Intra-operative Blood Pressure Control by Prostaglandin E_1 in Patients with Hypertension and Ischemic Heart Disease

– A Multi-center Study –

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The purpose of this multi-center study was to evaluate the efficacy and safety of prostaglandin E_1 (PGE_1) administration in achieving deliberate hypotension and in treating intraoperative hypertension for patients with a history of hypertension and ischemic heart disease. PGE_1 (0.08 $\mu g \cdot kg^{-1} \cdot min^{-1}$) decreased systolic blood pressure from 125 ± 29 to 106 ± 22 mmHg (mean ± SD) in the deliberate hypotension group (n=158) and from 155 ± 34 to 125 ± 32 mmHg in the antihypertension group (n=55). The heart rate significantly increased from 80 ± 15 to 85 ± 18 beats·min^{-1} in the deliberate hypotension group, but was not significantly altered in the antihypertension group. The time required to obtain the desired level of blood pressure was approximately 20 min in the deliberate hypotension group. When the infusion was stopped, blood pressure returned approximately to the preinfusion level within about 20 min. No rebound hypertension was observed. PGE_1 significantly increased the urine flow in patients who had a low urine flow before PGE_1 infusion. Thirteen out of 213 patients (5.6%) had side effects such as excessive hypotension (1%), phlebitis (3%), and unexpected tachycardia (1%), which were alleviated gradually after discontinuation of PGE_1 infusion. No dysarrhythmia and further ST segment changes in the electrocardiograms were observed. These findings suggest that PGE_1 can be safely used to control arterial blood pressure during surgery in patients having preoperative hypertension and ischemic heart disease. (Key words: prostaglandin E_1, deliberate hypotension, intra-operative hypertension, ischemic heart disease)

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Intra-operative blood pressure control such as deliberate hypotension and antihypertension is an integral part of anesthetic management during surgery, but agents used to achieve this purpose can give rise to side effects.

Deep inhalational anesthesia causes myocardial depression[1]. The use of sodium nitroprusside is associated with tachyphylaxis[2], rebound hypertension[3], and potential cyanide toxicity[4], while nitroglycerin has been shown to increase intrapulmonary shunting[5].

It has been reported that prostaglandin E_1 (PGE_1), a natural product of many mammalian tissues[6], is a potent vasodilator of all peripheral blood vessels which increases blood flow in the coronary, pulmonary, hepatic and renal arteries[7–9]. PGE_1 is being used clinically in the treatment of severe ischemia of the extremities[10], ductus-dependent congenital heart defects[11], viral hepatitis[12], adult respiratory distress syndrome[13], and pulmonary hypertension[14,15]. Also, PGE_1 has been shown to reduce the work of the left ventricle[16] and to possess an antiarrhythmic effect[17]. These findings suggested PGE_1 as being a suitable agent for blood pressure control during anesthesia in medically compromised patients. We, therefore, conducted this study to examine changes in hemodynamics and urine volume when PGE_1 was administered either for deliberate hypotension or for the treatment of hypertension during anesthesia in patients who had a history of hypertension and/or ischemic heart disease, and to evaluate the efficacy and safety of PGE_1 administration in the intraoperative control of blood pressure in these patients.

Methods

Patient Population

The study population comprised 213 patients who underwent surgery under general (n=197) or epidural (n=16) anesthesia at 10 university hospitals in the Kyushu district of Japan. The study protocol was approved by the regional ethical committee and informed consent was obtained. To evaluate the efficacy and safety of PGE_1 in the control of blood pressure during surgery, patients were enrolled in two groups. 1) A deliberate hypotension group (n=158): these were patients undergoing deliberate hypotension using PGE_1. They included 49 patients with essential hypertension defined as systolic blood pressure of more than 160 mmHg and/or diastolic blood pressure of more than 95 mmHg, 58 patients with borderline hypertension defined as systolic blood pressure of more than 140 mmHg and/or diastolic blood pressure of more than 90 mmHg, and 23 patients with ischemic heart disease having a past history of myocardial infarction or chest pain with ST-T change on ECG, with a New York Heart Association class I or class II physical status. 2) An intraoperative antihypertension group (n=55): these were patients to whom PGE_1 was administered to reduce blood pressure as a treatment for hypertension during surgery. They included 26 patients with essential hypertension, 12 patients with borderline hypertension, and 8 patients with ischemic heart disease.

Patients were excluded if they had severe systemic atherosclerosis, severe renal insufficiency, severe liver insufficiency, severe cardiovascular or cerebrovascular impairment, excessive hemorrhage, a shock state, or pregnancy.

Administration of PGE_1

PGE_1 (Prostandin 500, Ono Pharma., Japan) in which 500 μg of PGE_1 is contained in a vial was diluted by 10–100 ml of 0.9% saline solution or 5% glucose solution just before use. PGE_1 was initially infused at 0.01–0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$, followed by a maintenance dose of 0.05–0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$. The doses were adjusted by the attending anesthesiologists to obtain a desirable blood pressure.

Table 1. Patient Characteristics

Characteristic	Deliberate hypotension	Intra-operative antihypertension
Patients (n)	158	55
Gender (male/female)	71/87	29/26
Age (yr)	54 ± 16	63 ± 11
Weight (kg)	54 ± 9	56 ± 10
Anesthesia		
General		
Enf.	102	26
Hal.	6	2
NLA	21	11
others	18	11
Epidural	11	5
Anesthesia time (min)	386 ± 176	357 ± 175
Operation time (min)	275 ± 148	259 ± 147

Mean ± SD
Enf.: enflurane/nitrous oxide
Hal.: halothane/nitrous oxide
NLA: neurolepto-analgesia/nitrous oxide

Measurements

Electrocardiogram, systolic and diastolic blood pressure, heart rate, body temperature and urine volume were measured continually. Blood pressure was obtained with either a sphyngomanometer, automated blood pressure cuff, or intra-arterial cannulation. Measurements of blood chemistry {GOT (glutamate oxalacetic transaminase), GPT (glutamate pyruvate transaminase), LDH (lactate dehydrogenase), r-GTP (r-glutamyl transpeptidase), BUN (blood urea nitrogen), creatinine, and bilirubin}, PT (prothrombin time), and PTT (partial thromboplastin time) were performed within 1 week of preoperative and postoperative terms.

Anesthesia and surgery

Anesthetics were selected by the attending anesthesiologists at their own discretion. Surgery was classified as neurosurgery (n=50), vascular (n=33), thoraco-abdominal (n=75), orthopedic (n=28) and other (n=27).

Evaluation and analysis

The efficacy of PGE_1 administration in intraoperative blood pressure control was evaluated by the attending anesthesiologists, based on the following three criteria; 1) the magnitude of a fall in blood pressure was satisfactory, 2) the ability to control blood pressure was acceptable, 3) the degree of blood loss was considered to be less than that assumed if PGE_1 had not been used. The safety of PGE_1 administration was also evaluated by the anesthesiologists based on the occurrence of side effects, ECG abnormalities, and changes in urine flow. Efficacy was judged according to 4 levels; efficient, moderately efficient, inefficient, and adversely effective. Safety was also judged on the basis of 4 levels; safe, possibly safe, questionable, and not safe.

The data are presented as mean ± SD unless it is explicitly indicated that standard error of mean (SEM) is given. Statistical analysis was performed using analysis of variance and Student's t-test or paired t-test for comparison

Table 2. PGE_1 administration dosages and times

	Deliberate hypotension	Intra-operative antihypertension
PGE_1 initial dose ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	0.077 ± 0.058	0.083 ± 0.167
PGE_1 maintenance dose ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	0.080 ± 0.080	0.067 ± 0.075
PGE_1 total dose (μg)	503 ± 844	385 ± 576
Total infusion time (min)	132 ± 97 (n=158)	113 ± 94 (n=55)

Mean ± SD

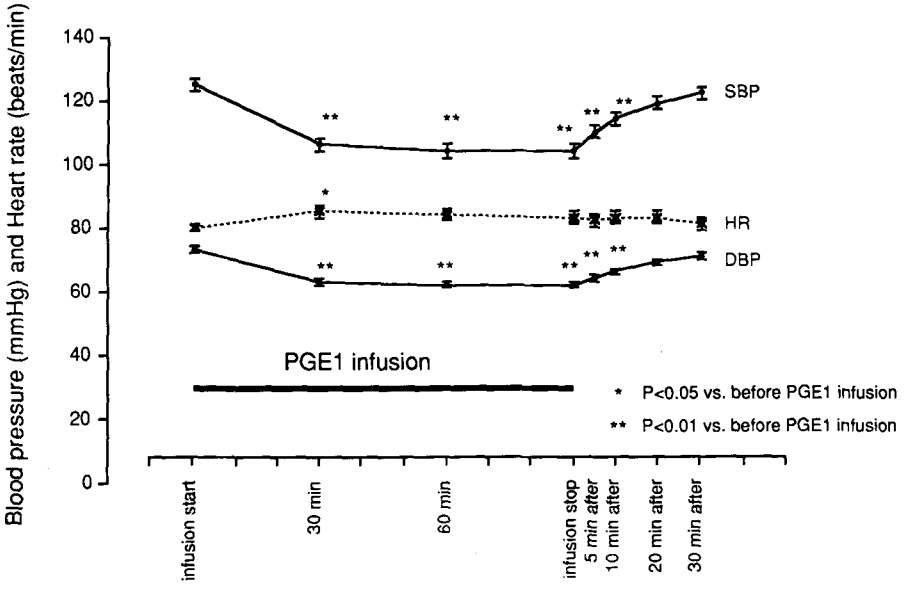

Fig. 1. Plots of systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) before, during, and after PGE_1 administration for deliberate hypotension. Values are mean ± SEM.

of the data obtained before, during and after PGE_1 infusion. $P < 0.05$ was considered significant.

Results

Table 1 shows the characteristics of the two groups of patients. Of the 213 patients, 158 were enrolled in the deliberate hypotension group, and 55 were in the intra-operative antihypertension group. Anesthesia employed were enflurane/nitrous oxide (60%), halothane/nitrous oxide (4%) neurolepto-analgesia/nitrous oxide (15%), epidural with or without supplements (8%), and others (13%). Of 158 deliberate hypotension patients, 31% had established hypertension, 37% borderline hypertension, and 15% ischemic heart disease. Of 55 intra-operative antihypertension patients, 47% had established hyperten-

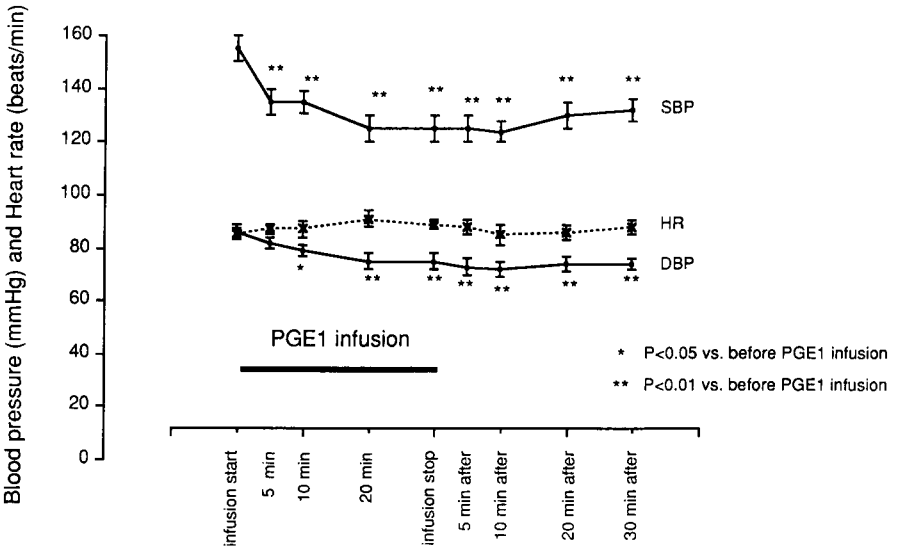

Fig. 2. Plots of systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) before, during, and after PGE_1 administration for intraoperative antihypertension. Values are mean ± SEM.

sion, 33% borderline hypertension, and 14% ischemic heart disease. Table 2 shows the dosages and times of PGE_1 administration. Maintenance doses of PGE_1 were 0.080 ± 0.080 and 0.067 ± 0.075 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in the deliberate hypotension and intra-operative antihypertension groups, respectively. The times required to obtain the desired blood pressure and for recovering the blood pressure were 22 ± 35 and 23 ± 30 min in the deliberte hypotension group, and 22 ± 36 and 19 ± 14 min in the intra-operative antihypertension group, respectively.

Figure 1 shows the changes in arterial blood pressure and heart rate in the deliberate hypotension group. PGE_1 significantly decreased systolic blood pressure from 125 ± 29 to 106 ± 23 mmHg ($P < 0.001$) and diastolic blood pressure from 73 ± 15 to 63 ± 14 mmHg ($P < 0.001$), and significantly increase the heart rate from 80 ± 15 to 85 ± 18 $beats \cdot min^{-1}$ ($P < 0.05$) after 30 min of infusion. Systolic and diastolic blood pressure returned to within 5% of the pre-infusion levels 20 min after cessation of PGE_1. No rebound hypertension was observed.

Figure 2 shows the changes in arterial blood pressure and heart rate in the intra-operative antihypertension group. Systolic and diastolic blood pressure was significantly reduced by PGE_1. The heart rate did not significantly change. The reduced blood pressure remained significantly lower than the pre-infusion levels, even 30 min after cessation of PGE_1.

Figure 3 shows urine flow before, during, and after PGE_1 infusion in all patients measured (*left*) and in patients who had urine flows of less than 1 $ml \cdot kg^{-1} \cdot min^{-1}$ before PGE_1 infusion (*right*). PGE_1 did not significantly alter the urine flow in the former patients, but it did significantly increase the flow in the latter.

Skin and rectal temperatures were not significantly altered by PGE_1 infusion. There were no abnormal elevations in the postoperative data of GOT, GPT, LDH, r-GPT, bililubin,

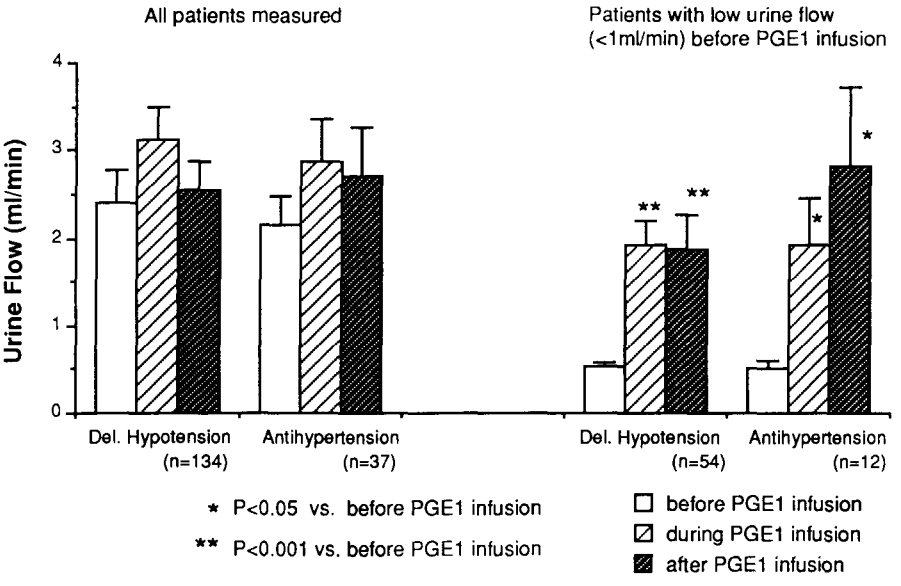

Fig. 3. Urine flow before, during, and after PGE_1 administration for deliberate hypotension and intraoperative antihypertension in all patients measured (*left*) and in patients who had urine flows of less than 1 $ml \cdot kg^{-1} \cdot min^{-1}$ before PGE_1 infusion (*right*). Values are mean ± SEM.

PT and PTT as compared with the preoperative data.

Out of the 213 patients, 13 (5.6%) experienced some side effects which were considered to be related to PGE_1 infusion. Three patients had excessive hypotension, but the undesirably decreased blood pressure was restored immediately after cessation of PGE_1 infusion. Seven patients had reddening at the injection sites and along the blood stream, indicating possible phlebitis. These changes disappeared after discontinuation or decrement of PGE_1 infusion. Three patients had unexpected tachycardia, which gradually decreased down following cessation of PGE_1. Abnormal ECG findings such as ST depression, ST elevation and ventricular dysarrythmia in association with PGE_1 administration did not occur.

Table 3 shows the efficacy and safety of PGE_1 administration. More than 90% of the attending anesthesiologists judged that PGE_1 was efficient or moderately efficient in the intraoperative blood pressure control for deliberate hypotension (95.5%) and antihypertension (91%). More than 95% judged that PGE_1 was safe or posssibly safe in deliberate hypotension (96.2%) and antihypertension (98.1%).

Discussion

PGE_1 has been administered safely in unanesthetized healthy human beings[18], and the effectiveness of PGE_1 administration has been demonstrated clinically in the treatment of severe ischemia of the extremities[10], ductus-dependent congenital heart defects[11], viral hepatitis[12], adult respiratory distress syndrome[13], and pulmonary hypertension[14,15].

In this study, we aimed to evaluate the efficacy and safety of PGE_1 administration for deliberate hypotension and antihypertension during surgery in patients having preoperative hypertension and ischemic heart disease. This

Table 3. Efficacy and safety of PGE_1 administration

	Deliberate hypotension	Intra-operative antihypertension
Efficacy		
efficient	64.7%	63.6%
moderately efficient	30.8%	27.3%
not efficient	4.5%	9.1%
adversely effective	0%	0%
Safety		
safe	47.1%	40.7%
possibly safe	49.1%	57.4%
questionable	3.8%	1.9%
not safe	0%	0%

study has several weak points. There is a lack of standardization with respect to treatment groups and anesthetic techniques. There is also no control group using a standard antihypertensive agent e.g. sodium nitroprusside. Although these factors may make the results vague, this study at least indicates that PGE_1 is an efficient and safe vasodilator, with no major adverse effects being observed in the patients. Minor side effects, including reddening of the injection sites, tachycardia and excessive hypotension, occurred in 5.6% of the patients, but these disappeared gradually after discontinuation or decrement of PGE_1 infusion without any problems.

PGE_1 is reported to be a potent vasodilator of all peripheral blood vessels, and to increase blood flow in the coronary, pulmonary, hepatic and renal arteries[7–9]. PGE_1 has also been shown to reduce the work of the left ventricle[16], to possess an antiarrhythmic effect[17], and to have minor or no inotropic effects[8,19]. These findings support the validity of PGE_1 to be used for intraoperative blood pressure control in cardiovascularly-compromised patients.

PGE_1 has several advantages as an intraoperative vasodilator over other agents. First, since it is a natural product of mammalian tissues[6] its toxicity may be less than that of other synthesized drugs such as sodium nitroprusside[2]. Second, PGE_1 has been reported to increase renal blood flow, urine flow, and the sodium excretion ratio without an increase in the glomerular filtration rate[8,20–22]. In this study, PGE_1 increased the urine flow in patients who had a low urine flow before PGE_1 infusion. This suggests that PGE_1 apparently exerts diuretic action when renal function has deteriorated. This effect of PGE_1 on urine flow may be a great advantage, since the flow tends to decrease during surgery and during deliberate hypotension[23] due to stimulation of the sympathetic nervous system and release of renin and vasopressin. PGE_1 has been shown to have a protective effect on renal function and hemodynamics in dogs with norepinephrine-induced acute renal failure. Third, PGE_1-induced vasodilation is due not only to direct dilatation of the vascular smooth muscles but also to the effects of interference with the constrictor action of catecholamine, angiotensin, and vasopressin[7,24–26]. These latter effects are promising, since instability of intraoperative blood pressure may arise from the stress-induced release of these substances. It is suggested

that PGE_1 protects against untoward renal, vascular, and metabolic effects of norepinephrine[7,24–26]. Fourth, PGE_1 possesses an antiarrhythmic action[17]. Intravenous injection of PGE_1 suppressed dysrhythmic activity due to coronary occlusion in anesthetized dogs[27]. Kelliher and Glenn[28] showed that PGE_1 injection raised the threshold of ouabain-induced arrhythmias in anesthetized cats. We experienced no PGE_1-related arrhythmia in this study. In addition, PGE_1 increases the coronary flow[29–31], and PGE_1 in anesthetized cats prevents ST segment elevation in the electrocardiogram and an increase in plasma creatine phosphokinase levels owing to coronary ligation[32], suggesting that PGE_1 is suitable for patients with ischemic heart disease. Moreover, PGE_1 has cytoprotective actions such as suppressing macrophage activation[33] and inhibiting the release of oxygen radicals and lysosomal enzymes from neutrophils[34]. It has been shown to decrease the damage caused by ischemia in a variety of tissues including liver[35], lung[36], and heart[37]. These actions favor PGE_1 as a promising agent not only for intra-operative blood pressure control but also for the protection of vital organs when they are exposed to hypoperfusion or ischemia during anesthesia.

The maintenance dose of PGE_1 (0.08 $\mu g \cdot kg^{-1} \cdot min^{-1}$) used in this study is compatible with previous studies in which PGE_1 was used for deliberate hypotension[21,38]. The time required to obtain the desired levels is approximately 20 min. This seems rather long in terms of the controllability of blood pressure during anesthesia. Some attending anesthesiologists believed that a longer time and deeper basal anesthetic level were needed to obtain the desired hypotension by PGE_1 as compared with other vasodilators. Nevertheless, overall, more than 90% of the attending anesthesiologists judged that PGE_1 was efficient or moderately efficient.

Increases in heart rate following PGE_1 administration have been reported in man[16,39,40]. We observed a significant heart rate increase during deliberate hypotension by PGE_1. This may be baroreflex-induced tachycardia in response to the decrease in blood pressure. Excessive tachycardia, however, occurred in only 2 out of the 213 patients. It is reported that prostaglandins depress the arterial baroreflex due in part to the stimulation of cardiac receptors[41]. Thus, baroreflex-induced tachycardia may be, if anything, less than with other vasodilators.

Changes in platelet aggregation have been described with experimental PGE_1 administration in human beings[42,43], but none of our patients had clinically apparent bleeding abnormalities. This is in agreement with Carlson et al, who reported that PGE_1 infused intravenously to healthy man at rates of 0.05 to 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 30 min had no discernible effects on platelet aggregation[44].

In summary, intravenous infusion of PGE_1 effectively reduced blood pressure while maintaining urine flow, with a minor increase in heart rate and without major side effects in patients having previous hypertension and ischemic heart disease. Although it was in part pointed out that the hypotensive effect of PGE_1 was slow and mild, the results indicate that PGE_1 is a promising agent for intra-operative blood pressure control.

Appendix: The Kyushu-Japan Intraoperative PGE_1 Study Group included the following centers and individuals.
Kyushu University Hospital, Fukuoka: Sumio Hoka (principal investigator), Junichi Yoshitake (chief coordinator), Takeyoshi Sata. Fukuoka University Hospital, Fukuoka: Kenjiro Dan, Keiichi

Tanaka. Nagasaki University Hospital, Nagasaki: Yutaka Goto, Makoto Fukuzaki, Ken Tuzaki. Ooita MedicalCollege Hospital, Ooita: Natsuo Honda, Kuniyasu Takahashi, Shunsuke Oda. Kumamoto University Hospital, Kumamoto: Tohru Morioka, Jiro Takeshita. Kurume University Hospital, Kurume: Takesuke Muteki, Kazuo Ooishi. Ryukyu University Hospital, Naha: Yoshiro Okuda, Hiroshi Iha, Yutaka Taira. Occupational and Environmental Health University Hospital, Kitakyushu: Akio Shigematsu, Jun Fukui. Miyazaki Medical College Hospital, Mayumi Takasaki, Naoto Nagata, Takako Izumi. Saga Medical College, Saga: Tadahide Totoki, Yoshio Taniguchi. Kagoshima University Hospital, Kagoshima: Nozomu Yoshimura, Toshiyuki Oda

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