Effects of Intravenously Administered Human Atrial Natriuretic Peptide on Elevated Blood Pressure during Surgery

Naofumi IWATSUKI, Masato KATOH, Akio YASUDA, Shuya SAITOH and Mitsuya ASANO

The effect of human atrial natriuretic peptide (hANP) on blood pressure (Bp) was evaluated in 11 patients who had elevated systoric Bp of over 150 mmHg during surgery. A bolus injection of 50 μg or 100 μg of hANP decreased Bp with an immediate response by 27.6 ± 3.1 mmHg (P <0.001) or 40.7 ± 4.2 mmHg (P <0.001), respectively, accompanying with tremendously increased urine output. Heart rate and Pa_{O_2} were not altered. Thus, a intravenous bolus injection of hANP is an useful therapeutic tool for the treatment of acutely elevated Bp during anesthesia. (Key words: human atrial natriuretic peptide, hypotensive effect)

(Iwatsuki N, Katoh M, Yasuda A et al.: Effect of intravenously administered human atrial natriuretic peptide on elevated blood pressure during surgery. J Anesth 3: 218–222, 1989)

Human atrial natriuretic peptide (hANP) is a peptide which is present in human blood serum. It is assumed to be responsible for regulating the sodium-fluid volume state as well as blood pressure[1]. The administration of hANP to anesthetized experimental animals causes such hemodynamic changes as a decrease in systemic blood pressure (Bp) and cardiac output (CO)[2–4]. Total peripheral resistance (TPR) either decreases or increases[3,4]. In normal healthy human volunteers in conscious state, hANP administered by infusion caused decreases in Bp associated with increases in heart rate (HR) and no changes in CO[5–8]. However, in patients with congestive heart failure, hANP decreased Bp with significant increases in CO and unchanged HR, especially when injected in bolus[7,9,10]. The effect of hANP on hemodynamics, therefore, may depend on whether the patient is healthy or suffering from congestive failure, conscious or anesthetized, and on the manner of drug administration–bolus injection or continuous infusion.

The purpose of this study is to evaluate the efficacy of hANP as a drug for the treatment of elevated Bp during surgery and to determine the hemodynamic effects of the drug when administerd by bolus injection under anesthesia.

Materials and Methods

Eleven patients who fit in ASA's anesthsia physical risk 1 or 2, having elevated systolic Bp over 150 mmHg, participated in our study. They were aged 57.3 ± 9.0 years (mean ± SD) (37–72 years) and their weight was 60.1 ± 10.3 Kg (mean ± SD) (46–81 Kg). Anesthesia was maintained with GO-enflurane in 8 patients and GO-halothane in 3 patients. Characteristics of patients are shown in table 1.

Alpha type hANP was used for this study.

Department of Anesthesiology, Tohoku University School of Medicine, Sendai, Japan

Address reprint requests to Dr. Iwatsuki: Department of Anesthesiology, Tohoku University School of Medicine, 1-1 Seiryou-machi, Aoba-ku, Sendai, 980 Japan

Table 1. Patient characteristics

	Age	Sex	Diagnosis	Operations	Disorders	ANP (μg)
1	64	M	ASO	Femoral BG	Hyp	100
2	72	F	Gastric Ca	Gastrectomy		100
3	37	M	Pituitary Adenoma	Removal	LVH	50×5
4	56	M	Esophageal Ca	Radical Op	DM	100
5	51	F	Mediastinal Tumor	Removal	Hyp,IHD	50×3
6	49	F	Myoma Uteri	Hysterectomy		100
7	49	M	Laryngeal Tumor	Removal		50
8	57	F	Gastric Ca	Gastrectomy		100
9	62	M	ASO	Femoral BG	Hyp, Af, RBBB, DM	100×3
10	62	M	Abdominal Aneurysma	Y Graft	Hyp	50×3
11	64	M	ASO	Femolar BG	Hyp	50

ASO = Arterial Sclerotic Obstraction, BG = Bypass Graft, Ca = Cancer, Hyp = Hypertension, LVH = Left Ventricular Hypertrophy, IHD = Ischemic Heart Disease, DM = Diabetes Mellitus

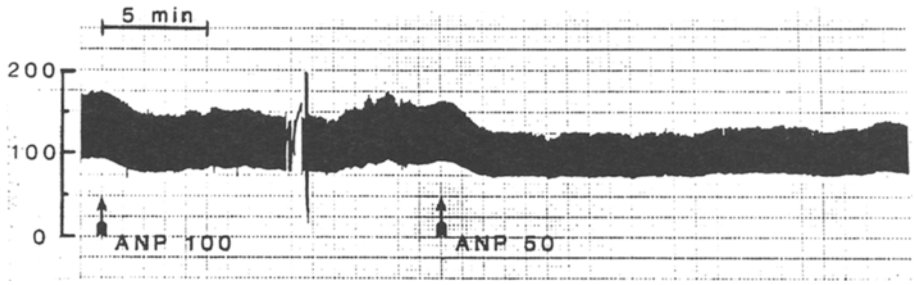

Fig. 1. Systemic blood pressure recording obtained directly from radial artery, following administration of 100 μg (100) and 50 μg (50) of hANP (ANP). The drug's onset is within one minutes of the injection and a maximum effect appears within 2 to 3 min.

Fifty μg of alpha hANP in powder form was dissolved with 2 ml of sterile water. In cases where patient's systolic Bp elevated and remained over 150 mmHg for more than 10 min, 50 or 100 μg of hANP was administered by bolus injection. The injection was repeated in cases where Bp failed to decrease to a desirable level or where transiently decreased Bp rose again over 150 mmHg within 15 min of the injection. A single injection of 50 μg of hANP was found to be effective in 2 patients, 3 injections in 2 other patients and 5 injections in one patient. In the 100 μg injection group, 5 patients received only a single injection and one patient received 3 injections.

Measurement of Bp by sphygmomanometry on forearm and heart rate by ECG was done before the first injection of hANP, every 1 min for the first 5 min after the every injection, then every 5 min for the next 30 min after final injection. Urine was collected through a urinary catheter for the time from the start of anesthesia to the first injection of hANP, for the 30 min after the final injection, and then for another 30 min.

Statistical analysis of the data was performed using Student's t-test, and P values of less than 0.05 were considered to be statistically significant.

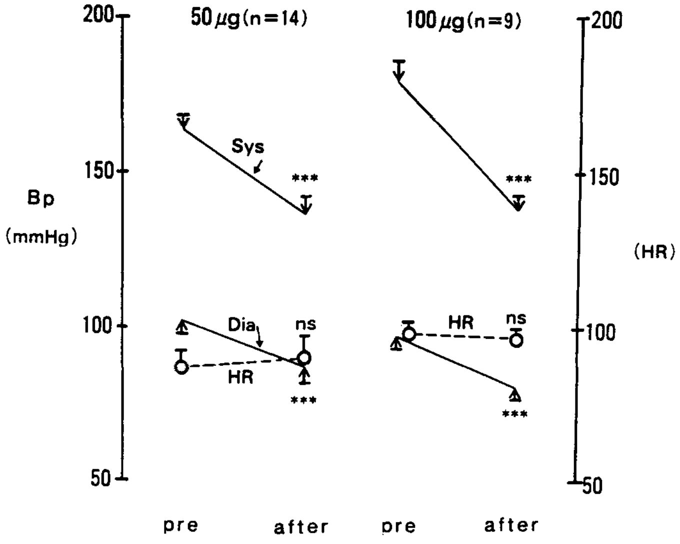

Fig. 2. Changes in systolic (Sys) and diastolic (Dia) blood pressure (Bp), and heart rate (HR) produced by the bolus injection of 50 and 100 μg of hANP. Pre and after = mean values ($\pm$ SE) before and after the injection of hANP, respectively. ***: $P < 0.001$. ns: not statistically significant.

Results

In every case, an intravenous bolus injection of hANP decreased Bp. The effect of this drug appeared within one minute of the injection, reaching a maximum within 2 to 3 min (fig. 1). Fifty μg of hANP reduced systolic Bp from 164 to 135 mmHg, diastolic Bp from 102 to 87 mmHg and mean Bp from 123 to 103 mmHg (n = 14, fig. 2). The degree of this decrease in systolic, diastolic and mean Bp were 27.6 $\pm$ 3.1 mmHg, 15.4 $\pm$ 2.4 and 19.4 $\pm$ 2.3 (mean $\pm$ SE) ($P < 0.001$), respectively. The injection of 100 μg of hANP decreased systolic Bp from 180 to 139 mmHg, diastolic Bp from 97 to 81 and mean Bp from 125 to 100 (n = 9, fig. 2). The degree of decrease was 40.7 $\pm$ 4.2 in systolic Bp, 15.8 $\pm$ 2.7 in diastolic Bp and 24.2 $\pm$ 2.6 in mean Bp (mean $\pm$ SE, $P < 0.001$). There was a significant difference in the degree of decrease in systolic Bp between the group given 50 μg and that given 100 μg ($P < 0.05$). Heart rate (HR) was neither altered by the injection of 50 μg nor 100 μg of hANP (fig. 2).

The volume of urine collected for 30 min after the final injection of hANP was extremely high compared to that collected in the next 30 min period as well as that collected prior to the injection ($P < 0.05$ and $P < 0.01$, repectively) in the both groups given 50 μg and 100 μg (fig. 3). The data of blood gas analysis obtained by 50 μg administration was put together with that obtained by 100 μg administration. The administration of hANP produced no significant changes in Pa_{O_2}, PH, and Pa_{CO_2} (fig. 4).

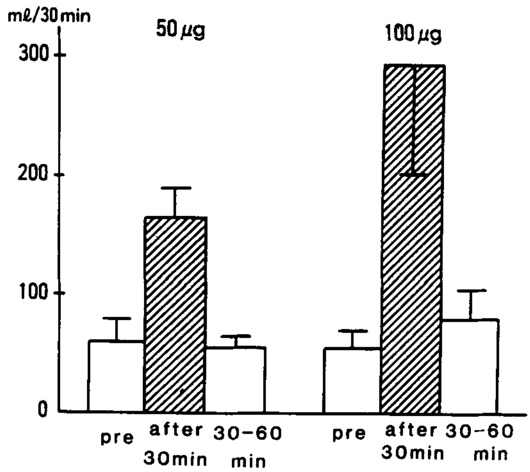

Fig. 3. Changes in volume of urine following administration of 50 and 100 μg of hANP (mean $\pm$ SE). Note, hANP tremendously increased urine output.

Discussion

This study demonstrates that an intravenous bolus injection of hANP is effective in reducing elevated Bp during surgery. A dose of 100 μg is considered to be more effective

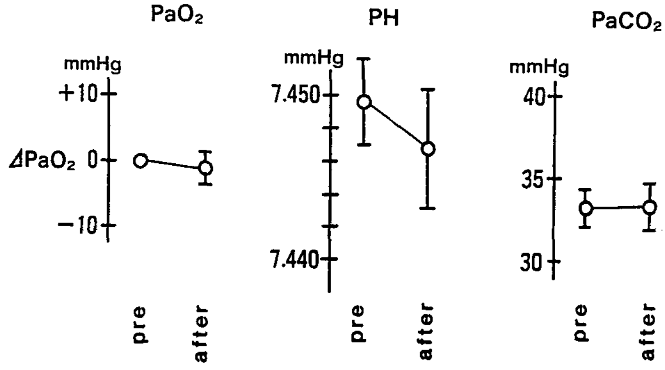

Fig. 4. Changes in arterial blood Pa_{O_2}, PH and Pa_{CO_2} produced by the injection of hANP. Mean ± SE. Pa_{O_2} is expressed by the change between the value before and after the injection of hANP (△ change), since given-FI_{O_2} differs between each patients. No significant changes are observed.

than 50 μg in this treatment, because a single 100 μg injection was shown to be effective in most cases, but a 50 μg injection often had to be repeated in order to achieve the desired effect. The bolus injection of 100 μg decreased systoric Bp by about 40 mmHg. This degree of reduction may be a useful standard for selecting an appropriate dosage of hANP in the treatment of hypertension observed during anesthesia.

Heart rate (HR) was found to be unaltered by the administration of hANP in this study. Reflex mediated increases in HR following the injection of hANP have been observed in conscious human volunteers[5-8], while in patients with congestive heart failure (CHF) hANP did not alter HR[7,9,10]. The presence of anesthetic and the state of HR at the time of hANP administration may account for this difference, since anesthetic depresses reflex mediated tachycardia[11]. HR tended to be higher both in patients of this study and those with CHF, thus the possibility and the degree of a further increase in HR might be small.

The main mechanism of Bp reduction produced by hANP may be a decrease in TPR mediated by vasodilation. A direct vasodilative effect of hANP has been recognized in previous studies[1]. The decrease in TPR produced by the injection of hANP has been observed in human[7-10]. The decrease in CO is another factor which reduces Bp. The effect of hANP on CO in patients under inhalational anesthesia has not been studied. We did not measure CO in the present study, either. In animal experiments CO has been shown to decrease with the administration of hANP, accompanied with reduced pulmonary capillary wedge pressure (PCWP), cardiac preload[2,3]. However in human studies for patients with CHF, CO has been shown to increase following the intravenous bolus injection of hANP without any reduction of PCWP[7,9,10]. A reduction in left ventricular afterload mediated by decreased TPR is known to increase CO. Since hANP alters both preload and afterload, it is reasonable to speculate that the balance of this two loads playes an important role to elicite change in CO produced by hANP. More detailed studies of CO as well as myocardial contractility which is another factor controlling CO, are required in order to clarify the cardiovascular effect of hANP. In anesthetized dogs, an intracoronary infusion of hANP did not depress regional myocardial contraction, suggesting no negative inotropic effect of hANP[4]. In normal man, Doppler measurments of ascending aortic blood flow suggested that hANP is not negatively inotropic[8].

The rapidity of the onset in the Bp reduction suggests that the change in Bp produced by the bolus injection is not mediated by an indirect secondary effect of hANP resulting from changes in cardiovascular hormones, such as renin-angiotensine, aldosterone, and epinephrine-norepinephrine, although these hormonal changes produced by hANP have been reported[1,5-7,9,10].

Vasodilators, such as nitroglycerine, usually decrease Pa_{O_2} by increasing pulmonary shunting[12,13], but hANP did not decrease

Pa_{O_2} in the present study. This drug may not influence pulmonary circulation, or any change in Pa_{O_2} may be too small to detect in such a small sample of patients.

A notable effect of hANP in our study was tremendously increased urine output. No other vasodilators or drugs for the treatment of acutely elevated Bp have been noted for such a distinct accompanying diuretic effect. According to our observations, the duration of the diuretic effect due to the intravenous bolus injection of 50 to 100 μg of hANP is about 30 to 60 min.

In conclusion, the intravenous bolus injection of 50 μg or 100 μg of hANP has been shown to effectively reduce Bp elevated during surgery. This response is immediate and of short duration, and accompanied by a definite diuretic effect. Thus the intravenous bolus injection of hANP has been proven to be convenient and practical as a therapeutic tool for the treatment of acutely elevated Bp during anesthesia.

(Received Mar. 22, 1989, accepted for publication Apr. 10, 1989)

References

1. Laragh JH: Atrial natriuretic hormone, the renin-aldosterone axis, and blood pressure-electrolyte homeostasis. N Engl J Med 313:1330–1340, 1985.
2. Ackermann U, Irizawa TG, Milojevic S, Sounenberg H: Cardiovascular effects of atrial extracts in anesthetized rats. Can J Physiol Pharmacol 62: 819–826, 1984.
3. Hirata Y, Ishii M, Sugimoto T, Matsuoka H, Sugimoto T, Kangawa K, Matsuo H: The effects of human atrial 28-amino acid peptide on systemic and renal hemodynamic in anesthetized rats. Circ Res 57: 634–639, 1985.
4. Iwanaga R, Hori S, Suzuki H, Nakajima S, Saruta T, Kojima S, Fukuda K, Satoh T, Kusuhara M, Handa S, Nakamura Y, Yoshinaga K, Yamaguchi K: Cardiovascular effects of intravenous and intracoronary administration of atrial natriuretic peptide in halothane anesthetized dogs. Life Sci 42: 1279–1286, 1988.
5. Ishii M, Sugimoto T, Matsuoka H, Ishimitsu T, Atarashi K, Hirata Y, Sugimoto T, Kangawa K, Matsuo H: Hemodynamic, renal and endocrine responses to alpha-human atrial natriuretic polypeptide (α-hANP) in healthy volunteers. Circulation 72: suppl III, 294, 1985.
6. Weidmann P, Hellmueller B, Vehlinger DE, Lang RE, Gnaedinger MP, Hasler L, Shaw S, Bachmann C: Plasma levels and cardiovascular, endocrine, and excretory effects of atrial natriuretic peptide during different sodium intakes in man. J Clin Endocrinol Metab 62:1027–1036, 1986.
7. Cody RJ, Atlas SA, Laragh JH, Kubo SH, Covit AB, Ryman KS, Shaknovich A, Pondolfino K, Clark M, Camargo MJF, Scarborough RM, Lewicki JA: Atrial natriuretic factor in normal subjects and heart failure patients. J Clin Invest 78:1362–1374, 1986.
8. Allen MJ, Gilmour SM, Singer M, Bennett ED: Effects of atrial natriuretic peptide on systemic haemodynamics and cardiac function in normal man. Cardiovasc Res 23:70–75, 1989.
9. Riegger GAJ, Kromer EP, Kochsiek K: Human atrial natriuretic peptide: Plasma levels, hemodynamic, hormonal, and renal effects in patients with severe congestive heart failure. J Cardiovascul Pharmacol 8:1107–1112, 1986.
10. Saito H, Ogihara T, Nakamura M, Hara H, Higaki J, Rakugi H, Takeyama H, Minamino T, Iimura K, Kumahara Y: Hemodynamic, renal, and hormonal responses to alpha-human atrial natriuretic peptide in patients with congestive heart failure. Clin Pharmacol Ther 42:142–147, 1987.
11. Stoelting RK: Autonomic regulation of cardiovascular function. ASA Annual Refresher Course Lecture 1981, 201.
12. Kopman EA, Weygandt GR, Bauer S, Feruson TB: Arterial hypoxemia following the administration of sublingual nitroglycerine. Am Heart J 96:444–447, 1978.
13. Casthely PA, Lear S, Cottrell JE, Lear E: Intrapulmonary shunting during induced hypotension. Anesth Analg 61:231–235, 1982.