The Hemodynamic and Metabolic Changes in Prostaglandin E_1-induced Hypotension in Dogs

-A Comparative Study with Trimetaphan-induced Hypotension-

Yong Taek NAM*, Shosuke TAKAHASHI, Masamune TOMINAGA and Junichi YOSHITAKE

The hemodynamic and metabolic changes in hypotensive state induced with prostaglandin E_1 (PGE_1) or trimetaphan (TMT) infusion were investigated in dogs. Mean arterial pressure was decreased by about 50% with 1.58μg/kg/min of PGE_1 or 45 μg/kg/min of TMT. Heart rate, pulmonary capillary wedge pressure and central venous pressure remained virtually unchanged in the two groups. Cardiac output was well maintained in PGE_1 group, whereas cardiac output showed the tendency to decline in TMT group.

Greater reduction in systemic vascular resistance was seen in PGE_1 group than in TMT group. Pulmonary vascular resistance showed no significant change in PGE_1 group, whereas it increased significantly in TMT group. Gradual decreases in arterial pH, Pa_{O_2} and base excess and slight but significant increase in Pa_{CO_2} was observed in PGE_1 group, and these abnormalities recovered 30 min after hypotension. Abnormalities in blood gases and acid-base balance were considerably more severe and prolonged in TMT group compared with those in PGE_1 group. Blood lactate and pyruvate concentrations showed no significant changes in PGE_1 group, whereas substantial elevation was seen in L/P ratio especially 30 min after induction of hypotension in TMT group. Oxygen consumption showed minimal changes in PGE_1 group, whereas a significant decrease was observed in TMT group. The conclusions derived from these results are as follows;

1) PGE_1 maintained cardiac output better than TMT, probably because of its direct inotropic action on the heart, and of its greater reduction of systemic vascular resistance than TMT.

2) PGE_1 seemed to provide the better blood perfusion throughout the body than TMT.

3) PGE_1 showed less possibility to produce the metabolic derangement compared with TMT. (Key words: PGE_1-induced hypotension, hemodynamic effects of PGE_1, metabolic effects of PGE_1)

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Department of Anesthesiology, Kyushu University School of Medicine, Fukuoka, Japan.

**Department of Anesthesiology, Yonsei University College of Medicine, Severance Hospital, Seoul, 120 Korea*

Address reprint requests to Dr. Takahashi: Department of Anesthesiology, Kyushu University School of Medicine, Maidashi 3-1-1, Higashi-ku, Fukuoka, 812 Japan

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Currently controlled hypotension in most often induced by intravenous infusion of a short-acting vasodilator such as trimetaphan (TMT), sodium nitroprusside (SNP), trinitroglycerine (TMT) or adenosine triphosphate (ATP). TMT is an effective hypotensive drug by virtue of its direct vasodilating action as well as ganglionic blocking ac-

tion. TMT, however, may reduce cardiac output and subsequently decrease blood flow to the vital organs during hypotension. SNP is a potent hypotensive agent that directly dilates peripheral vessels without reducing cardiac output. SNP may lead to cyanide intoxication because its metabolite converts into cyanide. Although TNG increases coronary blood flow, it tends to reduce preload and cardiac output. TNG sometime fails to lower blood pressure to the required levels due to its weak potency. ATP, a new hypotensive agent, sometime causes bradycardia and other dysrrhythmias during rapidly induced hypotension.

Prostaglandins (PGs) are naturally occuring acidic, lipid soluble substances discovered independently by Goldblatt[1] and Euler[2,3]. Since Bergstrom and Sjovall[4] isolated a pure form of PG and a host of analog and determined its chemical structure, several different PGs have been recognized to be present in body tissues. Carlson et al.[5] reported that PGE_1 decreases systemic arterial pressure and cardiac output and increases heart rate in man and dog. Since then there have been many reports (Nakano and McCurdy[6], Zulstra et al.[7], Pace et al.[8], and Goto et al.[9]) in PGE_1 as a hypotensive agent with many advantages such as increase in cardiac output, stroke volume and blood flow to vital organs, antidysrrhythmic effect and little metabolic derangement. Most of these effects were observed during short period of mild hypotensive state. The purpose of this study was to investigate the hemodynamic and metabolic changes in PGE_1-induced hypotensive state, in which the mean arterial blood pressure was lowered 50% from the control value for 60 min and compare with those in TMT-induced hypotensive state under the same experimental conditons in dogs.

Methods

Fifteen mongrel dogs with a weight of 9 to 15 kg were used. In eleven out of fifteen dogs hypotension was induced with PGE_1 (PGE_1 group) and four dogs with TMT (TMT group). General anesthesia was induced by the administration of thiopental sodium 20 mg/kg and pancuromium bromide 0.1 mg/kg intravenously. After tracheal intubation anesthesia was maintained with inhalation of 0.2–0.5% halothane in 50% nitrous oxide and oxygen. Mechanical vetilation was adjusted to maintain Pa_{CO_2} between 30–40 mmHg with Harvard pump respirator and the setting of the respirator was kept unchanged throughout study. Rectal temperature was maintained around 37 degree centigrade with warming blanket. Femoral artery was cannulated with 20 gauge angiocatheter. A central venous catheter of 20 gauge polyethylene catheter was inserted via the right femoral vein and 7.5 french sized Swan-Ganz catheter was inserted into the pulmonary artery through the left femoral vein. An internal jugular venous catheter was inserted with 22 gauge angiocatheter to obtain blood sample. Normal saline was administered at a rate of 3 ml/kg/hr intravenously throughout the study. PGE_1 and TMT were prepared in 5% dextrose solution, 20 μg/ml and 5 mg/ml, respectively. Hypotensive agents were infused with Truth A-II microinfusion pump. PGE_1 and TMT were initially infused at a rate of 0.5μg/kg/min. and 10 μg/kg/min., respectively. The infusion rate of each drug was adjusted to decrease and maintain the systemic arterial pressure at 50% of the control value.

Systemic arterial pressure (BP), heart rate (HR), central venous pressure (CVP), pulmonary capillary wedge pressure (PCWP) and electrocardiogram were continously monitored with Hewlett 7758B system. Cardiac output (CO) was measured by thermodilution technique with Edward CO computer 9520. Blood gas analysis were performed with Corning 168 pH/blood gas analyzer. Lactate and pyruvate concentrations in internal jugular blood which mainly drains the brain, and mixed venous blood were measured enzymatically. The following values were also calculated based upon the equations described below.

SVR (mmHg/l per min.) = (MAP-CVP)/CO, PVR (mmHg/l per min.) = (PAP-PCWP)/CO, A-VD_{O_2} (ml/dl) = Ca_{O_2} –

Table 1. Hemodynamic changes after 30 min of experimental preparation (I),

		SYSTEMIC systolic (mmHg)	diastolic mean (mmHg)	(mmHg)	HR rate/min
	I	141 ± 6	93 ± 6	111 ± 6	125 ± 8
PGE_1	II	79 ± 3	45 ± 2	56 ± 2	125 ± 8
(n=11)	III	79 ± 4	45 ± 2	54 ± 3	118 ± 7
	IV	138 ± 6	91 ± 6	106 ± 6	123 ± 8
	I	148 ± 6	88 ± 6	109 ± 5	129 ± 11
TMT	II	84 ± 4	44 ± 4	58 ± 3	118 ± 2
(n=4)	III	90 ± 4	45 ± 6	61 ± 4	115 ± 3
	IV	131 ± 4	79 ± 7	99 ± 3	121 ± 6

Table 2. Changes of hemodynamic parameters. CO = cardiac

TRIMETAPHAN (n = 4)			
I	II	III	IV
1.45 ± 0.05	1.33 ± 0.17*	1.26 ± 0.06*	1.45 ± 0.07
72.48 ± 4.83	42.63 ± 5.59**	46.16 ± 4.79	65.01 ± 3.00
4.15 ± 0.41	7.26 ± 1.34*	7.25 ± 0.86*	6.91 ± 0.49*

*$P < 0.05$ and **$P < 0.01$ as compared to the control (I)

Table 3. Changes of blood

		PROSTAGLANDIN E1 (n = 11) pH	P_{O_2} (mmHg)	P_{CO_2} (mmHg)	H_{CO_3} (mEq/l)	BE (mEq/l)
	I	7.348±0.026	211±20	34.3±2.2	18.6±1.0	-5.63±1.22
ARTERY	II	7.310±0.023	203±14	34.5±2.5	17.1±0.7	-7.86±0.86
	III	7.242±0.024*	181±16	42.2±2.6*	18.0±0.6	-9.02±0.87*
	IV	7.304±0.027	212±12	38.1±2.8	18.5±0.5	-6.87±0.70
	I	7.320±0.018	56.4±2.4	40.7±8.6	20.8±1.1	-4.70±1.20
MIXED	II	7.271±0.025	58.7±3.2	44.2±3.8	19.9±0.8	-6.72±0.91
VEIN	III	7.211±0.023*	63.3±2.6	51.6±3.9*	20.4±1.1	-7.90±1.12
	IV	7.267±0.022	62.4±3.9	45.6±2.8	20.5±0.7	-6.30±0.86
	I	7.316±0.004	67.0±5.8	40.8±2.3	20.6±0.7	-4.96±0.96
INT.	II	7.263±0.023	67.1±5.9	43.8±2.9	19.5±0.7	-7.30±0.89
JUG.	III	7.217±0.027*	73.6±5.1	48.4±3.1	19.4±0.7	-8.54±1.02*
VEIN	IV	7.274±0.024	77.0±5.3	44.1±3.6	19.9±0.6	-6.59±0.66

*$P < 0.05$ and **$P < 0.01$ as compared to the control (I)

30 min of hypotension (II), 60 min of hypotension (III) and 30 min after recovery

PULMONARY systolic (mmHg)	PULMONARY diastolic mean (mmHg)	PULMONARY mean (mmHg)	CVP (mmHg)	PCWP (mmHg)
19.3 ± 1.5	10.2 ± 1.2	13.7 ± 1.3	5.3 ± 1.0	7.5 ± 0.9
16.6 ± 1.8	9.4 ± 1.4	12.2 ± 1.4	5.0 ± 1.0	5.9 ± 0.9
18.4 ± 1.8	10.0 ± 0.6	13.4 ± 1.0	5.7 ± 0.8	6.3 ± 1.0
20.4 ± 1.7	10.7 ± 0.8	14.9 ± 1.1	5.2 ± 0.6	7.2 ± 0.9
17.5 ± 2.1	8.5 ± 0.6	12.4 ± 0.8	4.3 ± 0.5	6.0 ± 0.6
20.5 ± 1.3	9.0 ± 1.2	14.2 ± 0.7	3.3 ± 0.3	4.8 ± 0.3
21.8 ± 0.6	7.8 ± 0.8	13.8 ± 0.8	4.0 ± 0.4	4.8 ± 0.3
22.0 ± 1.2	9.5 ± 0.5	14.3 ± 0.5	4.8 ± 0.3	4.8 ± 0.3

Mean ± SE

output, SVR = systemic vascular resistance and PVR = pulmonary vascular resistance

	PROSTAGLANDIN E1 (n = 11)			
	I	II	III	IV
CO (l/min)	1.54 ± 0.07	1.52 ± 0.09	1.49 ± 0.08	1.52 ± 0.09
SVR (mmHg/l·min)	69.45 ± 3.85	34.57 ± 2.19**	32.79 ± 2.43**	69.15 ± 4.28
PVR (mmHg/l·min)	4.02 ± 0.52	3.44 ± 0.36	4.84 ± 0.44	5.00 ± 0.58

Mean ± SE

gas analysis

	TRIMETAPHAN (n = 4)			
pH	P_{O_2} (mmHg)	P_{CO_2} (mmHg)	H_{CO_3} (mEq/l)	BE (mEq/l)
7.335±0.030	204±8	33.2±2.0	17.7±0.4	−6.78±1.01
7.148±0.045**	156±17*	47.4±3.6*	16.4±1.0	−12.83±1.82*
7.149±0.035**	169±10*	45.2±3.4*	15.6±0.6	−13.35±1.30**
7.170±0.048*	190±12	45.0±5.4	16.0±0.9	−12.63±1.57*
7.290±0.034	53.5±4.4	39.6±3.2	18.9±0.4	−7.05±0.94
7.117±0.047*	60.7±3.5	58.0±6.8*	18.3±1.0	−12.10±1.37*
7.113±0.040*	61.7±4.1	56.0±4.6*	17.9±1.6	−12.50±2.12*
7.132±0.048*	65.9±5.2	58.2±6.4*	19.5±1.5	−10.98±1.36
7.281±0.039	55.2±5.0	41.6±3.5	19.1±0.5	−6.70±0.093
7.121±0.058	66.9±3.6	56.6±6.3	17.7±0.9	−12.38±1.23*
7.128±0.036*	67.3±3.8	56.0±4.7	18.4±1.5	−11.60±1.40*
7.163±0.058	73.2±6.7	55.7±5.5	18.6±1.7	−11.78±2.04

Mean ± SE

Table 4. Metabolic changes of hypotension. AVD_{O_2} = arterio-venous (internal jugular vein) oxygen content difference

	PROSTAGLANDIN E1 (n = 11)			
	I	II	III	IV
AVD_{O_2} (ml/dl)	7.547±0.698	7.104±0.590	5.805±0.532	7.072±0.608
$AVijD_{O_2}$ (ml/dl)	6.488±0.580	6.348±0.698	4.894±0.507	5.705±0.645
O2 consumption (ml/min)	11.68±1.24	10.61±0.88	8.71±0.89	10.51±0.84
O2 extract. rate	0.28	0.27	0.22	0.26
MIXED VEIN				
lactate (mg/dl)	15.12±2.70	14.34±2.00	13.29±1.64	13.18±1.81
pyruvate (mg/dl)	0.789±0.117	0.783±0.103	0.663±0.094	0.422±0.068
L/P ratio	19	18	20	31
INT. JUG. VEIN				
lactate (mg/dl)	16.24±2.41	15.77±1.97	15.54±1.97	14.95±2.07
pyruvate (mg/dl)	0.849±0.122	0.695±0.084	0.601±0.089	0.483±0.123
L/P ratio	19	23	26	31

Mean ± SE

Cvo_2, $A\text{-}V_{ij}D_{O_2}$ (ml/dl) = $Cao_2 - C_{vij}o_2$, whole body O_2 consumption (ml/min.) = $(Cao_2 - Cvo_2) \times CO \times 10$, and whole body O_2 extaction rate = $(Cao_2 - Cvo_2)/Cao_2$.

SVR: systemic vascular resistance, PVR: pulmonary vascular resistance, $A\text{-}VD_{O_2}$: arterio-venous (mixed vein) oxygen content difference, $A\text{-}V_{ij}D_{O_2}$: arterio-venous (internal jugular vein) oxygen content difference, Cao_2: arterial oxygen content, Cvo_2: venous (mixed) oxygen content, $C_{vij}o_2$: internal jugular vein blood oxygen content.

These were measured repeatedly in four phases, i.e. phase I as control (30 min after completion of experimental preparation), phase II (30 min after the onset of hypotension), phase III (60 min after the onset of hypotension) and phaseIV as recovery (30 min after MAP returned to at least 85% of the control).

All of these values were compared to those of the control using Student's t-test and $P < 0.05$ was regarded as significant.

Results

Hypotension was induced smoothly within 5–10 min in both groups. The required doses for reduction and maintenance of MAP at 50% of the controls were 1.58 μg/kg/min in PGE_1 group or 45 μg/kg/min in TMT group.

The changes of hemodynamic values are shown in table 1. PAP, PCWP and CVP remained virtually unchanged throughout the investigation in both groups. HR did not show any significant change in PGE_1 group, whereas slightly but significant decrease ($P < 0.05$) was found in TMT group. BP recovered gradually (15–30 min) after the termination of the drug infusion without rebound hypertension or other complications.

The changes in CO, SVR and PVR are shown in table 2. CO did not change in PGE_1 group but in TMT group was decreased in CO phase II ($P < 0.05$) and aggrevated in phase III ($P < 0.05$). CO recovered completely after BP returned to the control value. SVR was significantly decreased in both groups, 53% of the control value in PGE_1 group and 41% in TMT group, respectively. PVR did not change in PGE_1 group but increased in TMT group and did not recover until 30 minutes of recovery.

Table 3 shows the results of blood gas analysis. Arterial pH, P_{O_2}, P_{CO_2} and base deficit in PGE_1 group did not change sig-

(mixed vein) oxygen content difference, $AVijD_{O_2}$ = arterio-venous

TRIMETAPHAN (n =4)			
I	II	III	IV
7.845±0.653	5.269±0.719*	5.718±0.293*	5.535±0.617*
7.595±0.646	4.679±0.669*	4.943±0.333*	5.140±0.231*
11.37±1.01	6.94±1.10*	7.16±0.34*	8.05±0.97
0.30	0.21	0.22	0.21
18.91±2.80	22.04±3.53	21.17±3.30	17.32±2.90
1.067±0.244	1.099±0.372	0.993±0.348	0.225±0.084*
18	20	21	77
20.26±2.83	23.17±2.82	21.87±3.27	19.19±3.19
0.936±0.196	1.108±0.301	0.821±0.237	0.213±0.059*
22	21	27	90

*$P < 0.05$ as compared to the control (I)

nificantly in phase II, but pH decreased, whereas Pa_{CO_2} and base deficit increased significantly in phase III. These changes returned to the control values during phase IV. In TMT group, changes in arterial pH, P_{O_2}, P_{CO_2} and base deficit were greater than in PGE_1 group. And these changes in TMT group did not recover even in phase IV. Blood gas in mixed venous and internal jugular venous blood which mainly drains the brain showed virtually the same tendency as seen in arterial blood in both groups.

The metabolic effects of PGE_1 and TMT were summarized in table 4. Whole body oxygen consumption did not change in PGE_1 group, whereas it was significantly decreased in TMT group. Oxygen extraction rate was somewhat decreased in both groups but greater extent in TMT group. $A\text{-}VD_{O_2}$ and $A\text{-}V_{ij}D_{O_2}$ decreased slightly in phase III but returned to the control value in phase IV in PGE_1 group. In TMT group $A\text{-}VD_{O_2}$ and $A\text{-}V_{ij}D_{O_2}$ decreased significantly from phase II to phase III and remained at lower level in phase IV. Both groups did not reveal significant changes in lactate concentrations in mixed venous blood but there was some reduction in pyruvate concentrations, which consequently increased the lactate/pyruvate (L/P) ratio especially in recovery phase. The changes in lactate and pyruvate concentrations in internal jugular venous blood were almost similar to those in mixed venous blood. However, TMT group revealed higher L/P ratio than PGE_1 group especially in internal jugular venous blood rather than in mixed venous blood.

Discussion

Although PGE_1 has been shown to possess a potent vasodilating activity, the mechanism of this action is not well understood. It has been suggested that PGs specifically interfere with the constricting action of catecholamines on blood vessels,[10,11], modulate autonomic nervous system[12], or inhibit catechoamine release from the adrenal medulla[13]. There are many reports on the actions of PGE_1 with direct inotropic effect which increases CO, and coronary and renal blood flow. Therefore it is suggested that PGE_1 can be used safely as a hypotensive agent during surgery. However, these effects of PGE_1 were studied under rather mild hypotension with relatively short duration. In this study MAP was lowered to 50% of the control for 60 min by PGE_1 or TMT. In PGE_1 group, CO was well maintained

with substantial reduction in SVR. It is controversial if PGE_1 increase HR in conscious man. The fact that HR did not increase in our study may be due to the inhalation of halothane (0.2–0.5%). In TMT group HR and CO decreased and PAP and PVR increased during and after hypotension. From these results we concluded that the main advantage of PGE_1 over TMT as a hypotensive agent is that PGE_1 has no significant effects on CO, HR and PVR.

There are many reports about the impairment of pulmonary gas exchange caused by vasodilators used for deliberate hypotension[14–16]. Increased pulmonary shunting associated with low cardiac output, pulmonary vasodilataton or interference for hypoxic pulmonary vasoconstriction by vasodilating agent is considered to be one of the pathophysiologic mechanisms. With constant setting of the venilator throughout the study, PGE_1 group revealed considerably less abnormalities in arterial blood gases as well as those in mixed and internal jugular venous blood, and easy recovery to the control after cessation of PGE_1 administration as compared with those of TMT group.

Total body oxygen consumption was slightly decreased in PGE_1 group, and a considerably greater decrease was observed in TMT group. The lactate concentration in mixed venous blood as well as in internal jugular venous blood showed minimal changes in both groups. The L/P ratio in mixed venous and internal jugular venous blood showed slight elevation in both groups, however, greater elevation in the L/P ratio was observed in the recovery period in TMT group, especially in internal jugular venous blood. It is stated that lactate and pyruvate primarily originated from cytoplasmic glycolytic pathway can pass freely through the cell membrace into blood. Therefore, lactate and L/P ratio in blood can be taken as an index reflecting intracellular lactate and L/P ratio[17]. As indicated by the following equation, the intracellular L/P ratio shows the redox state of cytoplasmic space:

$$\text{Lactate} + NAD^+ + \overset{LDH}{\rightleftharpoons} \text{Pyruvate} + NADH$$

$$NAD^+/NADH = K_1 \times \text{pyruvate/lactate}$$

According to Krebs and Veech[18], in cytoplasm, the regulatory link between the redox state of the NAD^+-NADH system and the phosphorylation state of the adenine nucleotides are provided by the following equation;

$$NAD^+/NADH = K_1 \times \text{pyruvate/lactate} = K_2 \times ATP/ADP \times Pi$$

This equation shows that a high L/P ratio will be asscociated with a low (ATP)/(ADP) (Pi) ratio and vice versa. Accordingly, the increased L/P ratio in the period of recovery in TMT hypotension especially in internal jugular venous blood indicates the decrease in blood flow to the tissue especially to the brain. But the oxygen tension in internal jugular venous blood was far above the critical level of 25 mmHg reported by Fink and Haschke[19]. In conclusion, PGE_1-induced hypotension is more suitable than TMT-induced hypotension even when systemic mean arterial pressure was lowered to 50% of the control for 60 min in dogs.

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