COMPARATIVE STUDY OF EFFECTS OF ADRENALINE, DOBUTAMINE AND DOPAMINE ON SYSTEMIC HEMODYNAMICS AND RENAL BLOOD FLOW IN PATIENTS FOLLOWING OPEN HEART SURGERY

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In 10 patients following open heart surgery, adrenaline, dobutamine and dopamine were administered, and the changes in hemodynamic parameters and renal blood flow (RBF) were examined. RBF was determined by the local thermodilution method. Prior to the application of this method in clinical measurement, reliability of the method was checked using a model circuit. The correlation between the actual flow and flow obtained with this method was high ($r = 0.999$, $p < 0.005$, $n = 8$). Reproducibility in repeated measurements was excellent, $r = 0.997$ ($p < 0.005$, $n = 8$) in the model circuit and $r = 0.985$ ($p < 0.005$, $n = 89$) in the clinical measurement.

Adrenaline at rates of 0.02 – 0.08 $\mu\text{g/kg/min}$ showed a marked inotropic action without any significant change in RBF. With 0.04 $\mu\text{g/kg/min}$ of adrenaline, the RBF/CO (cardiac output) ratio declined significantly. We conclude that adrenaline is often effective in patients following open heart surgery, but renal vasoconstriction is the major disadvantage.

After a 10-min administration of 2 , 4 and 8 $\mu\text{g/kg/min}$ of dobutamine, cardiac index (CI) and stroke volume index (SVI) showed a stepwise increase in accordance with an increase of dosage, and RBF also increased with CO. Consequently, no significant change in RBF/CO was found. Mean left atrial pressure (LAP) or mean pulmonary arterial wedge pressure (PAWP) decreased in 4 of 7 patients with 8.0 $\mu\text{g/kg/min}$ of dobutamine. Thus, dobutamine is an excellent β_1 -adrenergic agonist with a weak α -action on both peripheral and renal vessels.

With 2.0 – 2.5 $\mu\text{g/kg/min}$ of dopamine, RBF increased by 15.5% ($p < 0.05$), while no significant increase appeared in CI. With 4.0 $\mu\text{g/kg/min}$ or more of dopamine, CI and SVI increased. With 16 – 20 $\mu\text{g/kg/min}$ of dopamine, RBF increased by up to 44.8% . Significant increase of mean LAP or mean PAWP was observed with 8.0 – 10.0 $\mu\text{g/kg/min}$ or more of dopamine. These findings

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indicate that the potential increase of LVEDP (left ventricular end-diastolic pressure) with 8–10 $\mu\text{g/kg/min}$ or more of dopamine exerts a disadvantageous effect in patients following open heart surgery. However, the effect on the renal hemodynamics, especially with small doses of dopamine, is unique and not observed with adrenaline or dobutamine.

POTENT beta-adrenergic stimulants are widely used and frequently effective in acute heart failure, cardiogenic shock, or low cardiac output syndrome following open heart surgery.

In the selection of beta-adrenergic stimulants or of vasodilators, their effect on the distribution of the blood flow to vital organs should be taken into consideration as well as their effect on systemic hemodynamics.

While the kidneys can be affected significantly by hemodynamic changes in a low cardiac output syndrome and in cardiogenic shock, knowledge as to changes in renal blood flow after administration of beta-adrenergic stimulants, particularly during the short period of time after administration, is limited because of the difficulty associated with repeated measurements.

We examined the reliability of the local thermodilution method by Horynch et al.¹ and confirmed that with this method repeated measurements of renal blood flow in human subjects in a short period of time were feasible. The validation of the local thermodilution method and the reliability of the method are discussed in the Appendix.

The present report deals with our findings on the effects of adrenaline, dobutamine and dopamine on systemic hemodynamics and renal blood flow in human subjects.

MATERIALS AND METHODS

Ten patients (7 men and 3 women) hospitalized at Niigata University Hospital for open heart surgery were studied (Table I). Their ages ranged from 18 to 48 years, with an average of 36.3. The cardiopulmonary bypass technique, utilizing hemodilution, the Harvey H-1000 disposable bubble oxygenator and a perfusion rate of 2.4 L/min/m² at mild hypothermia, was used.

On the day before operation, the catheter for renal blood flow measurement was introduced from the right great saphenous vein under X-ray control into the right renal vein.

After the reproducibility of thermodilution curves was verified, the catheter was fixed with an adhesive tape to the inguinal region. Cardiac

TABLE I SUBJECTS

Case	Age and Sex	Diagnosis	Operation
1. M.I.	44, male	ASD	Closure
2. M.A.	33, male	MS	OMC
3. C.S.	31, female	ECD	Closure
4. T.S.	48, male	ECD	Closure
5. J.A.	43, female	MS	OMC
6. N.K.	36, male	AS	AVR
7. M.S.	18, female	MSi	OMC
8. S.K.	43, male	AI	AVR
9. A.S.	23, male	MI	MVR
10. G.A.	44, male	AI	Ao.plasty

Abbreviations: OMC = open mitral commissurotomy, AVR = aortic valve replacement, MVR = mitral valve replacement, Ao.plasty = aortoplasty

output was determined by the thermodilution method (Model 5910, Edwards Co.).

Left atrial pressure (LAP) or pulmonary arterial wedge pressure (PAWP) and radial arterial pressure were obtained from Statham P23Db pressure transducers using the midchest as the zero reference point and were recorded at a 25 or 50 mm/sec paper speed on a multichannel recorder. Mean values of pressures were obtained using an electronic integrating circuit. The hemodynamic variables were calculated from the data as follows:

- cardiac index (CI)
 - = cardiac output/body surface area (BSA) (L/min/m²)
- stroke index (SI)
 - = stroke volume/BSA (ml/m²)
- systemic vascular resistance (SVR)
 - = mean blood pressure (MBP)/CI (units/m²)
- renal vascular resistance (RVR)
 - = MBP/RBF/BSA (units/m²)
- RBF ratio for cardiac output
 - = RBF/CO $\times$ 100 (%)

Studies were carried out within 6 hours after weaning from the bypass when the patients were hemodynamically stable.

Fig.1. Systemic hemodynamic changes with 0.02 to 0.08 µg/kg/min of adrenaline. Heart rate (HR) and mean blood pressure (BP) did not show any significant change. Cardiac index (CI) and stroke index (SI) showed significant increase with each dose level employed. Systemic vascular resistance (SVR) decreased significantly with 0.04 µg/kg/min or more of adrenaline.

After confirming that the patient was in a hemodynamically stable state, adrenaline 0.02, 0.04 and 0.08 µg/kg/min, dobutamine 2, 4 and 8 µg/kg/min, and dopamine 1.0–1.25, 2.0–2.5, 4.0–5.0, 8.0–10.0 and 16.0–20.0 µg/kg/min were injected.

Each dosis of drug was infused for 10 min respectively, and 30-min intervals were employed between the administration of each drug. Drugs were given in random order.

Statistical analysis utilized the Student's *t*-test on a paired basis as appropriate. A *p* value of less than 0.05 was considered to indicate a significant difference between the compared groups of data.

RESULTS

All results are summarized in Tables II and III.

Effects of Adrenaline (Figs. 1 and 2)

Effects of adrenaline in 6 subjects were examined. The control value of heart rate (HR) was 87.1 ± 15.1 /min (mean $\pm$ SD). HR increased by 8.7% with 0.04 µg/kg/min and by 14.0% with 0.08 µg/kg/min. However, HR did not show any statistically significant change with 0.02 to 0.08 µg/kg/min of adrenaline as compared with the control value.

Nor did the mean blood pressure (BP) show any significant change with any dose level employed. SVR decreased stepwise with increase in dosage. It decreased by 17.3% ($p < 0.005$) with 0.04 µg/kg/min from its control value of 27.7 ± 3.3 u/m² and by 22.4% ($p < 0.005$) with 0.08 µg/kg/min.

CI increased by 13.5, 30.4 and 34.8% with 0.02, 0.04 and 0.08 µg/kg/min, respectively, and

TABLE II SYSTEMIC HEMODYNAMIC

Infusion Rate ($\mu\text{g/kg/min}$)	N	HR		SBP (mean)		LAP or PAW
		beats/min	% change	mmHg	% change	(mean)
Adr	control	6	87.1 $\pm$ 15.1	78.8 $\pm$ 12.2		12.5 $\pm$ 1.0
	0.02	6	88.5 $\pm$ 14.3	102.0 $\pm$ 4.0	81.7 $\pm$ 8.5	104.6 $\pm$ 8.0
	0.04	6	94.3 $\pm$ 17.9	108.7 $\pm$ 11.4	84.0 $\pm$ 9.6	107.6 $\pm$ 8.6
	0.08	5	93.6 $\pm$ 15.2	114.0 $\pm$ 19.3	78.6 $\pm$ 5.9	105.2 $\pm$ 9.7
	off	10 min	4	92.8 $\pm$ 21.1	102.7 $\pm$ 4.5	81.8 $\pm$ 10.4
DOB	control	10	80.6 $\pm$ 9.1	79.8 $\pm$ 13.1		11.5 $\pm$ 3.2
	2	10	82.3 $\pm$ 10.9	102.0 $\pm$ 4.4	81.1 $\pm$ 12.7	101.9 $\pm$ 7.6
	4	10	87.7 $\pm$ 10.8*	109.0 $\pm$ 9.0	84.4 $\pm$ 13.5	106.4 $\pm$ 10.7
	8	10	99.7 $\pm$ 18.7*	123.3 $\pm$ 14.9	89.1 $\pm$ 12.2**	112.6 $\pm$ 12.1
	off	10 min	8	87.6 $\pm$ 15.4	108.5 $\pm$ 13.6	80.3 $\pm$ 13.6
off	20 min	8	80.4 $\pm$ 13.1	101.0 $\pm$ 8.6	79.3 $\pm$ 8.9	100.6 $\pm$ 9.5
DOP	control	8	76.1 $\pm$ 11.5	77.4 $\pm$ 11.4		11.0 $\pm$ 2.7
	1.0–1.25	5	70.4 $\pm$ 10.8	97.2 $\pm$ 8.6	70.8 $\pm$ 11.9	98.2 $\pm$ 7.6
	2.0–2.5	7	77.9 $\pm$ 11.3	101.4 $\pm$ 9.3	78.9 $\pm$ 11.4	100.2 $\pm$ 7.3
	4.0–5.0	8	77.5 $\pm$ 9.0	102.8 $\pm$ 10.7	77.0 $\pm$ 7.8	100.2 $\pm$ 7.2
	8.0–10.0	8	84.1 $\pm$ 11.1	112.2 $\pm$ 18.7	83.3 $\pm$ 12.1	108.3 $\pm$ 13.7
	16.0–20.0	7	94.7 $\pm$ 11.4***	127.9 $\pm$ 23.9	86.9 $\pm$ 11.1*	113.3 $\pm$ 11.0
	off	10 min	8	81.6 $\pm$ 10.2	109.5 $\pm$ 23.4	76.9 $\pm$ 11.7
off	20 min	8	76.6 $\pm$ 10.4	101.3 $\pm$ 9.3	75.8 $\pm$ 12.6	97.9 $\pm$ 7.1

Values given are mean $\pm$ 1 standard deviation of the mean. N = number of studies.

Each infusion rate was maintained for 10 min.

* = significantly different from control ($p < 0.05$ by paired t-test), ** $p < 0.01$, *** $p < 0.005$,

**** $p < 0.001$

each increase was statistically significant ($p < 0.005$). SI also showed significant increase with 0.02 $\mu\text{g/kg/min}$ or more of adrenaline. No significant change appeared in the left atrial pressure or pulmonary arterial wedge pressure.

In contrast, RBF varied little in spite of the increase in CI, and the change as compared to the control value of 461.3 ml/min was +7.5%, -2.9% and +4.0% with 0.02, 0.04 and 0.08 $\mu\text{g/kg/min}$, respectively. RVR showed a tendency to increase, but the increase was not statistically significant. The RBF/CO ratio decreased from the control value of 11.3% to 8.0% with 0.04 $\mu\text{g/kg/min}$ and to 8.3% with 0.08 $\mu\text{g/kg/min}$. The decrease was statistically significant ($p < 0.05$).

Effects of Dobutamine (Figs. 3 and 4)

Effects of dobutamine in 10 patients were examined. HR increased from the control value of 80.6 $\pm$ 9.1 /min (mean $\pm$ SD) by 9.0% ($p < 0.05$) and 23.3% ($p < 0.05$) with 4.0 and 8.0 $\mu\text{g/kg/min}$, respectively.

kg/min, respectively.

Mean BP increased only slightly and was 12.6% higher than the control value with 8.0 $\mu\text{g/kg/min}$ ($p < 0.01$).

SVR decreased from the control value of 26.7 u/m², to 24.3 ($p < 0.005$), 23.4 ($p < 0.05$) and 22.4 u/m² ($p < 0.05$) at 2.0, 4.0 and 8.0 $\mu\text{g/kg/min}$, respectively. The decrease ranged from 8.5 to 14.6%.

CI increased stepwise with an increase of dosage. It increased from the control value of 3.00 $\pm$ 0.20 L/min/m² (mean $\pm$ SD) by 13.6% ($p < 0.005$), 21.0% ($p < 0.001$) and 34.6% ($p < 0.005$) with 2.0, 4.0 and 8.0 $\mu\text{g/kg/min}$, respectively.

SI showed significant increase with 2.0 and 4.0 $\mu\text{g/kg/min}$, but the increase was not significant with 8.0 $\mu\text{g/kg/min}$.

Both CI and SI returned to the control values 10 min after administration ceased.

Mean LAP or mean PAWP decreased in 4 of 7 patients with 8.0 $\mu\text{g/kg/min}$ of dobutamine (Fig. 5).

CHANGES DURING DRUG INFUSION

CI		SI		SVR	
L/min/m ²	% change	ml/m ²	% change	units/m ²	% change
2.84±0.37		33.3±5.9		27.7±3.3	
3.22±0.35***	113.5± 8.2	37.0±5.9*	111.3± 6.9	24.5±1.9	92.0± 8.3
3.68±0.33***	130.4±16.1	39.7±5.2***	120.1± 9.1	22.8±0.8***	82.7± 7.5
3.87±0.46***	134.8±13.9	42.4±9.5***	122.4±19.5	20.8±2.7***	77.6± 5.9
3.30±0.37	114.6±11.8	36.5±5.0*	111.5± 7.1	24.8±1.9	88.6±10.0
3.00±0.20		37.9±5.2		26.7±4.6	
3.42±0.44***	113.6± 9.1	42.4±7.4***	111.4± 6.6	24.3±4.1***	91.5± 6.0
3.63±0.38***	121.0±11.3	42.2±7.3***	112.0±16.4	23.4±3.9*	88.8±14.9
4.02±0.46***	134.6±18.4	40.8±7.0	109.0±22.5	22.4±3.8*	85.4±15.6
3.20±0.33	107.1±12.4	37.4±4.7	99.9±14.8	26.0±5.4	98.9±23.9
2.83±0.35	94.0± 9.2	35.7±5.2	102.2±15.7	28.3±3.9	108.4±18.1
2.84±0.38		37.3±3.9		27.5±4.0	
2.77±0.58	101.0± 6.8	39.5±6.4	106.2±15.9	27.3±2.6	97.3± 8.8
3.01±0.46	108.3± 8.3	38.7±3.1	107.1± 9.7	26.2±1.5	92.7± 7.5
3.22±0.50***	113.4± 8.3	41.7±5.7*	112.0±13.4	24.3±3.7*	88.6± 8.6
3.74±0.58***	132.8±21.3	45.1±8.4*	120.6±18.6	22.5±3.1***	82.4±10.3
4.57±0.58***	165.2±25.7	48.3±3.9***	131.2±14.5	19.2±2.6****	69.7±10.7
3.05±0.33	108.9±16.2	37.8±5.3	101.8±15.1	26.5±4.2	96.9±13.3
2.76±0.57	95.8±13.4	35.8±5.1	97.0±16.7	28.1±4.7	103.0±17.7

Abbreviations: Adr = adrenaline, DOB = dobutamine, DOP = dopamine, HR = heart rate, SBP = systemic blood pressure, LAP = left atrial pressure, PAW = pulmonary arterial wedge pressure, CI = cardiac index, SI = stroke index, SVR = systemic vascular resistance

RBF showed significant increase from the control value of 411.6 ± 79.8 ml/min (mean $\pm$ SD) by 17.4% ($p < 0.005$), 27.3% ($p < 0.005$) and 28.4% ($p < 0.005$) with 2.0, 4.0 and 8.0 μ g/kg/min, respectively. Ten min after administration ceased, RBF was still higher by 16.2% than the control value ($p < 0.01$).

RVR showed a significant decrease by 10.2–5.5% with a dosage of 2.0 μ g/kg/min or more, and the decrease was still observable 10 min after administration stopped. However, as described previously, the mean BP varied only slightly. The RBF/CO ratio remained between 8.6 and 10.0% and did not vary significantly.

Effects of Dopamine (Figs. 6 and 7)

Effects of dopamine in 8 patients were examined. HR varied only slightly with 4–5 μ g/kg/min or less of dopamine, showed a tendency to increase with 8–10 μ g/kg/min and increased by 27.9% with 16–20 μ g/kg/min ($p < 0.005$).

Mean BP showed a change similar to HR and

increased by 13.3% with 16–20 μ g/kg/min ($p < 0.05$).

SVR decreased by 11.4% ($p < 0.05$), 17.6% ($p < 0.005$) and 30.3% ($p < 0.001$) with 4–5, 8–10 and 16–20 μ g/kg/min of dopamine, respectively.

CI did not show any significant change with 2.5 μ g/kg/min as compared with the control value of 2.84 ± 0.38 L/min/m², but increased by 13.4% ($p < 0.005$), 32.8% ($p < 0.005$) and 65.2% ($p < 0.005$) with 4–5, 8–10 and 16–20 μ g/kg/min, respectively.

SI also increased significantly with 4–5 μ g/kg/min or more of dopamine. A significant increase of mean LAP or mean PAWP was observed with 8–10 μ g/kg/min or more of dopamine ($p < 0.05$, Fig. 5).

RBF began to increase before the CI increased. While CI did not show a significant increase with 2.0–2.5 μ g/kg/min, RBF increased by 15.5% from the control value of 431.0 ± 71.5 ml/min ($p < 0.05$). With an increase in dosage of

TABLE III RENAL HEMODYNAMIC CHANGES DURING DRUG INFUSION

Infusion Rate ($\mu\text{g/kg/min}$)		N	CI		RBF		
			L/min/m ²	% change	ml/min	% change	
Adr	control	6	2.84 $\pm$ 0.37		461.3 $\pm$ 138.7		
	0.02	6	3.22 $\pm$ 0.35***	113.5 $\pm$ 8.2	485.3 $\pm$ 137.6	107.5 $\pm$ 21.9	
	0.04	6	3.68 $\pm$ 0.33***	130.4 $\pm$ 16.1	439.0 $\pm$ 88.0	97.1 $\pm$ 18.1	
	0.08	5	3.87 $\pm$ 0.46***	134.8 $\pm$ 13.9	458.8 $\pm$ 94.4	104.0 $\pm$ 22.0	
	off	10 min	4	3.30 $\pm$ 0.37	114.6 $\pm$ 11.8	457.3 $\pm$ 75.4	98.5 $\pm$ 9.1
DOB	control	10	3.00 $\pm$ 0.20		411.6 $\pm$ 79.8		
	2	10	3.42 $\pm$ 0.44***	113.6 $\pm$ 9.1	481.6 $\pm$ 101.4***	117.4 $\pm$ 10.9	
	4	10	3.63 $\pm$ 0.38***	121.0 $\pm$ 11.3	521.5 $\pm$ 105.0***	127.3 $\pm$ 15.0	
	8	10	4.02 $\pm$ 0.46***	134.6 $\pm$ 18.4	517.6 $\pm$ 80.8***	128.4 $\pm$ 25.6	
	off	10 min	10	3.20 $\pm$ 0.33	107.1 $\pm$ 12.4	474.5 $\pm$ 92.4**	116.2 $\pm$ 14.3
	off	20 min	8	2.83 $\pm$ 0.35	94.0 $\pm$ 9.2	443.9 $\pm$ 61.0	106.5 $\pm$ 15.0
DOP	control	8	2.84 $\pm$ 0.38		431.0 $\pm$ 71.5		
	1.0–1.25	5	2.77 $\pm$ 0.58	101.0 $\pm$ 6.8	464.6 $\pm$ 44.4	116.1 $\pm$ 17.6	
	2.0–2.5	7	3.01 $\pm$ 0.46	108.3 $\pm$ 8.2	487.3 $\pm$ 83.3*	115.5 $\pm$ 13.1	
	4.0–5.0	8	3.22 $\pm$ 0.50***	113.4 $\pm$ 8.3	559.3 $\pm$ 92.4***	130.7 $\pm$ 16.0	
	8.0–10.0	8	3.74 $\pm$ 0.58***	132.8 $\pm$ 21.3	593.8 $\pm$ 113.9***	139.3 $\pm$ 26.0	
	16.0–20.0	7	4.57 $\pm$ 0.58***	165.2 $\pm$ 25.7	645.0 $\pm$ 141.7***	144.8 $\pm$ 26.0	
	off	10 min	8	3.05 $\pm$ 0.33	108.9 $\pm$ 16.2	553.1 $\pm$ 83.0***	130.0 $\pm$ 21.9
	off	20 min	8	2.76 $\pm$ 0.57	95.8 $\pm$ 13.4	503.3 $\pm$ 89.0*	117.5 $\pm$ 15.4

Values given are mean $\pm$ 1 standard deviation of the mean. N = number of studies.

Each infusion rate was maintained for 10 min.

* = significantly different from control ($p < 0.05$ by paired *t*-test), ** $p < 0.01$, *** $p < 0.005$.

Abbreviations: Adr = adrenaline, DOB = dobutamine, DOP = dopamine, CI = cardiac index, CO = cardiac output, RBF = renal blood flow, RVR = renal vascular resistance

dopamine, RBF further increased by up to 44.8% ($p < 0.005$) and was still higher than the control value by 30.0% ($p < 0.005$) and 17.5% ($p < 0.05$) respectively, 10 and 20 min after administration ceased.

RVR showed a significant decrease with 1.0–1.25 $\mu\text{g/kg/min}$ or more of dopamine and remained significantly lower than the control value 20 min after administration ceased.

The RBF/CO ratio increased significantly with administration of low doses of dopamine and after administration stopped.

DISCUSSION

Effects of Adrenaline on Systemic and Renal Hemodynamics

Adrenaline has both α - and β -adrenergic action and has been used widely in cardiac resuscitation.

In the present study, CI and SI showed stepwise an increase with an administration of

increasing doses of adrenaline. This result confirmed the excellent dose-related inotropic effect of adrenaline. HR and mean BP varied only slightly after administration of adrenaline.

In spite of the increase in CO, RBF did not increase with adrenaline. The RBF/CO ratio decreased, and RVR increased with 0.04 $\mu\text{g/kg/min}$ or more of adrenaline.

Aviado et al.² observed constriction of renal vessels and decrease in the renal blood flow when they administered in anesthetized dogs (0.1 μg of adrenaline into the renal artery or 3 $\mu\text{g/kg}$ into the peripheral vein).

Moyer et al.³ administered adrenaline (diluted 100,000 times) continuously into the peripheral vein of a dog, observed a marked decline of RPF (renal plasma flow) and Tmg (maximum tubular transport of glucose), and attributed it to renal afferent arteriolar vasoconstriction. As Ahlquist⁴ and Carriers et al.⁵ pointed out, α -receptors are dominant in the kidney. Because of this

RBF/CO $\times 100(\%)$	RVR	
	units/m ²	% change
11.3 $\pm$ 3.2	127.6 $\pm$ 40.0	
10.6 $\pm$ 3.2	123.1 $\pm$ 28.2	101.4 $\pm$ 23.9
8.0 $\pm$ 2.0*	135.4 $\pm$ 25.5	111.3 $\pm$ 21.9
8.3 $\pm$ 1.8*	122.0 $\pm$ 26.9	102.8 $\pm$ 16.2
9.5 $\pm$ 2.4	122.8 $\pm$ 28.1	103.2 $\pm$ 13.6
9.1 $\pm$ 1.9	131.9 $\pm$ 23.7	
9.6 $\pm$ 2.7	115.1 $\pm$ 24.4***	87.3 $\pm$ 9.1
9.4 $\pm$ 2.0	112.8 $\pm$ 32.9**	84.5 $\pm$ 13.1
8.6 $\pm$ 1.4	118.3 $\pm$ 30.8	89.8 $\pm$ 15.5
9.9 $\pm$ 1.8	116.5 $\pm$ 30.3**	87.7 $\pm$ 11.1
10.1 $\pm$ 1.5	122.0 $\pm$ 21.4	95.3 $\pm$ 14.5
10.0 $\pm$ 1.6	119.2 $\pm$ 23.3	
11.0 $\pm$ 1.6*	104.6 $\pm$ 22.0*	86.2 $\pm$ 15.4
10.6 $\pm$ 1.5	108.1 $\pm$ 20.7*	87.5 $\pm$ 10.6
11.4 $\pm$ 1.5*	91.5 $\pm$ 14.3***	77.6 $\pm$ 10.7
10.5 $\pm$ 2.5	94.2 $\pm$ 21.0*	80.0 $\pm$ 17.2
9.3 $\pm$ 1.9	91.8 $\pm$ 20.1*	80.8 $\pm$ 18.4
12.6 $\pm$ 1.9***	90.1 $\pm$ 15.5*	77.1 $\pm$ 15.1
12.2 $\pm$ 2.6*	100.0 $\pm$ 19.9*	85.0 $\pm$ 15.4

dominance, the vasoconstriction in the kidney described above may have developed from a small dose of adrenaline which did not show a α -effect on peripheral vessels.

Effects of Dobutamine on Systemic and Renal Hemodynamics

Dobutamine is a new synthetic catecholamine developed by Tuttle et al.⁶ It is a β_1 -adrenergic agonist with weak β_2 - and α -action and is reported to have selective action on the heart.

In the present study, HR increased significantly with 4 μ g/kg/min or more of dobutamine, and it increased by 23.3% with 8 μ g/kg/min. These figures obtained in the present study were higher than those reported by Akhtar et al.⁷ (7.3% with 10 μ g/kg/min) and Jewitt et al.⁸ (13.6% with 10 μ g/kg/min) and were similar to the results reported by Sakamoto et al.⁹ (24% with 8 μ g/kg/min) in patients following open heart surgery.

In the present study, mean BP increased by

12.6% with 8 μ g/kg/min of dobutamine. This is similar to previous reports⁸⁻¹¹ that the effect of dobutamine on arterial pressure is rather slight.

Total peripheral vascular resistance fell by as much as 14.6%, but the decrease was less marked than with adrenaline or dopamine.

There are many reports⁶⁻¹⁹ both experimental and clinical, concerning the effects of dobutamine on cardiac functions. All of these reports agree in supporting the excellent inotropic action of dobutamine. In the present study also, we observed an increase of CI which was dose-dependent and increased as much as 34.6% after a dose of 8 μ g/kg/min. SI increased by only 10%, indicating that the increase in CI was partially due to an increase in HR. In addition to dobutamine's strong action in relieving the low cardiac output state, which has been reported by many investigators,^{7-11,13} our results also showed its effectiveness in reducing the LVEDP (left ventricular end-diastolic pressure) in most of the cases.^{10,11,13,16,18} Therefore, from the view point of myocardial metabolism and coronary circulation, dobutamine is advantageous, and its usefulness should be appreciated also in ischemic heart disease cases.¹⁸

No agreement exists among investigators concerning the effect of dobutamine on RBF, some reporting no increase in RBF¹⁹ and some reporting the opposite.²⁰

In the present study, we measured RBF in our patients and observed a significant increase with 2 μ g/kg/min or more of dobutamine. However, no change occurred in the RBF/CO ratio. Thus, we conclude that the observed increase in RBF was a secondary change accompanying an increase in cardiac output.

Effects of Dopamine on Systemic and Renal Hemodynamics

Dopamine is a precursor of noradrenaline, and its hypertensive action and inotropic effect have been recognized since the 1930's.

Based on pharmacological studies by Goldberg,²¹ McDonald et al.²² and McNay et al.²³ dopamine was found to possess a characteristic selective vasodilatory action on the renal and superior mesenteric arteries as well as a positive inotropic action.

Dopamine is clinically used in various kinds of shock,^{24,25} after open heart surgery,^{26,27} and in congestive heart failure.²⁸

Although some authors report that dopamine's positive chronotropic effect is weak,^{29,30} other

Fig.2. Renal hemodynamic effects of adrenaline. Renal blood flow (RBF) varied little in spite of increase in CI with 0.02 to 0.08 $\mu\text{g/kg/min}$ of adrenaline. Renal vascular resistance (RVR) showed a tendency to increase. The RBF/CO ratio decreased significantly from the control value with 0.04 and 0.08 $\mu\text{g/kg/min}$.

Fig.3. Systemic hemodynamic effects of dobutamine. HR increased significantly from the control value with 4.0 and 8.0 $\mu\text{g/kg/min}$ of dobutamine. Although CI increased stepwise with an increase of doses, SI increased only slightly.

Fig.4. Renal hemodynamic effects of dobutamine. RBF increased significantly from the control value with 2 $\mu\text{g/kg/min}$ or more of dobutamine, accompanying an increase in CI. The RBF/CO ratio did not vary significantly. RVR decreased with a dosage of 2.0 $\mu\text{g/kg/min}$ or higher.

Fig.5. Changes of mean LAP or PAWP during (left) and after (right) the infusion of dobutamine and dopamine.

authors report, based on animal as well as clinical data, it shows positive chronotropic action with a wide range of doses^{28,29,31}

In the present study, HR increased with 8–10 $\mu\text{g/kg/min}$ or more of dopamine. With 16–20 $\mu\text{g/kg/min}$, the increase was by 27.9% ($p < 0.005$). These results suggest that the positive chrono-

tropic action of dopamine is rather weak and that with 10 $\mu\text{g/kg/min}$ or less, incidence of tachycardia or arrhythmia will be low. As to its action on peripheral vessels, some reports show that a low dose of dopamine reveals vasodilation reversed by a β -blocker and, as the dose is increased, it shows an increase in α -action^{21,31}

Fig.6. Systemic hemodynamic effects of dopamine. HR increased by 27.9% with 16–20 $\mu\text{g/kg/min}$ ($p < 0.005$). Mean BP showed a change similar to HR. CI and SI increased significantly with 4–5 $\mu\text{g/kg/min}$ or more of dopamine.

Fig.7. Renal hemodynamic effects of dopamine. RBF started to increase before CI increased. With increasing doses of dopamine, RBF further increased by up to 44.8% ($p < 0.005$). RVR decreased significantly with 1.0–1.25 $\mu\text{g/kg/min}$ or more of dopamine. The RBF/CO ratio increased significantly with low doses of dopamine.

The maximal dose that does not show systemic vasoconstriction is reported to be 30 $\mu\text{g/kg/min}$.³²

In the present study, because the change in blood pressure was minimal, the decrease in total

peripheral vascular resistance could not be ascribed to the direct action of dopamine on the peripheral vessels. The present data suggests that β_2 and α -action of dopamine are rather weak.

Fig. 8. Schematic representation of the thermodilution curve (right) and a simultaneous registration of the ohmic calibration (left). For details see Appendix.

Fig. 9. Flow determined by time collection in a graduated cylinder (y) and that by local thermodilution (x) showed a high correlation, $r = 0.998$ ($p < 0.005$). The regression equation obtained was $y = 0.7775x + 27.41$. Reproducibility was high ($r = 0.997$).

In contrast, positive inotropic action of dopamine was strong. CI and SI increased significantly with $4.0 \mu\text{g/kg/min}$, while HR and mean BP did not change significantly. Excellent positive inotropic effect of dopamine observed in the present study was consistent with reports by other authors^{24,29,33}

Our results suggest that $4.0 \mu\text{g/kg/min}$ or more are required to obtain an increase in CO. This is consistent with previous results of other authors concerning the clinical dosage of dopamine.

The results also showed, in contrast with dobutamine, a significant increase of LAP (or

Fig. 10. Reproducibility in clinical measurement. ($r = 0.985$, $p < 0.005$, $n = 89$)

PAWP) from 11.0 ± 2.68 (mean $\pm$ SD) mmHg to 13.5 ± 3.78 mmHg with $8-10 \mu\text{g/kg/min}$ doses of dopamine (Fig. 5).

The increase of LVEDP is most likely due to the increase of afterload, but there is a possibility that the reduced compliance of the myocardium is the cause of the LVEDP increase.

Therefore, in congestive heart failure or in stage of shock when systemic vasoconstriction existed, dopamine should be used in combination with vasodilating agents^{21,34,35}

Effects on the renal vessels not observed in other catecholamines are specific to dopamine. Dopamine reduces renal vascular resistance selectively and dilates the renal vessels^{21,22,29,36}. Consequently, renal blood flow and GFR increase. Since this action is not inhibited by α or β -blockers but antagonized by haloperidol, existence of specific receptors in the renal vascular bed has been postulated^{38,39}

Although urinary output increases with dopamine, various causes other than dilatation of the renal vessels (e.g., inhibition of ADH³⁸ and redistribution of intrarenal blood flow³⁹) have been postulated. Thus, the improvement of renal functions, natriuresis, and increase in urinary output observed with dopamine may not be solely due to dilatation of renal vessels.

Many authors have reported favorable effects of dopamine on renal circulation. However, there have been very few reports on serial measurement of RBF when dopamine is administered to human subjects.

Hollenberg et al.³⁹ determined RBF with a xenon washout technique and observed that RBF increased significantly with $3 \mu\text{g/kg/min}$ of

dopamine. With higher doses, however, RBF did not change, while other hemodynamic parameters showed improvement.

Breakenridge et al.⁴⁰ determined RBF using the indicator dilution method and observed that increased 4 times as much as the increase in CO with 1–2 $\mu\text{g/kg/min}$ of dopamine.

Although the number of reports on dose-related response of RBF to dopamine is still low, it should be noted that in all of the reports RBF increased with a low dosage of dopamine.

In the present study, renal vascular resistance began to decrease with 1.0–1.25 $\mu\text{g/kg/min}$, and the RBF/CO ratio increased significantly with 2 $\mu\text{g/kg/min}$ of dopamine and further increase with each dose to the maximal increase by 44.8%.

Because renal vascular resistance decreased with a low dose of dopamine, with no change either in mean BP or peripheral vascular resistance, this suggests selective dilation of the renal vascular bed.

However, with 16–20 $\mu\text{g/kg/min}$ of dopamine, which was the maximal dose used, BP increased significantly, and the increase of RBF was only about 5% of that with 8–10 $\mu\text{g/kg/min}$, suggesting that α -adrenergic action might have reduced renal vasodilatory action.

These results suggest that in order to improve renal function and increase urinary output, 2–4 $\mu\text{g/kg/min}$ of dopamine is adequate.

APPENDIX

In Vitro Validation of Local Thermodilution Method

Method

A specially constructed 6F thermistor thermodilution catheter (Wilton Webster Lab.) was used.

A Wheatstone bridge (Fukuda Elect. Lab.) was used for measurement of changes in thermistor resistance due to temperature changes by indicator injection.

Flow was calculated from the following formula proposed by Horynch et al.¹ (Fig. 8):

$$F = \frac{m \cdot 60 \cdot r \cdot Si \cdot Ci}{f \cdot Sb \cdot Cb \left[\frac{A_2}{(Tb - Ti)} + \frac{A_1 \cdot e \cdot r}{(Tb - Ti) \cdot e \cdot r - A_1 f} \right]}$$

F = flow (ml/min); m = amount of the injected indicator in ml; r = speed of the paper (mm/sec); Sb, Si = specific heat of the blood (b) and

indicator (i) (cal/g); Cb, Ci = specific gravity of the blood (b) and indicator (i) (g/cm^3); f = the coefficient expressing the change of temperature in centigrades for 1 mm of the height of the curve ($^{\circ}\text{C/mm}$); Tb, Ti = temperature of the blood (b) and indicator (i) ($^{\circ}\text{C}$); A_1 = area of the curve described during the time of injection of the indicator calculated planimetrically (mm^2); A_2 = the remaining part of the area of the total curve (mm^2); e = time of injection of the indicator (expressed in mm of the paper speed).

Model Experiment

Model experiments were carried out following the method of Horynch. The catheter was introduced into a silicone rubber tube with an internal diameter of 14 mm.

Through this tube was a non-pulsatile flow of water at 37°C . The flow rate, controlled by a roller pump, varied from 200 to 1200 ml/min, and was determined by the collection of fluid in a graduated cylinder.

Three ml of 5% dextrose at room temperature were used as indicator and were injected by manual push. Two measurements were taken at each flow rate. The flow was calculated by the formula mentioned above (using $SiCi/SbCb = 1$).

Results of the Model Experiment

Flow determined by time collection in a graduated cylinder (y) and by local thermodilution (x) showed a high correlation, $r = 0.998$ ($p < 0.005$).

Reproducibility in 2 repeat measurements was also very high, $r = 0.997$ ($p < 0.005$). We concluded that within the range of 200–1200 ml/min the reliability obtained by the local thermodilution method was very high. Because the regression equation obtained was $y = 0.78x + 27$, the value obtained by local thermodilution was corrected with the equation, and the value thus obtained was regarded as “true flow” (Fig. 9).

Conceivable reasons for the discrepancy between x and y include difficulty in obtaining accurate temperature of indicator because indicator picks up some heat from the catheter when passing through, error in the volume of indicator given, and characteristics of the Wheatstone bridge employed.

Thus the discrepancy between the 2 values seems to be the sum of all of these errors inherent in the system.

Reproducibility was high, both in the model

circuit ($r = 0.997$) and in clinical measurement ($r = 0.985$, $p < 0.005$, $n = 89$), indicating that local thermodilution can be employed clinically with sufficient reliability (Fig. 10).

Clinical Application of Local Thermodilution Method

Renal clearance is the method most widely employed for measurement of renal blood flow in human subjects. Renal blood flow can also be determined by the local thermodilution method.

While the clearance method has the advantage of being a noninvasive technique, it requires a steady state of about 30 min, provides mean blood flow only, and does not allow repeated measurement within a short time interval.

In contrast, the limitations of the local thermodilution method include the fact that it is an invasive technique requiring catheterization under X-ray fluoroscopy and that effects of intrarenal shunt can not be eliminated with this method.

However, once the catheter is in place, this method allows repeated measurements within short time intervals and enables serial determination of renal blood flow even in oliguria or shock.

Thus local thermodilution is an excellent method for examining renal hemodynamics associated with rapid changes in systemic hemodynamics.

Horynch et al.¹ showed in their experiments that the actual flow and the flow determined by local thermodilution technique had very high correlations, $r = 0.981-0.998$.

The experiments by the present authors also confirmed a high correlation with excellent linearity between the two. The present experiments, both in the model and in human subjects, also showed a high correlation among the values obtained through repeated determination, thus confirming the effective reproducibility of this method.

In order that the values obtained by the local thermodilution method be reliable, indicator and blood must be mixed homogeneously, and there must be no heat transfer from or to the flow circuit during determination.

The results of the model experiments by the present authors showed excellent reproducibility and linearity, thus indicating homogeneous mixture of blood and indicator.

It is possible that the indicator acquires some heat through the catheter wall in passing through, leading, therefore, to an error in the temperature

of the injected indicator.

In the determination of cardiac output by the thermodilution method, Cordy and Swan⁴¹ set an additional thermistor near the injection orifice, determined the correct temperature of the injected indicator, and used it in calculating the blood flow. Based on the results of separate model experiments, they later proposed a correction factor of 0.82 in calculating cardiac output by using 10 ml of 0°C water as indicator.

Currently this correction factor is widely used instead of using the actual temperature of the indicator.

We found, in our experiment, that a correction factor of 0.78 should be multiplied with the calculated flow to obtain the "true flow" when 3 ml of indicator at room temperature are injected.

We conclude that, prior to the application of this method in clinical measurement, reliability of the method should be checked using a model circuit.

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