CHANGES OF KALLIKREIN AND SEROTONIN IN PLASMA DURING AND AFTER OPEN-HEART SURGERY

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Plasma kallikrein activity and plasma serotonin were studied during and after open-heart surgery in 15 patients with extracorporeal circulation and in 15 patients with surface-induced deep hypothermia. Following results were obtained: 1) Plasma kallikrein activity which reflects the activation of the kinin system, showed no significant change during extracorporeal circulation, and significantly increased three hours after the termination of perfusion. However, there was no significant difference in plasma kallikrein activity between the patients with and without low cardiac output syndrome (LOS). In surface-induced deep hypothermia, plasma kallikrein activity showed no significant change during and after operation. 2) Plasma serotonin significantly decreased during both extracorporeal circulation and hypothermia. Moreover, there was no significant difference in plasma serotonin between the patients with and without postoperative LOS or pulmonary hypertension. It is assumed that plasma serotonin may not play an important role in regulating blood pressure during or after open-heart surgery with either extracorporeal circulation or surface-induced deep hypothermia.

IT has been recently apparent that the lungs play an important role in the metabolism of such vasoactive substances as norepinephrine, angiotensin I, serotonin, bradykinin and so on! In open-heart surgery under extracorporeal circulation the lungs are bypassed during the operation, while in open-heart surgery under surface-induced deep hypothermia metabolic activity of the whole body including the lungs decreases with a lowering of body temperature. Therefore, it is assumed that the abnormal metabolism of the lungs results in some changes in vasoactive

substances in plasma during and after open-heart surgery. However, no definite conclusion has been obtained.

The present studies were performed to investigate the changes of kinin system and serotonin in plasma during and after open-heart surgery in relation to hypotension during the operation and postoperative low cardiac output syndrome (LOS).

MATERIALS AND METHODS

In open-heart surgery with extracorporeal circulation, 15 patients, including 9 patients with acquired heart diseases and 6 patients with congenital heart diseases were subjected to the present studies. Age distribution ranged from 11 years old to 58 years old with an average age of 35 years.

Key Words:

Plasma kallikrein activity
Plasma serotonin
Kinin system
Extracorporeal circulation
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TABLE 1 CHANGES OF PLASMA KALLIKREIN ACTIVITY AND PLASMA SEROTONIN DURING AND AFTER OPEN-HEART SURGERY UNDERGOING EXTRA-CORPOREAL CIRCULATION

	ECC				Postoperative Periods					
	T ₀	T ₁	T ₂	T ₃	T ₄	T ₅	T ₆	T ₇	T ₈	T ₉
Plasma Kallikrein Activity (U/ml)	0.47*	0.33	0.32	0.40	0.45	0.63	0.45	0.39	0.37	0.34
	±0.15	±0.13	±0.15	±0.13	±0.13	±0.16	±0.14	±0.13	±0.11	±0.09
		<i>p</i> < 0.001	<i>p</i> < 0.001	<i>p</i> < 0.05	NS	<i>p</i> < 0.001	NS	<i>p</i> < 0.05	<i>p</i> < 0.05	<i>p</i> < 0.01
		(0.44 ±0.16)	(0.43 ±0.17)	(0.53 ±0.15)						
		NS	NS	NS						
Plasma Serotonin (μg/ml)	0.24*	0.12	0.12	0.14	0.17	0.26	0.28	0.27	0.23	0.33
	±0.05	±0.05	±0.05	±0.07	±0.07	±0.10	±0.09	±0.12	±0.08	±0.12
		<i>p</i> < 0.001	<i>p</i> < 0.001	<i>p</i> < 0.01	<i>p</i> < 0.01	NS	NS	NS	NS	<i>p</i> < 0.05
		(0.16 ±0.06)	(0.16 ±0.05)	(0.18 ±0.09)						
		<i>p</i> < 0.01	<i>p</i> < 0.01	<i>p</i> < 0.05						

T₀: before extracorporeal circulation (ECC)

T₂: 30 to 60 minutes after onset of ECC

T₄: 5 minutes after termination of ECC

T₆: 8 hours after ECC

T₈: 3 days after ECC

*: basal value for statistical analysis

NS: no significance

T₁: 5 minutes after onset of ECC

T₃: 61 to 120 minutes after onset of ECC

T₅: 3 hours after ECC

T₇: 1 day after ECC

T₉: 5 days after ECC

( ): recalculated value in terms of 25% hemodilution

In extracorporeal circulation a roller pump and a disposable bubble oxygenator were used. The returned venous blood was drawn back into the oxygenator by gravity. The hemodilution rate was about 25%, and the core cooling was added to $29.7 \pm 2.2^\circ\text{C}$ in the rectal temperature. The flow rate was $2.2 \pm 0.3 \text{ L/m}^2/\text{min}$. The total perfusion time was 34 to 334 minutes with an average of 110 minutes. Infusion of Young's solution (1 ml/kg) into the aortic root immediately after aortic cross-clamping and topical cardiac cooling by ice slush was carried out for myocardial protection. Priming fluids into the heart lung machine contained 20 ml/kg of heparinized blood, 10 ml/kg of 10% maltose and 4 ml/kg of mannitol. Heparin (3 mg/kg) was administered intravenously prior to the cannulation for perfusion, and protamine sulfate (6 mg/kg) was used for neutralization of heparin at the termination of the perfusion. Anesthesia was induced with pentobarbital and succinylcholine and maintained with halothane or neurolepto-anesthesia.

In open-heart surgery with surface-induced

deep hypothermia, 15 patients with congenital heart diseases were subjected to the present studies. Age distribution ranged from 7 months to 8 years with an average age of 3.1 years. Surface-induced deep hypothermia was performed according to the method reported by Okamura.² Anesthesia was induced with pentobarbital and succinylcholine and maintained with ether and oxygen in a closed system. After deep anesthesia was induced with ether, the patient wrapped in a vinyl sheet was placed in an ice water bath until the anticipated esophageal temperature was reached. Immediately after completion of the intracardiac repair, resuscitation was carried out by coronary perfusion of blood using the pulsatile fashion by syringe, and the cold water was replaced with warm water of 42°C . The rewarming was carried out up to 34°C . The transfusion was made with 10 ml per kg of low molecular weight dextran during the cooling period and with 5 per cent xylitol and blood during the rewarming period. One mg per kg of heparin was given intravenously at 30°C in the cooling period, and 2 mg per kg of protamine sulfate was used

TABLE II CHANGES OF PLASMA KALLIKREIN ACTIVITY AND PLASMA SEROTONIN DURING AND AFTER OPEN-HEART SURGERY UNDERGOING SURFACE-INDUCED DEEP HYPOTHERMIA

	Cooling			Rewarming		Postoperative Periods			
	t_0	t_1	t_2	t_3	t_4	t_5	t_6	t_7	t_8
Plasma Kallikrein Activity (U/ml)	0.43*	0.34	0.38	0.38	0.48	0.44	0.36	0.41	0.38
	± 0.14	± 0.07	± 0.10	± 0.08	± 0.14	± 0.10	± 0.14	± 0.10	± 0.18
		NS	NS	NS	NS	NS	NS	NS	NS
Plasma Serotonin ($\mu\text{g/ml}$)	0.26*	0.18	0.13	0.24	0.39	0.37	0.29	0.31	0.30
	± 0.08	± 0.06	± 0.04	± 0.11	± 0.13	± 0.14	± 0.13	± 0.14	± 0.11
		$p < 0.02$	$p < 0.01$	NS	NS	NS	NS	NS	NS

t_0 : before cooling

t_2 : the lowest temperature

t_4 : recovery to normal body temperature

t_6 : 1 day after operation

t_8 : 5 days after operation

NS: no significance

t_1 : 30°C during cooling period

t_3 : 30°C during rewarming period

t_5 : 3 to 6 hours after operation

t_7 : 3 days after operation

*: basal value for statistical analysis

for neutralization of heparin. The lowest esophageal temperature reached was from 20 to 24°C with an average of 23°C, and the period of circulatory arrest was from 19 to 55 minutes with an average of 33 minutes.

Plasma kallikrein activity was measured by the method utilizing a synthetic chromogenic substrate reported by Amundsen and Svendsen.³ Plasma serotonin content was measured by Snyder's fluorometric method.⁴ Arterial blood drawn from a peripheral artery (radial or cubital artery) was used for measurement of plasma kallikrein activity and plasma serotonin. In extracorporeal circulation blood samples were collected before extracorporeal circulation (ECC), during ECC (5 minutes, 60 minutes and 120 minutes after the onset of perfusion), after ECC (5 minutes, 3 hours, and 8 hours after termination of ECC) and 1 day, 3 days, and 5 days postoperatively. In hypothermia blood samples were collected before cooling, at 30°C during the cooling period, at the lowest temperature, at 30°C during the rewarming period, at the recovery to normal body temperature, and 1 day, 3 days and 5 days postoperatively. Values were expressed as mean $\pm$ SD. Statistical analysis of the data was performed by Student's test with $p < 0.05$ as a significant level.

RESULTS

1. Plasma kallikrein activity

In the patients undergoing open-heart surgery

with the extracorporeal circulation plasma kallikrein activity decreased during the extracorporeal circulation. However, the recalculated values in terms of hemodilution did not show a significant change. Immediately after the termination of perfusion the plasma kallikrein activity returned to the preoperative level and increased significantly three hours after the operation followed by a continuous decrease during a successive five days (Table I). In the patients undergoing open-heart surgery with surface-induced deep hypothermia, plasma kallikrein activity showed no change throughout the cooling period, the rewarming period, and the postoperative period (Table II).

2. Plasma serotonin

In the extracorporeal circulation, plasma serotonin decreased even in the recalculated value in terms of 25% hemodilution during the extracorporeal circulation and immediately after the termination of perfusion. Postoperatively, plasma serotonin showed no change with the exception of a transient increase five days after the operation (Table I). In the surface-induced deep hypothermia, plasma serotonin decreased only during the cooling period, and showed no significant change during the rewarming period and the postoperative period (Table II).

3. Interrelation between plasma kallikrein or plasma serotonin and LOS

TABLE III CHANGES OF PLASMA KALLIKREIN ACTIVITY IN PATIENTS WITH AND WITHOUT LOW CARDIAC OUTPUT SYNDROME AFTER OPEN-HEART SURGERY UNDERGOING EXTRACORPOREAL CIRCULATION

	Preoperative Value	Postoperative Periods				
		3 hrs	8 hrs	1 day	3 days	5 days
Plasma Kallikrein Activity (U/ml) Without LOS n = 7	0.47* ±0.07	0.60 ±0.13	0.44 ±0.13	0.35 ±0.08	0.35 ±0.09	0.33 ±0.09
		p < 0.01	NS	p < 0.001	p < 0.001	p < 0.001
Plasma Kallikrein Activity (U/ml) With LOS n = 8	0.40** ±0.07	0.59 ±0.12	0.41 ±0.13	0.43 ±0.08	0.39 ±0.09	0.34 ±0.10
		p < 0.02	NS	NS	NS	NS
	NS***	NS	NS	NS	NS	NS

LOS: Low cardiac output syndrome

* control value for statistical analysis of without LOS group

** control value for statistical analysis of with LOS group

*** Statistical analysis: Plasma kallikrein without LOS versus with LOS

NS: no significance

TABLE IV CHANGES OF PLASMA SEROTONIN IN THE PATIENTS WITH AND WITHOUT LOW CARDIAC OUTPUT SYNDROME AFTER OPEN-HEART SURGERY UNDERGOING EXTRACORPOREAL CIRCULATION

	Preoperative Value	Postoperative Periods			
		3-8 hrs	1 day	3 days	5 days
Plasma Serotonin (µg/ml) Without LOS n = 7	0.25 ±0.05	0.20 ±0.09	0.31 ±0.14	0.20 ±0.05	0.39 ±0.09
Plasma Serotonin (µg/ml) With LOS n = 8	0.24 ±0.06	0.31 ±0.13	0.24 ±0.11	0.25 ±0.10	0.27 ±0.13
	NS	NS	NS	NS	NS

LOS: low cardiac output syndrome

Statistical analysis: Plasma serotonin without LOS versus with LOS

NS: no significance

In order to evaluate an interrelation between plasma kallikrein or plasma serotonin and LOS in the extracorporeal circulation, these values in the patients with LOS were compared with those in the patients without LOS. In the patients with LOS, blood pressure was less than 90 mm Hg and inotropic support was required from 24 to 48 hours after the operation. There was no significant difference in either plasma kallikrein activity and plasma serotonin content between the patients with and without LOS (Table III, IV).

4. Interrelation between plasma serotonin and pulmonary hypertension

In order to investigate an interrelation between the change of plasma serotonin and pulmonary hypertension in the surface-induced deep hypothermia, plasma serotonin level in the patients with severe pulmonary hypertension was compared with that in the patients without pulmonary hypertension. In the present studies, 6 patients showed a severe pulmonary hypertension in which systolic pulmonary pressure/systolic systemic pressure (Pp/Ps) was more than 0.75, and 5 patients had a pulmonary pressure

TABLE V CHANGES OF PLASMA SEROTONIN DURING AND AFTER HYPOTHERMIC OPEN-HEART SURGERY IN THE PATIENTS WITH AND WITHOUT PULMONARY HYPERTENSION

	Cooling			Rewarming		Postoperative Periods	
	t_0	t_1	t_2	t_3	t_4	t_5	t_6
Plasma Serotonin ($\mu\text{g/ml}$) Without PH $n = 5$	0.25 ± 0.06	0.19 ± 0.06	0.10 ± 0.04	0.27 ± 0.17	0.34 ± 0.17	0.34 ± 0.18	0.27 ± 0.10
Plasma Serotonin ($\mu\text{g/ml}$) With PH ($\text{Pp/Ps} \geq 0.75$) $n = 6$	0.26 ± 0.10	0.17 ± 0.06	0.15 ± 0.04	0.22 ± 0.03	0.43 ± 0.20	0.27 ± 0.10	0.33 ± 0.17
	NS	NS	NS	NS	NS	NS	NS

PH: Pulmonary hypertension

Pp/Ps: Pulmonary systolic pressure/Systemic systolic pressure

t_0 : before cooling

t_1 : 30°C during cooling period

t_2 : the lowest temperature

t_3 : 30°C during rewarming period

t_4 : recovery to normal body temperature

t_5 : 1 day after operation

t_6 : 3 days after operation

Statistical analysis: Plasma serotonin without PH versus with PH

NS: no significance

in which Pp/Ps was less than 0.45. There was no significant difference in plasma serotonin level between them throughout the cooling period, the rewarming period, and the postoperative period (Table V).

DISCUSSION

Bradykinin and serotonin are recognized as potent pharmacological agents modifying systemic hypotension. Moreover, it is known that the greater part of these agents is metabolized in a single passage through the pulmonary circulation^{4,5,6}. However, there is no definite opinion regarding the role of bradykinin and serotonin either in extracorporeal circulation in which pulmonary circulation is bypassed during open-heart surgery or in surface-induced deep hypothermia in which the metabolism of the whole body including the lungs is transiently depressed during open-heart surgery.

On the involvement of the kinin system associated with extracorporeal circulation, Wiegand⁷ suggested an activation of the kinin system after extracorporeal circulation. Seidel⁸ reported no involvement of the kinin system during extracorporeal circulation. Nagaoka⁹, on the other hand, reported that with the lapse of perfusion time plasma kininogen significantly decreased, while blood kinin significantly increased. The reduction of plasma kininogen was explained as real consumption of kininogen for kinin for-

mation, indicating the activation of the kinin system during extracorporeal circulation. However, the mechanism of activation of the kinin system remains to be clarified.

It is generally recognized that kallikreins are defined as protease which release pharmacologically highly active kinins from kininogens. Namely, plasma kallikrein generates the nonapeptide bradykinin from kininogen. Therefore, it is assumed that plasma kallikrein activity reflects the activation of the kinin system. In the present studies, plasma kallikrein activity decreased during extracorporeal circulation. The decrease was explained as hemodilution. After extracorporeal circulation plasma kallikrein activity significantly increased three hours after the termination of perfusion. It is assumed that the kinin system is not activated during extracorporeal circulation, but activated several hours after the termination of perfusion. There are little information regarding the involvement of the kinin system in low cardiac output syndrome after open-heart surgery. Nagaoka⁹ suggested that the continuous and more marked activation of the kinin system may provide a partial explanation for cardiovascular disturbances which appear during and after extracorporeal circulation, when the heart-lung machine has been used for a long period. However, in the present studies, there was no significant difference in plasma kallikrein between the patients with and without postoperative low cardi-

ac output syndrome. In surface-induced deep hypothermia, plasma kallikrein activity decreased, but not significantly, during the cooling period. After that, plasma kallikrein activity showed no change throughout the rewarming and post-operative period, suggesting no involvement of the kinin system in hypothermic open-heart surgery.

It has been discussed in the surgical field that serotonin is a contributing factor in endotoxin shock,¹⁰ anaphylatic shock,^{11,12} shock lung,¹³⁻¹⁶ pulmonary embolism,¹⁷⁻¹⁹ and hypoxia-induced pulmonary hypertension.²⁰⁻²² Moreover, experimental serotonin-induced pulmonary injuries²³⁻²⁴ or embolisms²⁵⁻²⁷ following serotonin administration have been reported. In extracorporeal circulation, it has been reported that serotonin²⁸ and histamine²⁹ may be the chemical mediators for development of post-perfusion lung syndrome³⁰ because plasma serotonin and histamine are not inactivated in the lungs in the cardiopulmonary bypass circulation and the destruction of platelets during extracorporeal circulation results in an increase of releasing serotonin from platelets.³¹ However, controversy exists in the clinical significance of serotonin associated with open-heart surgery under extracorporeal circulation. In the present studies, plasma serotonin showed a significant decrease during extracorporeal circulation and no significant change postoperatively. Moreover, there was no significant difference in plasma serotonin between the patients with and without postoperative low cardiac output syndrome, suggesting no involvement of serotonin for the regulation of blood pressure during and after extracorporeal circulation. However, we had a patient who died of thromboembolism and renal failure seven days after mitral valve replacement whose plasma serotonin significantly increased postoperatively. On the mechanism of a decrease of serotonin during extracorporeal circulation, Gillis³² reported that pulmonary extraction of serotonin was enhanced after extracorporeal circulation, suggesting that cardiopulmonary bypass may alter the process. Our previous experimental work²³ suggested that a decrease of plasma serotonin during extracorporeal circulation is attributable to the decrease of serotonin production. In surface-induced deep hypothermia, the present work indicated that plasma serotonin transiently decreased only during the cooling period and showed no significant change postoperatively. On the mechanism of the decrease of plasma

serotonin during the cooling period, our previous experimental work³⁴ showed that the decrease of serotonin is presumably due to the decrease of serotonin production because the metabolizing activity of serotonin in the lungs decreases and pulmonary extraction of serotonin in the lungs shows no change during hypothermia. Gillis reported that pulmonary hypertension was associated with increased serotonin extraction by the lungs and return of pulmonary arterial pressure toward normal tended to reverse this abnormality in serotonin removal by the lungs.³⁵ In the present studies there was no significant difference in plasma serotonin between the patients with and without pulmonary hypertension. From the above-mentioned results, it is unlikely that serotonin may play an important role in regulating blood pressure during and after open-heart surgery with either extracorporeal circulation or surface-induced deep hypothermia.

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