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Adrenal Medullary Secretion in Response to Intestinal Strangulation in the Dog

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In dogs caused experimental strangulation obstruction by ligation of the upper small intestine together with the mesentery measuring 80 cm in length, adrenal venous blood was observed for the secretion rate of adrenaline and noradrenaline by the fluorimetric method. Increase of adrenal medullary secretion was not induced by the continued strangulation alone. However, when the strangulation was released three hours after the onset, the secretion rate of adrenaline and noradrenaline increased rapidly. When 250 mg of kanamycin was injected into the strangulated intestinal loop and the obstruction was released three hours later, the increase of adrenal medullary secretion was slight. When the strangulated intestinal loop was resected and anastomosed three hours after the onset of obstruction, the adrenal medullary secretion showed no increase. When strangulation was released after resection of the greater and lesser splanchnic nerves on the side wherefrom the adrenal venous blood was drawn, any increase in secretion rate of adrenaline and noradrenaline did not occur.

In brief, the release of strangulation obstruction was followed by a remarkable increase of adrenal medullary secretion rate and the state of sympathetic overactivity in experimental animals. Therefore one must be careful in the administration of catecholamines at the time of intestinal obstruction and at the time of shock after release.

INTRODUCTION

The lethal factor of intestinal obstruction has not been elucidated. However, from the facts that symptoms of ileus are improved by the use of antibiotics[1)22)] and that the life span of germ-free animals with ileus is elongated and their ascites and intestinal contents are not toxic[5)25)], it is evident that bacteria play an important role in death due to ileus.

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In the studies on the role of bacterial factor in ileus, some investigators emphasized bacteria themselves[19)24)], some placed great importance on endotoxin[2)] or consider exotoxin as the main factor[4)], and others placed great importance on humoral factors which are related to bacteria[13)23)].

Concerning the change of catecholamines as one of the humoral factors, MATSUKURA et al[17)] reported that, at the time of intestinal strangulation, endotoxin produced by gram negative organism such as Escherichia coli is increased in the blood and at the acetylcholine and catecholamines are also increased. However, there have been no studies which observed the change in secretion of catecholamines in the adrenal venous blood at the time of intestinal strangulation. Hence, the author observed the secretion of catecholamines in the adrenal venous blood upon providing strangulation of the upper small intestine in dogs.

METHODS

Dogs weighing 10 to 17 kg were used. The animals were anesthetized with sodium pentobarbital (Nembutal) in a dose of 25mg/kg of body weight injected intravenously. In order to collect the adrenal venous blood, the lumbo-adrenal vein was exposed through the lumbar route and a small glass cannula connected to a rubber tube was inserted into the vein at the site lateral to the adrenal gland[21)]. The cannula and the rubber tube were filled with heparin-saline solution in order to prevent coagulation of blood. A soft silicon tape was placed around the adrenal vein between the posterior vena cava and the adrenal gland. The blood pressure was measured at the femoral artery with mercury manometer. Four hours after these procedures, the adrenal venous blood samples were collected for determination of basal secretion rate. At that time, the silicon tape around the adrenal vein was pulled and the clamp of rubber tube was removed to allow the blood to drip into the test tube. The collection of blood samples was followed by provision of strangulation. For this purpose, laparotomy was performed by means of median incision and the loop of small intestine together with the mesentery extending 80 cm downward from the point 40 cm distant from the Treitz's ligament was tightly ligated with rubber band. This rubber band was fixed on the abdominal wall so that it may be pulled to release the strangulation without performing relaparotomy.

Animals were divided into five groups as follows.

Group 1: Five dogs with strangulation of the small intestine.

Group 2: Five dogs with strangulation of the small intestine released three hours thereafter.

Group 3: Five dogs with stragulation of the small intestine together with injection of 250 mg of kanamycin dissolved in 20 ml of physiological saline solution into the strangulated loop, which was released three hours thereafter.

Group 4: Five dogs with strangulation of the small intestine followed by resection and anastomosis three hours thereafter.

Group 5: Five dogs with resection of the greater and lesser splanchnic nerves and strangulation of the small intestine released three hours thereafter.

The adrenal venous blood samples after production of strangulation were collected at intervals of 60 to 180 minutes in the same procedure as conducted for determination of basal secretion rate, and after release of strangulation, at intervals of 15, 30, 60, 120, 180 and 240 minutes for determination of catecholamines secretion rate. The decrease rate of plasma volume was calculated from the hematocrit values before strangulation and at the time of the collection of adrenal venous blood, using the following equation[14].

$$P = \frac{Ht_1}{100-Ht_1} \times \frac{100-Ht_2}{Ht_2} \times 100\ (\%)$$

The greater and lesser splanchnic nerves were resected on the side of the gland where determination of adrenal medullary secretion rate was made.

The adrenal venous blood samples were immediately centrifuged and 1 ml of the adrenal venous plasma was mixed with 1 ml of 2 per cent sodium fluoride −3 per cent sodium thiosulphate solution. Then, 10 ml of acetate buffer solution were added. The estimation of adrenaline and noradrenaline was carried out by the method of Euler and Lishajko[6].

RESULTS

Group 1

The respiratory rate increased gradually from six hours after strangulation except in dog No. 2, which showed decreased respiratory rate and increased respiratory depth six hours after the strangulation and died in seven hours. All animals died within 7 to 14 hours. The rate of heartbeat, mean blood pressure, secretion rates of adrenaline and noradrenaline are summarized in Table 1. The blood pressure decreased gradually in all cases. Whereas the basal secretion rates of adrenaline and noradrenaline were 0.001−0.008 μg/kg/min and 0.000−0.009 μg/kg/min, respectively, increase of secretion rate was not

observed in this group except for No.1 which showed a slight increase in secrtion rate of adrenaline measuring 0.046 μg/kg/min 12 hours after strangulation. The mean plasma volume decreased by 13.1 per cent in 3 hours, 30.3 per cent in 6 hours and 45.9 per cent in 9 hours after strangulation.

Group 2

Three hours after strangulation, the respiratory rate showed no change. Upon release of strangulation after three hours, the respiration became deep and rough and the respiratory rate increased in 15 to 30 minutes. All cases of this group died within four hours after the release except for No. 8 and No. 10 that died seven and eight hours after the release, respectively. The rate of heartbeat, mean blood pressure and secretion rates of adrenaline and noradrenaline are shown in Table 2. The heartbeat increased remarkably after the release except in No. 8 that showed no change. The blood pressure did not decrease remarkably in any case during the three hours of

Table 1. The Adrenal Medullary Secretion (μg/kg/min), and the Mean Arterial Blood Pressure (mm Hg) and Rate of Heartbeat in the Group 1

Dog No.	B.W.	Sex		before		1	2	3	6	9	12 hr	
1	17.0	M	A	0.008	Strangulation	0.002	0.005	0.005	0.003	0.015	0.046	
			N	0.000		0.000	0.001	0.001	0.002	0.010	0.034	
			BP	100		96	90	90	75	62	40	
			Hr	120		120	124	124	128	132	144	
2	11.2	F	A	0.005		0.003	0.005	0.013	0.004			
			N	0.004		0.007	0.006	0.005	0.006	+		
			BP	110		100	100	60	45			
			Hr	120		120	84	90	66			
3	16.5	M	A	0.001		0.001	0.001	0.001	0.001	0.001		
			N	0.000		0.002	0.001	0.001	0.007	0.005	+	
			BP	124		122	100	90	80	60		
			Hr	130		130	134	134	140	180		
4	19.3	M	A	0.002		0.002	0.001	0.001	0.001	0.003	0.014	
			N	0.009		0.007	0.007	0.016	0.006	0.009	0·010	*
			BP	100		102	100	104	80	44	40	
			Hr	100		108	100	96	140	144	148	
5	10.0	M	A	0.001		0.001	0.002	0.002	0.002	0.002	0.003	
			N	0.005		0.005	0.002	0.003	0.003	0.003	0.001	
			BP	122		120	110	100	90	82	30	
			Hr	130		130	140	144	144	150	180	

B.W. : Body weight A : Adrenaline N : Noradrenaline
BP : Mean arterial blood pressure Hr : Rate of heartbeat
+ : Died * : Survived for 14 hours

strangulation, but after the release, it decreased to below 60 mmHg within 120 minutes except in No. 8 that required 300 minutes before the drop of blood pressure to 60 mmHg. The basal secretion rates of adrenaline and noradrenaline in this group being 0.001−0.002 μg/kg/min and 0.000−0.004 μg/kg/min respectively, the secretion rates after three hours of strangulation marked 0.002−0.012 μg/kg/min and 0.000−0.011 μg/kg/min respectively, indicating little increase. After the release, however, the secretion rate of adrenaline increased to 0.116 μg/kg/min in 15 minutes in No. 9. The increase was remarkable in all other four cases. The secretion rate of noradrenaline increased in No.7, No.9 and No.10. The mean plasma volume decreased by 9.6 per cent three hours after strangulation, by 34.2 per cent 15 minutes after the release and by 52.4 per cent in 120 minutes.

Group 3

The changes of respiration in this group were the same as those

Table 2. The Adrenal Medullary Secretion (μg/kg/min), and the Mean Arterial Blood Pressure (mmHg) and Rate of Heartbeat in the Group 2

Dog No.	B.W.	Sex		before		3 hr		15 min.	30 min.	60 min.	120 min.	180 min.	240 min.	
6	10.2	M	A	0.001	Strangulation	0.007	Release	0.008	0.058	0.072	0.277	0.211		
			N	0.000		0.000		0.000	0.012	0.019	0.000	0.000	+	
			BP	132		120		100	80	74	40	34		
			Hr	120		140		180	180	180	160	170		
7	10.5	M	A	0.001		0.012		0.084	0.213	0.322	0.180			
			N	0.002		0.011		0.040	0.024	0.199	0.147	+		
			BP	118		115		105	96	66	30			
			Hr	140		120		144	130	150	160			
8	10.7	F	A	0.002		0.003		0.009	0.028	0.036	0.084	0.136	0.046	
			N	0.003		0.006		0.004	0.004	0.008	0.020	0.019	0.023	*
			BP	120		122		130	105	95	95	115	118	
			Hr	118		108		96	100	104	104	108	104	
9	14.0	M	A	0.001		0.011		0.116	0.111	0.088	0.092	0.076		
			N	0.001		0.003		0.027	0.028	0.022	0.072	0.065	+	
			BP	120		110		50	50	40	20	22		
			Hr	124		128		144	138	150	120	122		
10	12.0	M	A	0.002		0.002		0.011	0.025	0.113	0.112	0.077	0.076	
			N	0.004		0.004		0.002	0.011	0.033	0.078	0.043	0.048	**
			BP	115		102		124	95	52	54	58	46	
			Hr	142		148		150	160	134	160	166	192	

B.W. : Body weight A : Adrenaline N : Noradaenaline
BP : Mean arterial blood pressure Hr : Rate of heartbeat
+ : Died * : Survived for 7 hours after release
** : Survived for 8 hours after release

in group 2. The rate of heartbeat, mean blood pressure, secretion rates of adrenaline and noradrenaline are shown in Table 3. The rate of heartbeat decreased in 15 to 30 minutes after the release of strangulation and the heartbeat became irregular in most cases. The blood pressure decreased transiently in the 30 to 60 minutes and remained somewhat lower than that before the release in most cases. In No. 15, the blood pressure decreased gradually after the release and reached 60 mmHg in 240 minutes. However, there was no deceased case within a short period unlike in group 2.

The basal secretion rates of adrenaline and noradrenaline in this group were 0.001−0.008 μg/kg/min and 0.002−0.006 μg/kg/min respectively. Three hours after strangulation, the respective values were 0.001−0.007 μg/kg/min and 0.002−0.007 μg/kg/min showing no increase in secretion rate. The secretion rate of adrenaline did not increase after release except in No. 12 showing an increase to 0.090 μg/kg/min in 30 minutes and in No. 15 showing an increase to 0.063 μg/kg/min in 60 minutes. The secretion rate of noradrenaline did not increase in any animal. The mean plasma volume decreased by 9.0 per cent

Table 3. The Adrenal Medullary Secretion (μg/kg/min), and the Mean Arterial Blood Pressure (mmHg) and Rate of Heartbeat in the Group 3

Dog No.	B.W.	Sex		before		3 hr		15	30	60	120	180	min. 240
11	15.1	M	A	0.008	Strangulation	0.003	Release	0.007	0.003	0.002	0.006	0.001	0.007
			N	0.005		0.004		0.008	0.004	0.003	0.002	0.002	0.003
			BP	115		110		102	90	85	96	108	108
			Hr	118		116		120	124	132	136	132	120
12	11.5	F	A	0.005		0.007		0.057	0.090	0.083	0.044	0.028	0.030
			N	0.004		0.004		0.008	0.015	0.016	0.014	0.014	0.010
			BP	120		102		92	80	74	88	90	90
			Hr	160		150		156	100	120	124	102	108
13	16.2	M	A	0.001		0.001		0.006	0.007	0.020	0.021	0.028	0.027
			N	0.004		0.005		0.002	0.002	0.004	0.004	0.004	0.005
			BP	120		118		115	100	65	92	102	104
			Hr	112		104		116	132	108	160	108	116
14	14.0	M	A	0.002		0.001		0.010	0.026	0.026	0.016	0.007	0.010
			N	0.002		0.002		0.002	0.002	0.006	0.003	0.003	0.004
			BP	102		110		120	105	88	95	98	98
			Hr	160		160		164	88	128	124	128	100
15	14.2	F	A	0.005		0.004		0.025	0.060	0.063	0.065	0.051	0.038
			N	0.006		0.007		0.005	0.012	0.028	0.029	0.023	0.019
			BP	128		130		110	84	65	70	78	60
			Hr	178		180		100	104	100	120	120	124

B.W. : Boy weigh1 A : Adrenaline N : Noradrenaline
BP : Mean arterial plood pressure Hr : Rate of heartbeat

three hours after strangulation, by 22.6 per cent 15 minutes after release and by 42.3 per cent in 120 minutes.

Group 4

The respiratory rate showed no remarkable change three hours after strangulation as well as after resection and anastomosis. The rate of heartbeat, mean blood pressure, and secretion rate of adrenaline and noradrenaline are shown in Table 4. The rate of heartbeat showed no remarkable change and the blood pressure somewhat decreased after resection. Only in No. 19, the blood pressure dropped to 60 mmHg 30 minutes after resection and this state persisted. There was no deceased case within a short period of time.

The basal secretion rates of adrenaline and noradrenaline in this group were 0.002−0.009 μg/kg/min and 0.000−0.003 μg/kg/min respectively. The respective values three hours after strangulation were 0.002−0.010 μg/kg/min and 0.000−0.007 μg/kg/min and no significant increase was observed even after resection. The mean plasma

Table 4. The Adrenal Medullary Secretion (μg/kg/min), and the Mean Arterial Blood Pressure (mmHg) and Rate of Heartbeat in the Group 4

Dog No.	B.W.	Sex		before		3 hr		15	30	60	120	180	min. 240
16	12.1	F	A	0.002	Strangulation	0.006	Resection	0.006	0.020	0.013	0.021	0.021	0.023
			N	0.001		0.000		0.004	0.007	0.008	0.004	0.011	0.024
			BP	118		118		115	112	115	96	95	100
			Hr	120		108		108	110	110	114	114	112
17	11.0	M	A	0.002		0.003		0.002	0.001	0.001	0.001	0.001	0.002
			N	0.003		0.001		0.000	0.001	0.000	0.000	0.000	0.001
			BP	110		112		112	110	114	112	120	125
			Hr	118		108		108	108	104	115	120	128
18	12.5	F	A	0.006		0.004			0.029	0.025	0.020	0.024	0.012
			N	0.003		0.007			0.005	0.007	0.011	0.016	0.009
			BP	108		125			120	120	124	124	122
			Hr	128		130			120	122	120	128	132
19	10.0	M	A	0.009		0.010			0.014	0.010	0.012	0.020	0.020
			N	0.000		0.000			0.003	0.003	0.000	0.000	0.000
			BP	120		90			60	70	65	62	60
			Hr	132		138			132	132	128	128	128
20	11.3	M	A	0.002		0.002			0.010	0.003	0.001	0.001	0.001
			N	0.001		0.004			0.002	0.007	0.002	0.002	0.002
			BP	105		108			102	104	98	98	102
			Hr	138		140			148	140	134	134	138

B.W. : Body weight A : Adrenaline N : Noradrenaline
BP : Mean arterial blood pressure Hr : Rate of heartbeat

volume decreased by 9.7 per cent three hours after strangulation, by 16.7 per cent 30 minutes after release and by 23.1 per ceut in 120 minutes.

Group 5

The respiration showed the same changes as those in group 3. The rate of heartbeat, mean blood pressure, and secretion rates of adrenaline and noradrenaline are shown in Table 5. Except that the rate of heartbeat 180 minutes after release decreased to 80 in No. 22, the rate of heartbeat and the blood pressure tended to be the same as in group 3. Dogs in this group died within four hours after release except for No. 23 that died seven hours after release. In No. 25, the secretion rate of noradrenaline increased from the basal secretion rate of 0.012 μg/kg/min to 0.058 μg/kg/min but no other case of this group showed increased secretion rate.

The mean plasma volume decreased by 13.1 per cent three hours after strangulation and by 42.4 per cent 15 minutes after release and

Table. 5. The Adrenal Medullary Secretion (μg/kg/min), and the Mean Arterial Blood Pressure (mmHg) and Rate of Heartbeat in the Group 5

Dog No.	B.W.	Sex		before		3 hr		15	30	60	120	180	min. 240	
21	10.0	M	A	0.003	Strangulation	0.002	Release	0.004	0.010	0.013	0.011	+		
			N	0.005		0.003		0.001	0.001	0.000	0.000			
			BP	112		108		100	96	70	40			
			Hr	128		140		140	144	148	154			
22	15.0	M	A	0.003		0.003		0.003	0.002	0.008	0.004	0.002	+	
			N	0.005		0.001		0.007	0.003	0.007	0.003	0.001		
			BP	130		130		115	113	80	72	60		
			Hr	96		120		138	140	120	128	80		
23	14.2	M	A	0.001		0.001		0.001	0.001	0.001	0.001	0.002	0.002	*
			N	0.004		0.000		0.000	0.000	0.004	0.000	0.001	0.001	
			BP	125		120		115	105	95	90	92	60	
			Hr	120		130		138	140	138	148	156	168	
24	14.0	M	A	0.002		0.006		0.007	0.013	0.014	+			
			N	0.005		0.000		0.002	0.008	0.011				
			BP	102		98		84	60	32				
			Hr	120		124		140	148	154				
25	15.5	M	A	0.003		0.004		0.006	0.010	0.017	0.008	0.008	+	
			N	0.012		0.006		0.018	0.023	0.058	0.029	0.028		
			BP	104		100		94	90	90	66	40		
			Hr	140		148		158	160	168	164	180		

B.W. : Body weight A : Adrenaline N : Noradrenaline
BP : Mean arterial blood pressure Hr : Rate of heartbeat
* : Survived 7 hours after release

by 57.4 per cent in 120 minutes.

DISCUSSION

In their experimental studies on death due to intestinal obstruction, MATSUKURA et al[17] reported that ileus resulted in a remarkable increase of endotoxin and DNA as well as acetylcholine, and all these together with catecholamines concurrently increased in the blood played an important role in the occurrence of ileus shock. Fine[9] reported that the release of transient occlusion of the superior mesenteric artery caused shock and sympathetic overactivity in animals and the shock may be prevented by the administration of dibenamine which is an adrenergic blocking agent, thus placing great importance on the excessive adrenergic activity at the time of shock.

Despite the fact that such experimental results were reported, there have been no reports of study on the secretion of catecholamines from the adrenals on the occassion of strangulation ileus. The experimental results in the present study revealed that mere continuation of intestinal obstruction is not causative of an increase of adrenal medullary secretion.

However, the release of strangulation three hours after the onset resulted in a rapid increase of adrenal medullary secretion and in a drop of blood pressure to below 60 mmHg within two hours except in one case. The animals with release of strangulation died more rapidly than those without.

Fine[8] reported that patients of incarcerated hernia would experience similar shock when the released intestine seemed viable and resection was not made, and that, when the superior mesenteric artery was occluded for 30 to 60 minutes and then released in animal experiment, most of the animals fell in shock one to two hours thereafter and died more rapidly than those without release. The results of Fine's clinical experiences and experimental observation resemble greatly the results of the author's experimental observations of intestinal strangulation. He attributed the cause of these facts to the invasion of bacterial toxic factor into the circulation. HERSHEY et al[11] demonstrated that temporary (4 hrs) ligation of the superior mesenteric artery resulted in shock accompanied with abrupt fall of blood pressure and continued increase of hematocrit but the peripheral blood contained no circulating organism nor polysaccharide and vasodepressor (epinephrine inhibiting) materials increased remarkably after the re-establishment of circulation. They also proved that this vasodepressor response was abolished by the action of dibenzyline. MARSTON[16] demonstrated experimentally that, when the ischemic

bowel caused by mesenterial arterial occlusion was perfused with the arterial system of healthy mongrel dogs, the normal dogs died rapidly and the death was caused not by endotoxin absorption but by plasma loss.

In order to investigate whether the increase of adrenal medullary secretion after the release of strangulation as observed in the present experiment was induced by way of direct stimulation of the adrenal gland by peripheral factor or by way of nervous impulse from the adrenal medullary secretory center, the author resected the greater and lesser splanchnic nerves of dogs with strangulation obstruction. In these animals, hypotention, increase of pulse rate and decrease of plasma volume remained unchanged but the secretion of catecholamines after the release of strangulation did not occur. Accordingly it is presumed that increased secretion of catecholamines after the release of strangulation obstruction in animals without resection of the splanchnic nerves is attributable to the nervous impulse. EGDAHL[7] and NYKIEL et al.[18] indicated that the adrenal medullary response in dogs induced by intravenous injection of E. coli endotoxin in a large dose was abolished by the transection of the spinal cord at C−7 or by the denevertion of the adrenal gland. SAKAI[20] clarified that increase of the adrenal medullary secretion occuring in response to hemorrhage in dogs was neurogenic.

In the present study, it was not demonstrated that the shock and death after the release of strangulation obstruction were caused definitely by endotoxin. However, in the group that kanamycin was injected into the strangulated intestinal loop, no animal died shortly after release and the increase of adrenal medullary secretion rate was slight. In the group that the strangulated intestinal loop was resected, no animal died, the decrease of plasma volume was minimal and the secretion of catecholamines did not increase. From these results, it may be demonstrated that the acceleration of adrenal medullary secretion after revascularization of the strangulated loop is closely related to the strangulated loop itself or to its content.

The significance of increased secretion of catecholamines after the release of strangulation is not evident. However, FINE[10], LILLEHEI et al[15] and JACOBSON[12] reported that animals with shock due to endotoxin were in the state of sympathetic overactivity and excessive catecholamines produced in living animals by such overactivity aggra vated circulatory disturbances, and that combined use of adrenergic blocking agent (dibenzyline, dibenamine) and plasma was effective for the treatment. BARNETT et al[3] showed a similar view in a case report, in which dibenzyline was thought to contribute to the successful outcome of a patient with late gangrenous bowel obstruction and shock.

In view the above, it is suggested that any measure to accelerate

the secretion of catecholamines or any inconsiderate use of catecholamines should be avoided at the time of strangulation obstruction and after its release. It is needless to say that antibiotics, plasma and liquid transfusion are required for the treatment of strangulation obstruction, but it is suggested that resection of the strangulated loop should be cousidered in preference to releasing the strangulation.

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