Studies on the Massive Administration of Corticosteroid during Open Heart Surgery. Its Effect to Renal Function.

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FOR the prevention of the low cardiac output syndrome following cardiopulmonary bypass, which procedure has been likened to a kind of controlled clinical shock,¹⁻³ the effectiveness of the massive administration of corticosteroid has been well known. In a previous investigation,⁴ the authors administered massive doses of dexamethasone (0.4 to 2 mg/kg) prior to total body perfusion and found that this treatment improved the postoperative course in respect to the respiratory and circulatory states, renal function, and acid-base balance. In the present investigation, the authors investigated, clinically and experimentally, the effect of the massive administration of dexamethasone on renal function for purpose of clarifying the mechanism of its action on the kidney.

MATERIAL AND METHODS

The clinical materials consisted of sixty patients associated with congenital or acquired heart diseases. One group, in which the perfusion durations were expected to exceed one hour, consisted of forty-five patients, seventeen of them children under ten years of age, who were given massive doses of dexamethasone 30 to 60 minutes before extracorporeal circulation; this group was divided into two subgroups according to dexamethasone dosage, the one dosage being below 1 mg/kg, mainly 0.4 to 0.6 mg/kg, and the other being 1 to 2 mg/kg. The other group, in which the perfusion durations were expected to be less than one hour, consisted of ten adults and five children, who were investigated as a control group. The extracorporeal circulation was per-

formed at a flow rate of 2.4 L/M²/min under mild hypothermia with a DeBakey pump and a disposable bubble oxygenator. Furthermore, in all cases, the hemodilution method without priming with heparinized blood was adopted by using about 30 ml/kg of a Ringer-lactate solution.

The experimental materials consisted of ten adult mongrel dogs, weighing 15 to 20 kilograms. They were subjected to total body perfusion with a DeBakey pump and a disposable bubble oxygenator by the same hemodilution method; the perfusions were uniformly normothermic, of one hour's duration, and at a flow rate of 75 ml/kg/min. Two mg/kg of dexamethasone were administered 30 minutes before perfusion in five of the dogs. The other five dogs served as controls.

The arterial blood pressure, central venous pressure, and urinary output were continuously measured. The following measurements were intermittently undertaken before, during, and after perfusion: 1) the potassium and sodium in the plasma and urine (P_K , P_{Na} , U_K , and U_{Na}), which were measured with a flame photometer, 2) plasma and urinary osmolalities (P_{Osm} and U_{Osm}), which were determined with an osmometer (Fiske), 3) plasma and urinary creatinin, which were measured by means of JAFFE's method, 4) glomerular filtration rate, which was calculated from the creatinin clearance ($GFR = UV^* \times U_{creatinin} / P_{creatinin}$), 5) osmolar clearance, which was calculated from the osmolities ($C_{Osm} = UV^* \times U_{Osm} / P_{Osm}$) 6) free water clearance, which was calculated from the osmolar clearance ($CH_2O = UV^* - C_{Osm}$), 7) antidiuretic

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Fig.1. The urinary volume during and after perfusion.

hormone level in the plasma (ADH), which was measured according to YAMANE and KUNISHIGE's bioassay method⁵ after extraction by WEINSTEIN and YOSHIDA's modified method⁶ and 8) renal

blood flow (RBF), which was measured directly from the dogs by means of a noncannulating electromagnetic flowmeter.

*UV = urinary volume per ml per minute

RESULTS

1. Urinary Volume (UV)

Clinically, dexamethasone in massive doses produced an increase in urinary output from about 30 minutes after administration to about 24 hours after perfusion. In general, the urinary volume during and after perfusion rose up to 0.05 to 1 ml/kg/min until 4 to 6 hours after perfusion even in the control group where no dexamethasone had been administered, with relation to bypass undergone by the hemodilution method without priming with heparinized blood. Although no significant difference in urinary output between the control and administration group was demonstrated until 4 to 6 hours after perfusion, the urinary volume thereafter in the larger dosage sub-group increased to about twice that of the control value until 24 hours after perfusion; while the adults in the smaller dosage sub-group displayed no similar increase, the children in this sub-group, as well as those in the larger

Fig.2. The relationship between urinary volume (UV) and excretion of electrolytes in the urine (U_k and U_{Na}) (Clinical cases).

dosage sub-group, did, a finding may reveal a difference between child and adult reactions to the same dosage (Fig. 1).

Experimentally, the differences in urinary volume between the administration and control groups were more significant, and the urinary output in the administration group became four to eight times those of the controls.

2. Excreted Electrolytes in the Urine (Table I)

1) Urinary potassium (U_K)

Clinically, the excreted volumes of potassium in the urine increased according to the increases in urinary volume for about 12 hours after perfusion in both the control and administration groups. More particularly, the amounts of excreted potassium in the urine rose up to four times those of the control values within this period in the larger dosage sub-group, and this increase continued up to from 20 to 24 hours after perfusion in the adults and up to 40 hours after perfusion in the children.

Experimentally, the increases of urinary potassium excreted after administration were almost the same as those observed clinically.

2) Urinary sodium (U_{Na})

Clinically, dexamethasone may have no significant effect on the excretion of urinary sodium, although the excreted volume of sodium did increase to some extent in the larger dosage sub-group. Experimentally, however, the excretory

increases in urinary sodium in the administration group as compared with the controls were similar to those in urinary potassium.

3) Na/K ratio in the urine

Clinically, in the larger dosage sub-group, the Na/K ratio decreased significantly as compared with the control for from 2 to 20 hours after perfusion in the adults or for from 6 to 36 hours after perfusion in the children. Therefore, the increases in potassium excretion in the larger dosage sub-group seemed to exceed the increase in sodium increases, although the latter increases were considerable. In the smaller dosage sub-group, however, there was no significant difference in Na/K ratio as compared with the control group and, in both these groups, the ratio rather increased in the period of increased urinary output.

3. The Relationship between Urinary Volume and Excretion of Electrolytes in the Urine (Fig. 2)

Clinically, a mutual correlation was demonstrated between urinary volume and the excretion of urinary potassium in the larger dosage sub-group, whereas the urinary volume was proportional to the excreted volume of urinary sodium in the control group and the smaller dosage sub-group. Experimentally, in the administration group, the linear correlation between the urinary volume and the excreted amount of urinary po-

Fig.3. The relationship between urinary volume (UV) and excretion of electrolytes in the urine (U_K and U_{Na}) (DOGS).

A

TABLE I EXCRETED ELECTROLYTES

			before surgery	after anesthesia	sur- pre-perfusion
Adults	urinary potassium	larger dosage sub-group (dexamethasone > 1 mg/kg)	0.024 ± 0.007	0.029 ± 0.009	0.081 ± 0.019
		smaller dosage sub-group (dexamethasone < 1 mg/kg)	0.024 ± 0.007	0.029 ± 0.009	0.067 ± 0.021
		control	0.024 ± 0.007	0.029 ± 0.009	0.071 ± 0.018
	urinary sodium	larger dosage sub-group (dexamethasone > 1 mg/kg)	0.068 ± 0.028	0.167 ± 0.009	0.090 ± 0.040
		smaller dosage sub-group (dexamethasone < 1 mg/kg)	0.068 ± 0.028	0.167 ± 0.009	0.139 ± 0.052
		control	0.068 ± 0.028	0.167 ± 0.009	0.0501 ± 0.031
Children	urinary potassium	larger dosage sub-group (dexamethasone > 1 mg/kg)	0.025 ± 0.006	0.028 ± 0.007	0.078 ± 0.011
		smaller dosage sub-group (dexamethasone < 1 mg/kg)	0.025 ± 0.006	0.028 ± 0.007	0.025 ± 0.006
		control	0.025 ± 0.006	0.028 ± 0.007	0.025 ± 0.009
	urinary sodium	larger dosage sub-group (dexamethasone > 1 mg/kg)	0.069 ± 0.019	0.051 ± 0.01	0.144 ± 0.040
		smaller dosage sub-group (dexamethasone < 1 mg/kg)	0.069 ± 0.019	0.051 ± 0.01	0.042 ± 0.018
		control	0.069 ± 0.019	0.051 ± 0.01	0.050 ± 0.024

B

		pre-perfusion	during perfusion
Dogs	administration group		
	urinary potassium	0.0266 ± 0.0166	0.0367 ± 0.018
	urinary sodium	0.0757 ± 0.043	0.0987 ± 0.031
	control		
	urinary potassium	0.0266 ± 0.017	0.0065 ± 0.0027
	urinary sodium	0.0757 ± 0.043	0.0167 ± 0.007

IN THE URINE (mEq/min.)

<i>gery</i>	<i>after perfusion</i>					
<i>during perfusion</i>	<i>immediate to 2 hrs.</i>	<i>2 to 6 hrs.</i>	<i>6 to 12 hrs.</i>	<i>12 to 24 hrs.</i>	<i>24 to 36 hrs.</i>	<i>36 to 60 hrs.</i>
<i>0.143 ± 0.036</i>	<i>0.358 ± 0.107</i>	<i>0.203 ± 0.094</i>	<i>0.125 ± 0.057</i>	<i>0.051 ± 0.016</i>	<i>0.073 ± 0.018</i>	<i>0.063 ± 0.012</i>
<i>0.084 ± 0.027</i>	<i>0.067 ± 0.024</i>	<i>0.069 ± 0.027</i>	<i>0.059 ± 0.023</i>	<i>0.068 ± 0.014</i>	<i>0.062 ± 0.011</i>	<i>0.059 ± 0.016</i>
<i>0.101 ± 0.029</i>	<i>0.067 ± 0.019</i>	<i>0.078 ± 0.036</i>	<i>0.077 ± 0.028</i>	<i>0.055 ± 0.006</i>	<i>0.064 ± 0.013</i>	<i>0.060 ± 0.019</i>
<i>0.104 ± 0.017</i>	<i>0.395 ± 0.029</i>	<i>0.169 ± 0.003</i>	<i>0.147 ± 0.033</i>	<i>0.137 ± 0.065</i>	<i>0.070 ± 0.034</i>	<i>0.084 ± 0.022</i>
<i>0.212 ± 0.128</i>	<i>0.240 ± 0.080</i>	<i>0.175 ± 0.054</i>	<i>0.126 ± 0.070</i>	<i>0.133 ± 0.058</i>	<i>0.070 ± 0.013</i>	<i>0.085 ± 0.021</i>
<i>0.147 ± 0.032</i>	<i>0.187 ± 0.064</i>	<i>0.197 ± 0.057</i>	<i>0.124 ± 0.082</i>	<i>0.069 ± 0.024</i>	<i>0.070 ± 0.021</i>	<i>0.081 ± 0.018</i>
<i>0.049 ± 0.017</i>	<i>0.122 ± 0.022</i>	<i>0.168 ± 0.054</i>	<i>0.098 ± 0.032</i>	<i>0.098 ± 0.025</i>	<i>0.087 ± 0.027</i>	<i>0.053 ± 0.010</i>
<i>0.018 ± 0.010</i>	<i>0.025 ± 0.012</i>	<i>0.028 ± 0.029</i>	<i>0.037 ± 0.014</i>	<i>0.035 ± 0.012</i>	<i>0.034 ± 0.009</i>	<i>0.034 ± 0.013</i>
<i>0.014 ± 0.008</i>	<i>0.020 ± 0.009</i>	<i>0.021 ± 0.003</i>	<i>0.022 ± 0.008</i>	<i>0.025 ± 0.003</i>	<i>0.016 ± 0.011</i>	<i>0.018 ± 0.011</i>
<i>0.145 ± 0.015</i>	<i>0.295 ± 0.040</i>	<i>0.220 ± 0.085</i>	<i>0.211 ± 0.070</i>	<i>0.206 ± 0.040</i>	<i>0.167 ± 0.070</i>	<i>0.085 ± 0.021</i>
<i>0.034 ± 0.017</i>	<i>0.082 ± 0.037</i>	<i>0.054 ± 0.020</i>	<i>0.046 ± 0.011</i>	<i>0.045 ± 0.018</i>	<i>0.052 ± 0.013</i>	<i>0.054 ± 0.017</i>
<i>0.020 ± 0.008</i>	<i>0.055 ± 0.019</i>	<i>0.047 ± 0.016</i>	<i>0.038 ± 0.019</i>	<i>0.037 ± 0.014</i>	<i>0.042 ± 0.018</i>	<i>0.052 ± 0.016</i>

after perfusion			
30 min	60 min	90 min	120 min
0.0591 ± 0.026	0.0493 ± 0.027	0.0162 ± 0.008	0.0061 ± 0.0034
0.184 ± 0.067	0.082 ± 0.028	0.027 ± 0.009	0.022 ± 0.007
0.0093 ± 0.0038	0.0055 ± 0.0013	0.0031 ± 0.0017	0.0008 ± 0.001
0.0252 ± 0.006	0.0161 ± 0.007	0.0069 ± 0.004	0.0045 ± 0.002

ATABLE II THE URINARY OSMOTIC PRESSURE (U_{OSM}), OSMOLAR CLEARANCE (C_{OSM})

			before surgery	sur- pre- perfusion
U_{Osm} (mOsm/kg.H ₂ O)	Adults	larger dosage sub-group (dexamethasone >1 mg/kg)	568 ± 18	407 ± 42
		smaller dosage sub-group (dexamethasone <1 mg/kg)	568 ± 18	462 ± 74
		control	568 ± 18	677 ± 76
	Children	larger dosage sub-group (dexamethasone > 1 mg/kg)	576 ± 21	423 ± 29
		smaller dosage sub-group (dexamethasone <1 mg/kg)	576 ± 21	521 ± 57
		control	576 ± 21	508 ± 43
C_{Osm} (ml/min)	Adults	larger dosage sub-group (dexamethasone >1 mg/kg)	1.79 ± 0.27	1.78 ± 0.32
		smaller dosage sub-group (dexamethasone < 1 mg/kg)	1.79 ± 0.27	2.25 ± 0.38
		control	1.79 ± 0.27	2.03 ± 0.41
	Children	larger dosage sub-group (dexamethasone > 1 mg/kg)	1.58 ± 0.23	1.38 ± 0.17
		smaller dosage sub-group (dexamethasone <1 mg/kg)	1.58 ± 0.23	2.90 ± 0.47
		control	1.58 ± 0.23	2.13 ± 0.24
C_{H_2O} (ml/min)	Adults	larger dosage sub-group (dexamethasone >1 mg/kg)	-1.09 ± 0.17	-1.31 ± 0.11
		smaller dosage sub-group (dexamethasone <1 mg/kg)	-1.09 ± 0.17	-0.58 ± 0.31
		control	-1.09 ± 0.17	-0.18 ± 0.22
	Children	larger dosage sub-group (dexamethasone >1 mg/kg)	-0.39 ± 0.26	-0.28 ± 0.23
		smaller dosage sub-group (dexamethasone <1 mg/kg)	-0.39 ± 0.26	-0.47 ± 0.27
		control	-0.39 ± 0.26	-0.19 ± 0.21

AND FREE WATER CLEARANCE (C_{H_2O}) DURING AND AFTER PERFUSION

during perfusion	after perfusion					
	0 to 6 hrs.	6 to 12 hrs.	12 to 24 hrs.	24 to 36 hrs.	36 to 48 hrs.	48 to 60 hrs.
409 ± 53	414 ± 39	669 ± 48	647 ± 83	740 ± 75	635 ± 64	475 ± 51
454 ± 68	423 ± 64	624 ± 57	608 ± 63	582 ± 57	414 ± 77	471 ± 67
391 ± 78	419 ± 48	695 ± 18	587 ± 47	536 ± 50	484 ± 36	508 ± 49
409 ± 37	475 ± 23	625 ± 44	687 ± 47	739 ± 38	518 ± 41	500 ± 35
546 ± 38	476 ± 42	689 ± 77	637 ± 52	568 ± 54	625 ± 47	605 ± 35
448 ± 67	435 ± 34	603 ± 37	574 ± 24	509 ± 36	514 ± 47	548 ± 29
6.66 ± 1.01	6.88 ± 0.89	5.69 ± 0.68	4.53 ± 0.42	2.59 ± 0.41	2.14 ± 0.18	2.08 ± 0.21
7.77 ± 1.4	7.58 ± 1.0	5.79 ± 0.87	4.87 ± 0.63	3.95 ± 0.38	2.45 ± 0.25	2.12 ± 0.23
3.42 ± 0.63	5.38 ± 0.54	5.05 ± 0.67	5.65 ± 0.48	2.62 ± 0.33	2.38 ± 0.28	2.45 ± 0.31
4.16 ± 0.37	4.80 ± 0.39	4.69 ± 0.41	3.87 ± 0.41	3.29 ± 0.37	2.24 ± 0.25	1.50 ± 0.29
1.54 ± 0.13	4.54 ± 0.29	2.61 ± 0.36	1.08 ± 0.31	1.27 ± 0.28	1.06 ± 0.28	1.12 ± 0.26
2.38 ± 0.31	4.12 ± 0.28	2.08 ± 0.27	1.67 ± 0.40	1.43 ± 0.52	1.12 ± 0.31	1.08 ± 0.33
-1.60 ± 0.24	-1.83 ± 0.17	-2.00 ± 0.16	-1.83 ± 0.15	-1.68 ± 0.21	-2.00 ± 0.23	-0.45 ± 0.48
-2.42 ± 0.41	-2.12 ± 0.39	-3.00 ± 0.32	-2.53 ± 0.27	-1.97 ± 0.21	-0.62 ± 0.24	-1.19 ± 0.23
-0.89 ± 0.37	-1.77 ± 0.27	-2.68 ± 0.34	-2.03 ± 0.20	-1.06 ± 0.08	-1.00 ± 0.23	-1.08 ± 0.19
-0.83 ± 0.31	-0.80 ± 0.28	-2.44 ± 0.22	-2.21 ± 0.38	-1.99 ± 0.16	-1.38 ± 0.19	-0.86 ± 0.15
-0.67 ± 0.21	-1.49 ± 0.34	-1.44 ± 0.36	-1.00 ± 0.21	-0.62 ± 0.27	-0.62 ± 0.09	-0.28 ± 0.19
-0.43 ± 0.25	-1.15 ± 0.47	-1.68 ± 0.28	-1.42 ± 0.16	-0.87 ± 0.14	-0.48 ± 0.08	-0.36 ± 0.14

B

	before surgery	surgery		after perfusion			
		pre-perfusion	during perfusion	30 min	60 min	90 min	120 min
U_{osm} (mOsm/kg·H ₂ O)							
administration group	655 ± 58	629 ± 73	481 ± 47	391 ± 32	401 ± 41	436 ± 28	452 ± 42
control	655 ± 58	629 ± 73	491 ± 52	361 ± 42	364 ± 52	367 ± 15	370 ± 27
C_{osm} (ml/min)							
administration group	1.30 ± 0.11	0.88 ± 0.21	1.28 ± 0.18	2.89 ± 0.63	1.84 ± 0.37	0.97 ± 0.30	0.37 ± 0.14
control	1.30 ± 0.11	0.88 ± 0.21	0.49 ± 0.12	0.47 ± 0.14	0.27 ± 0.11	0.17 ± 0.08	0.09 ± 0.10
CH_2O (ml/min)							
administration group -	-0.80 ± 0.05	-0.63 ± 0.15	-0.87 ± 0.28	-0.73 ± 0.25	-0.69 ± 0.18	-0.25 ± 0.17	-0.07 ± 0.03
control	-0.80 ± 0.05	-0.46 ± 0.12	-0.10 ± 0.07	-0.13 ± 0.05	-0.04 ± 0.01	-0.016 ± 0.009	-0.01 ± 0.01

tassium was demonstrated. On the other hand, there was no relationship between the urinary volume and the excretion of urinary sodium (Fig. 3).

4. Osmolality (Table II)

Clinically, the plasma osmotic pressure (P_{osm}) increased slightly during and from 2 to 4 hours after perfusion and it returned to the normal level thereafter, irrespective of dexamethasone administration. On the other side, the urinary osmotic pressure (U_{osm}) decreased to a level of about 400 mOsm/kg·H₂O and continued up to 6 hours after perfusion, during which time the urinary output increased significantly, irrespective of dexamethasone administration. Thereafter, it rose up to 700 mOsm/kg·H₂O in the larger dosage sub-group, although it remained at nearly 600 mOsm/kg·H₂O in the other groups. Moreover, the urinary osmolality did not decrease below 400 mOsm/kg·H₂O in the administration group, although it did decrease to below 400 mOsm/kg·H₂O in the control group. Experimentally, no significant difference in urinary osmotic pressure was demonstrated between both groups.

5. Osmolar Clearance (C_{osm}) and Free Water Clearance (C_{H_2O}) (Table II)

Clinically, osmolar clearance was significantly higher in the larger dosage sub-group, especially in the children, where it doubled that of the other groups for 40 hours after perfusion. The free water clearances were negative in all clinical groups, but in the experimental dogs, a significant difference was demonstrated between both groups. Experimentally, the free water clearance in the administration group was above -0.5 ml/min, although the osmolar clearance was nearly 0.25 ml/min and the free water clearance was almost zero in the control group.

6. The Relationship between Urinary Volume and Osmolality (Fig. 4 and 5)

Clinically, there was no constant correlation between urinary volume and urinary osmotic pressure in the control group, whereas in the administration group, urinary volume was inversely proportional to urinary osmotic pressure. Moreover, a mutual correlation was observed between urinary volume and osmolar clearance in both the control and administration groups. Experimentally, in the administration group, the urinary osmotic pressure was maintained at a level of from nearly 400 to 600 mOsm/kg·H₂O irrespective of

Fig.4. The relationship between urinary osmotic pressure (U_{osm}), osmolar clearance (C_{osm}) and urinary volume (UV) (Clinical cases).

- larger dosage sub-group (dexamethasone > 1 mg/kg),
- smaller dosage sub-group (dexamethasone < 1 mg/kg),
- × control.

Fig.5. The relationship between urinary volume (UV) and osmolality (U_{osm} and C_{osm}) (DOGS)

the urinary volume, and the osmolar clearance was proportional to the urinary volume.

7. Glomerular Filtration Rate (GFR)

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Fig.6. Clinical cases. The alterations of glomerular filtration rate before, during and after perfusion, and the relationship between urinary volume (UV) and glomerular filtration rate (GFR) during and immediately after perfusion.

Clinically, irrespective of the administration of dexamethasone, glomerular filtration rate fell to from 70 to 75 per cent of the normal value during perfusion and immediately after perfusion; it recovered to from 80 to 85 per cent during the period of 3 to 12 hours after perfusion, and then returned to almost normal level during the period of 12 to 24 hours after perfusion. There was no significant difference in glomerular filtration rate between the control and the administration groups and no correlation was demonstrated between the urinary volume and glomerular filtration rate (Fig. 6).

Experimentally, however, glomerular filtration rate was maintained at the level of 60 per cent of normal value during perfusion and 50 per cent of the normal value after perfusion in the administration group, although it decreased to the level of 30 to 40 per cent of the normal value during perfusion and declined to 20 per cent or less after perfusion in the control group. No significant difference between urinary volume and glomerular filtration rate was observed even in the experimental dogs, but in the administration group,

Fig. 7. Dogs. The alterations of glomerular filtration rate before, during and after perfusion (left), and the relationship between urinary volume (UV) and glomerular filtration rate (GFR) before, during and after perfusion (right).

● administration group
 × control (non-administration group) } during and after perfusion
 □ before perfusion

Fig. 8. Dogs. The alterations of renal blood flow (RBF) before, during and after perfusion (left), and the relationship between urinary volume (UV) and renal blood flow (RBF) before, during and after perfusion (right).

● administration group
 × control (non-administration group) } during and after perfusion
 □ before perfusion

Fig. 9. Dogs. The relationships between glomerular filtration rate (GFR), renal blood flow (RBF) and mean arterial pressure (mean AP) during and immediately after perfusion.

● administration group during and immediately after perfusion.
 × control (non-administration group) during and immediately after perfusion.
 □ before perfusion.

the urinary output increased as compared with the control group even when the glomerular filtration rate decreased (Fig. 7).

8. Renal Blood Flow (RBF) (Fig. 8 and 9)

Experimentally, the renal blood flow was maintained at the level of 65 per cent of the normal value during perfusion and at the level of 90 per cent after perfusion in the administration group, although it decreased to 45 per cent of the normal value during perfusion and to 65 per cent after perfusion in the control group. The significant difference in renal blood flow occurring between both groups was similar to that regarding glomerular filtration rate. As to the relationship between glomerular filtration rate and renal

Fig.10. The alterations of ADH before, during and after perfusion (upper), and the relationships between urinary volume (UV) and ADH during and immediately after perfusion (lower).

blood flow, the former was relative to the latter during and after perfusion, although no correlation had been demonstrated before perfusion. Therefore, the decrease in glomerular filtration rate appeared to be directly proportional to the decrease in renal blood flow, which seemed to correlate with the change in renal vascular resistance. In the administration group, the urinary output exceeded that of the control group even when the renal blood flow decreased, although there was no significant difference between urinary volume and renal blood flow.

9. Antidiuretic Hormone (ADH) (Fig. 10)

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Dexamethasone might have no effect on the plasma antidiuretic hormone, because no significant relationship between the plasma antidiuretic hormone level and urinary output was seen, and the antidiuretic hormone value during perfusion reached to one hundred times or more of the control value irrespective of dexamethasone administration.

DISCUSSION

It has been asserted that cardiopulmonary bypass, even under the best circumstances, would be tantamount to a kind of controlled clinical shock,^{1-3,7} and that the "low output syndrome"

which is apt to occur following total body perfusion is characteristic of a shock-like state with its increased peripheral vascular resistance, reduced tissue perfusion, and failing heart. Corticosteroid, administered in massive doses, has been found to decrease peripheral vascular resistance and increase cardiac output and had therefore been used to prevent the low output syndrome following perfusion. Moreover, hemorrhagic shock,⁸⁻¹⁰ endotoxin shock,⁴ and cardiogenic shock due to myocardial infarction¹¹ can be improved by a large dose of corticosteroid.

Corticosteroid may depress the sympathetic action on the α -receptors at the myoneural junction to block and thus act hemodynamically as a vasodilator.^{1,2} Moreover, CHAWLA¹² demonstrated that massive doses of corticosteroid, by effecting the methylation of norepinephrine and participating in the final step of epinephrine synthesis, did not increase the catecholamine levels. In addition, corticosteroid, given in massive doses, has been supposed to preserve the balance of the cell membranes by acting on the intracellular or membranous lysosomes.¹³ However, the effects of large doses of corticosteroid has still not been adequately described, particularly the effect on renal function, although some investigators^{1,2} have reported that it can improve impaired renal function following perfusion by administration before surgery.

The following factors, such as reduced perfusion pressure, changes in rheological properties of the blood, redistribution of circulating blood volume, increased sympathetic nerve activity, and humoral vasoactive substances^{3,14-16} are considered to effect renal circulation on total body perfusion. In fact, as a result of a combination of these factors, renal vasoconstriction would occur and the renal blood flow and glomerular filtration rate would decrease. In the present report, the glomerular filtration rate decreased during and after perfusion clinically and experimentally, and the renal blood flow decreased correlatively to the changes in the renal vascular resistance experimentally.

The actual incidence of renal failure following cardiopulmonary bypass has been reported as ranging from 2 to 10 per cent of all cases.^{3,17,18} Under total body perfusion, some decrease in renal blood flow and glomerular filtration rate has also been reported even at the highest flow rates attainable.¹⁹ Moreover, it has been demonstrated that the relationship between measured extracorporeal flow and renal blood flow during

perfusion was not linear and that inadequacies in the former were reflected by large functional deficits in the latter.^{3,14}

Generally, renal blood flow could be maintained within the normal value for some time during total body perfusion or hemorrhagic shock, if the blood pressure could be maintained at a level of 60 to 80 mmHg. Subsequently, however, as a consequence of the gradually increased renal vasoconstriction, the renal vascular resistance would increase and the renal blood flow and glomerular filtration rate would rapidly decrease. It has also been reported that, in severe hemorrhagic shock, the renal blood flow decreases to one tenth of the control value and, at the same time, the glomerular filtration rate declines to almost zero in association with the decreased tubular reabsorption of sodium.²⁰

Hitherto, it has been demonstrated that corticosteroid would increase the glomerular filtration rate.²¹ Dexamethasone, given in massive doses, could depress the excess vasoconstriction and would decrease the renal vascular resistance, and therefore, the renal blood flow might be satisfactorily maintained and the decrease in the glomerular filtration rate might be prevented during and after perfusion.

As seen in the present investigation, however, the effects of the same dosage of dexamethasone on urinary excretion in adults and in children might differ; in adults, 1 mg/kg or more of dexamethasone was needed to increase the urinary output significantly, although 1 mg/kg or less of dexamethasone was effective in children. The same relationship was demonstrated in the excretion of electrolytes. In the larger dosage subgroup, the volume of potassium excreted in the urine increased more significantly than that of sodium, although the latter increase was considerable both clinically and experimentally. Therefore, in the same sub-group, the Na/K ratio decreased and the total amount of excreted potassium seemed to exceed that of sodium. Judging from these results, 1 mg/kg of dexamethasone is probably an adequate dosage.

In general, sodium is reabsorbed by the mechanism of active reabsorption against the electrical or chemical gradient in the proximal renal tubules, although the other electrolytes or fluids are reabsorbed by the isosmotic process which would arise in proportion to the osmotic gradient produced according to the active reabsorption of sodium. Furthermore, sodium, which reaches into the distal renal tubules, is again reabsorbed by

the exchanging mechanism for potassium or hydrogen in the distal nephrons. Therefore, the increased excretion of sodium would show that sodium is filtrated excessively in the glomeruli and that it is transported in excess of the reabsorption capacity of the distal nephrons at the same time, or that the reabsorption of sodium in the proximal renal tubules decreases if the glomerular filtration rate decreases.

Under dexamethasone administration, in the authors' observations, the excretion of potassium increased more significantly than that of sodium. The increased excretion of sodium associated with the excess excretion of potassium would mean that sodium and potassium are not reabsorbed in the proximal renal tubules or that sodium enters in the distal renal tubules excessively. Judging from these results, dexamethasone might act on the distal renal tubules, but it might also effect the proximal renal tubules.

It has been reported that corticosteroid would act on the distal tubular cells, and therefore water permeability in the distal nephrons would decrease to some extent, and, consequently, water excretion would increase.^{22,23} However, dexamethasone may depress the permeability in the distal nephrons, but it may also influence the reabsorption of electrolytes and water in the proximal renal tubules.

It is also undeniable that corticosteroid would effect the vasomotor of renal nephron and influence the distribution of fluid to the nephrons with their various reabsorption capacities.

It was also ascertained that dexamethasone might act on the distal renal tubules, but it might also effect the countercurrent multiplier-concentrating mechanism in the renal nephrons, because the urinary osmotic pressure and osmolar clearance were maintained at significantly higher levels as compared with the controls, and hypo-osmolar urine of increased volume did not take place as a result of dexamethasone administration. Moreover, the negative free water clearance would show that free water is reabsorbed, but not excreted, and therefore, the increase in urinary volume resulting from dexamethasone administration is not attributable to an increase in free water.

Dexamethasone might have no effect on the plasma antidiuretic hormone. Therefore, the explanations that corticosteroid might depress antidiuretic hormone production,^{24,25} or that dexamethasone might act to block the action of the antidiuretic hormone in the distal renal tu-

bules^{23,26} seemed to be untenable.

SUMMARY

The effects of the massive administration of dexamethasone on renal function during and after extracorporeal circulation have been studied clinically on sixty patients undergoing open heart surgery and experimentally on ten mongrel dogs undergoing total body perfusion, and the following results have been obtained:

1. Dexamethasone, given in massive doses, increases the urinary output during and after total body perfusion. The increased urinary volume is not due to water diuresis, but is due to solute diuresis.
2. One mg/kg of dexamethasone, given before perfusion, may be an adequate dose, but its effects on renal function might differ between children and adults.
3. Glomerular filtration rate and renal blood flow may be satisfactorily maintained during and after perfusion due to the decreased renal vascular resistance brought on by a massive administration of dexamethasone, although no significant difference could be clinically demonstrated.
4. Dexamethasone may act on the distal renal tubules, but, judging from the alterations of excreted electrolytes and osmolality in cases of massive administration, it may also effect the proximal renal tubules.
5. Dexamethasone may have no effect on the plasma antidiuretic hormone.

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