surgery	Reference
Enflurane	3.8±0.9	5.4±1.5	11.7±3.7	218±54		present study
Halothane	10.8±7.0	12.0±6.0	125±53	174±28	CAB	Philbin & Coggins, 1978a
Halothane	2.8±1.2	8.0± 5.0	102±29		CAB	Philbin & Coggins, 1978b
Morphine (1mg/kg)	3.9±1.0	3.6±1.4	4.3 ±25			
(2mg/kg)	2.8±1.8	6.0± 4.0	14.5±70			
Halothane + Fentanyl	6.1±1.4	17.0± 4.0	80±22	12 0±20	CAB	Wu et al., 1980
			56±13	93±13	AVR	
			34±9	72±13	MVR	
Fentanyl	5±2	5±2	4±2	47±8	CAB	Stanley et al., 1978
Fentanyl	7.9±0.9	5.6±1.1	4.8±0.8	27.7±1.4	mixed	Viinamaki et al., 1986
Alfentanil	11.9±0.9	7.7±0.3	8.3±0.8	8.1±0.3	CAB	de Lange et al., 1982
Sufentanil	8.1±1.0	7.4±0.3	8.6±0.4	7.0±0.4		

Values are means±SEM.

Abbreviations used are: AVP; arginine vasopressin, CAB; coronary artery bypass, AVR; aortic valve replacement, MVR; mitra valve replacement

in AVP release during CPB (de Lange et al., 1982).

The mechanisms producing increase in AVP release during CPB is not clear. AVP secretion is mainly affected by changes in blood osmolality and volume. Acute changes in systemic hemodynamics can stimulate volume receptors both in the low-pressure system (left-atrium) of the circulation and the high-pressure system (carotid and aortic circulation), and control AVP release via the parasympathetic pathways (Share, 1974; Schrier et al., 1979; Ledsome, 1985). During CPB, osmoreceptors, atrial volume receptors and barorecptors could all be stimulated for AVP release. Among these, atrial receptors seem to be stimulated the most. Plasma osmolality increased by approximately 20 mOsm/kg during CPB in the present study which may be expected to increase plasma AVP level only about 20 pg/ml (Liard, 1984). Mean arterial pressure decreased at the beginning of CPB but raised to the normal level soon. Therefore, the baroreceptors were only transiently stimulated for AVP release. On the other hand, the atrial pressure remained zero throughout the CPB, and there is a negative correlation between atrial distension and AVP release (Ledsome, 1985). Therefore, an abrupt increase in AVP secretion at the begining of the CPB and continuously massive increase during CPB seem to be mostly due to strong and continuous stimuli of the atrial volume receptors while the heart stopped pumping. There were considerable individual variations in the response of AVP release to perioperative stimuli. When the operation was completed, plasma AVP level fall fast during the first hour and gradually thereafter. Viinamaki et al. (1986) reported that it book 4 days for plasma AVP level to return to the preoperative level.

Plasma AVP concentrations during and after the CPB were high enough to produce pharmacological effects. In humans especially the old patients, a single injection of high dose of vasopressin (5-20 U) may lead to pallor, angina pectoris, myocardial ischemia or even infarction (Slotnik & Teigland, 1951). Deleterious effects on hemodynamics by acute rise in plasma AVP in CPB patients also have been reported (Philbin & Coggins, 1978; Philbin et al., 1979). In dogs, infusion of large amount of vasopressin produced powerful vasoconstrictions of coronary, iliac and mesenteric beds, while exerted only a minor effect on the renal bed (Heyndrickx et al., 1976). These observations suggest that the use of vasodilators, antihypertensive drugs or vasopressin V receptor antagonists is needed for reversing the harmful effects of strong vasoconstriction during CPB and recovery period.

Plasma AVP levels at the time of surgical operations in general were far higher than was required to achieve a maximum antidiuresis (Fieldman et al., 1985; Viinamaki et al., 1986). Under normal condi-

tions, maximum autidiuresis is produced when plasma AVP level becomes approximately 5-10 pg/ml (Schrier et al., 1979; Lee et al., 1987). An oliguria following surgical operation was firstly observed by Pringle et al. in 1905. Later, AVP was recognized to be responsible for the diminished urine flow in perioperative period (Le Quesne & Lewis, 1953; Eisen & Lewis, 1954; Dudley et al., 1954). Open heart surgery stimulated AVP secretion much greater than other operations. The magnitude and duration of the secretory response of AVP seemed to be proportional to the severity of the surgical procedure (Moran and Zimmerman, 1967). Renal failure during CPB is relatively low, whereas the mortality rate from this complication remains unacceptably high (Abel et al., 1976). To prevent the renal failure and to increase the urine formation during the surgery, diuretics have been routinely used. Although plasma AVP was extremely high during the present operation, urine flow and osmolar clearance were high because of mannitol and diuretics used. Since it takes several days for plasma AVP to return to the basal level after the CPB (Viinamaki et al., 1986), it is necessary to use diuretics until that time.

The present study demonstrates that pAVP during CPB in patients anesthetized with enflurane is remarkably higher than values reported in patients anesthetized with halothane or potent synthetic opioid like fentanyl, alfentanil and sufentanil. These opioid drugs are known not only to stabilize the cardiovascular dynamics, but also to suppress the rise in plasma glucose and release of hormones like AVP, cortisol and growth hormone. Therefore, it seems worthwhile to use fentanyl or other opioid anesthetics, and I suggest a cooperative multicenter trial to help resolve the comparative responses of different races.

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