原 著

Effects of Alpha Human Atrial Natriuretic Peptide on Cardiac Performance and Hormonal Responses in Anesthetized Beagles, and on Action Potential and Contractile Force in Guinea-Pig Papillary Muscles.

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Abstract

To evaluate usefulness of human atrial natriuretic peptide (hANP) in hypotensive anesthesia, we investigated the hemodynamic, hormonal changes and renal function in anesthetized beagles, Fifteen beagles were divided into three groups by infusion rate: 0.5 μg/kg/min (Group 1), 1 μg/kg/min (Group 2), 3 μg/kg/min (Group 3). The hANP was infused for 60 minutes then discontinued. Hypotensive values in steady-state were 84.1% (Group 1), 83.0% (Group 2) and 81.3% (Group 3) of the baseline levels, shown no significant differences. In the recovery period, systemic blood pressure (SBP) remained 88.7% (Group 1), 88.2% (Group 2) and 89.2% (Group 3) at 15min, followed by gradual recovery, HR and PAP did not change significantly throughout the study. On the other hand, cardiac output (CO) and left ventricular maximum dp/dt (LV dp/dt max) decreased gradually during the infusion period. And changes of systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR) indicated no vasodilatory effects of hANP. Urine volume (UV) and creatinine clearance (Ccr) showed no significant increases during the infusion period. Hormonal values were not significantly altered by hANP infusion. Superfusion of hANP up to 1000 ng/mℓ, did not change any contractile variables of isolated guinea-pig cardiac muscles. Hypotension induced by hANP may be neither due to decreased afterload nor due to cardiac contractility. These data indicate that the hANP-induced hypotension which is accompanied with a reduction of CO and not followed by prompt recovery, may be restrained from clinical uses in humans.

Key words : Human atrial natriuretic peptide, Induced hypotension, Hemodynamic effects, Hormonal effects, Cardiac contractility

Introduction

Human atrial natriuretic peptide (hANP) is a potent vasoactive[1] and natriuretic peptide[2], which has been considered to be in the regulation of body fluid volume and blood pressure. It was assumed that hANP acted as an arterial vasodilator and the blood pressure lowering effect was mainly due to a decrease in systemic vascular resistance[3]. However, recent studies have shown that a decrease in cardiac output mediated through reduction in central venous pressure[4]. As this peptide is endoge-

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nous, it may be safe if it will be applicable as a hypotensive agent during induced hypotension in anesthesia, Therefore, the aim of this study is to assess the hypotensive action of hANP evaluating hemodynamic, renal and hormonal effects in the anesthetized beagles, and to evaluate the clinical application of hANP to induced hypotension. The direct effects of hANP on cardiac muscle were also evaluated using isolated guinea-pig papillary muscles.

Materials and Methods

(1) Beagle studies

The study was approved by the Animal Care and Use Committee of Hokkaido University School of Medicine. Twenty beagles weighting 8.3 ± 1.2kg were studied in two experiments.

In experiment Ⅰ, 15 beagles were equally divided into three groups by infusion rates of hANP: 0.5 μg/kg/min (Group 1), 1 μg/kg/min (Group 2), 3 μg/kg/min (Group 3). Anesthesia was induced with intravenous administration of thiamylal 25mg/kg and the trachea was intubated. Anesthesia was maintained with enflurane 1% in nitrous oxide (50%) and oxygen (50%). Mechanical ventilation was adjusted to keep normocapnia ($PaCO_2$ 40 ± 5mmHg) monitoring end-tidal carbon dioxide concentration by a capnography (Capnomac, Datex, U.S.A.). The animals were curarized with intramuscular pancuronium 2mg. The left femoral vein was cannulated for the administration of fluids and the drug. An arterial catheter was inserted through the left femoral artery for continuous monitoring of arterial blood pressure and blood sampling. A 5-French pulmonary catheter was inserted through the right femoral vein to measure both pulmonary artery and central venous pressures. The left ventricular catheter was inserted through the right carotid artery to measure left ventricular pressure and LV dp/dt max. The ascending aortic blood flow (AAF) by a 14 mm probe, and the left renal blood flow (RBF) by a 3 mm of electromagnetic flow meter were continuously monitored. Urine volume was measured through a bladder catheter. Lactate Ringer's solution was administered at a rate of 10mℓ/kg/hr throughout the study. All pressures were measured with calibrated Gould 23 XL (Spectramed, U.S.A.) transducers. Electrocardiogram (lead Ⅱ), heart rate (HR), systolic, mean, and diastolic blood pressures (SBP, MBP, DBP), pulmonary arterial, pulmonary capillary wedge and central venous pressures (PAP, PCWP, CVP) and left ventricular maximum dp/dt (LV dp/dt max) were monitored and recorded in multi-channel recorder (Nihon-koden, Japan). RBF and AAF were measured with electromagnetic flowmeter (MFV-1200, Nihon-koden). Cardiac output (CO) was calculated by dividing AAF by body weight, and systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR) were calculated using standard formulae. Blood gas analysis was performed with ABL-1 (Radiometer, Denmark). Blood and urine samples were obtained to calculate creatinine clearance (Ccr).

Baseline hemodynamic and renal variables were measured. Then, synthetic alpha type hANP in powder form (supplied by Suntory Institute of Biomedical Research, Japan) was dissolved with sterile water to 0.1mg/mℓ and an infusion of hANP was started by different rates in three groups. Each infusion was continued for 60 min and followed by 60 min recovery period. Hemodynamic variables were measured 15, 30, 60 min during the infusion period and 15, 30, 60 min during the recovery period. Blood samplings for measurements of hANP concentrations were performed 5, 10, 15, 20, 30 and 60 min during the infusion period, and 1, 3, 5, 7, 9, 15, 30, 60 min during the recovery period. All blood samples were immediately on ice, and the plasma was separated in refrigerated centrifuge and stored in polyethylene tubes at -70℃ for subsequent assays. Plasma hANP concentrations were measured by a high performance liquid chromatography-radioimmunoassay using hANP kits (^{125}I labeled).

In experiment Ⅱ, hormonal responses during an infusion of hANP at a rate of 1μg/kg/min were studied in 5 beagles under enflurane-nitrous oxide

anesthesia. Blood samples for measurements of hematocrit, epinephrine, norepinephrine, renin acrivity, angiotensin I and II, and aldosterone were obtained before, 30 and 60min during infusion, and 60min after cessation of hANP infusion. They were stored on ice, and plasma was separated in refrigerated centrifuge and stored in polyethylene tubes at -70℃ for subsequent assay. Epinephrine and norepinephrine were measured by high-performance liquid chromatography. Renin activity, angiotensin I and II, and aldosterone were determined by radioimmunoassay. Results were given as means ±SEM. Each beagles served as its own control, and differences between control, infusion and recovery periods were analyzed by repeated measure ANOVA. Differences between groups were analyzed using one-factor ANOVA. Differences were deemed significant if $P<0.05$.

(2) Guinea-pig study

Male albino Hartley strain guinea-pigs (weighing 400-500 g) were anesthetized by intraperitoneal pentobarbital 40mg/kg, and hearts were quickly excised. The right ventricular papillary muscles were isolated and placed horizontally in a superfusion chamber of 2mℓ in volume using a Ag-AgCl wire. They were perfused with Tyrode's solution containing (in mM) : NaCl 137, KCl 2.7, $CaCl_2$ 1.9, $MgCl_2$ 1.0, $NaHCO_3$ 11.9, NaH_2PO_4 0.4 and glucose 5.5 which was bubbled with 95% O_2 and 5% CO_2 gas mixture. The bath temperature was kept constant at 31±0.2℃ during the experiment. The muscle preparations were extracellularly stimulated by rectangular pulses of 1 to 2 Hz through a bipolar ringed Ag-AgCl wire. Action potentials were measured by means of conventional glass micro-electrodes filled with 3 M KCl (DC-resistance 10-20 M). Action potential characteristics were analyzed by a signal processor (NEC Sanei/7T17, Japan). The electrode was connected to the input stage of a micro-electrode amplifier (WPI/M-707, Japan). The contractile force was measured with a force transducer (Shinko/U-gage UL-2GR, Japan), Which was connected to the tendon of papillary muscles. The action potential and contractile force were monitored on a storage oscilloscope (Tektronix/511A, U.S.A.) and simultaneously recorded on a penwriting recorder (Sanei Recti-Horiz 8K, Japan). The hANP was dissolved in Tyrode's solution at the concentrations of 1, 10, 100, and 1000 ng/mℓ before use and superfused in a chamber. Effects of the drug were evaluated after superfusion with the drug for 20 min. Only the date obtained during continuous impalement of a single cell before and after the drug superfusion were reported here. Statistical analysis of the data were performed using Dunnette's multiple t test.

Results

(1) Beagle study

Values of hemodynamic variables and renal function under enflurane-nitrous oxide anesthesia before an infusion of hANP are summarized in Table 1. There were no differences in these values between groups. Percentage changes from the baseline values in SBP, DBP, and HR after the infusion of hANP in 3 groups are shown in Figure 1. Systolic and diastolic blood pressures were significantly decreased in each group. The maximal decreases in SBP were 17% in Groups 1 and 2, and 23% in Group 3. However, there were no differences in changes of blood pressures between groups. These decreases of blood pressures were not dose-dependent. After cessation of the hANP infusion, blood pressures returned gradually to the baseline values. HR did not change throughout the study except the recovery period in Group 1. There were no changes in both PAP and PCWP throughout the study in 3 groups.

Figure 2 shows percentage changes from the baseline values in CO, LV dp/dt max and RBF in 3 groups. CO decreased gradually during the infusion of hANP and reached to 77% at the end of the infusion. These decreases of CO were not different between groups, and no dose-dependent decreases in CO were obtained. However, CO was restored to baseline values more quickly in Group 2 compared to Group 3. LV dp/dt max decreased as did CO, but restoration of LV dp/dt max was better than CO

Table 1 Baseline values of hemodynamic variables and renal function before an infusion of hANP.

	HR (beat/min)	SBP (mmHg)	DBP (mmHg)	PAP (mmHg)	PCWP (mmHg)
Group 1 (0.5 μg/kg/min)	130±4.4	132.8±12	95.2±9.5	23.2±2.5	6.8±1.2
Group 2 (1 μg/kg/min)	140.8±12	135.8±7.3	97.6±5.7	20±2	7.5±2.2
Group 3 (3 μg/kg/min)	129.6±4.8	148.6±9.3	110.2±7.2	18±7.2	6.5±1.5

	CO (ml/kg/min)	LVdp/dtmax (10mmHg/s)	RBF (ml/kg/min)	SVR (10^2mmHg min kg/l)
Group 1 (0.5 μg/kg/min)	94±9	151±13	9.7±1.4	11.5±1.2
Group 2 (1 μg/kg/min)	95±7	184±24	11.2±1.9	11.6±0.9
Group 3 (3 μg/kg/min)	89±11	175±22	11.4±1	15.5±2.2

	PVR (mmHg min kg/l)	UV (ml/kg/hr)	Ccr (ml/kg/min)
Group 1 (0.5 μg/kg/min)	65±9	3.5±0.8	7.6±3.4
Group 2 (1 μg/kg/min)	83±12	5.3±0.4	5.7±1.7
Group 3 (3 μg/kg/min)	74±19	5.9±0.7	5.4±1.4

HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; PAP, pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; CO, cardiac output; RBF, renal blood flow; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance; UV, urine volume; Ccr, creatinine clearance. Data are mean ± SEM (N=5).

during the recovery period. RBF also decreased gradually by the infusion. However, RBF remained decreased at 73-74% in Groups 1 and 2 and 61% in Group 3. This was different from the recovery pattern of CO and LV dp/dt max. SVR, PVR and PCWP did not change during and after the infusion of hANP except 20 min in Group 3 (Table 2).

Changes in UV and Ccr were shown in Table 3. UV in Group 2 was significantly increased during the infusion and decreased during the recovery period. There was no dose-dependent response in UV. Ccr decreased during the recovery period in Group 3.

Plasma concentration of hANP were dose-dependent and there was a good correlation between infusion rates and plasma concentrations (Figure 3). The plateau was achieved within 30min, and plasma hANP was eliminated rapidly.

Hematocrit significantly increased by the infusion of hANP at a rate of 1 μg/kg/min and remained at higher value at the end of the recovery period. Hormonal variables were not changed by the infusion of hANP (Table 4).

(2) Guinea-pig study

Effects of the drug on various variables of action potenital and maximum contractile force were shown in Table 5. The hANP at 1, 10, 100, and 10000 ng/mℓ had no changes on measured variables.

Discussion

There are many reports on the actions of hANP with blood pressure lowering effects. In humans, vasodilating[1] and diuretic[2] actions are thought to be main mechanisms of the effects. The inhibitions of plasma renin activity[5], catecholamine secre-

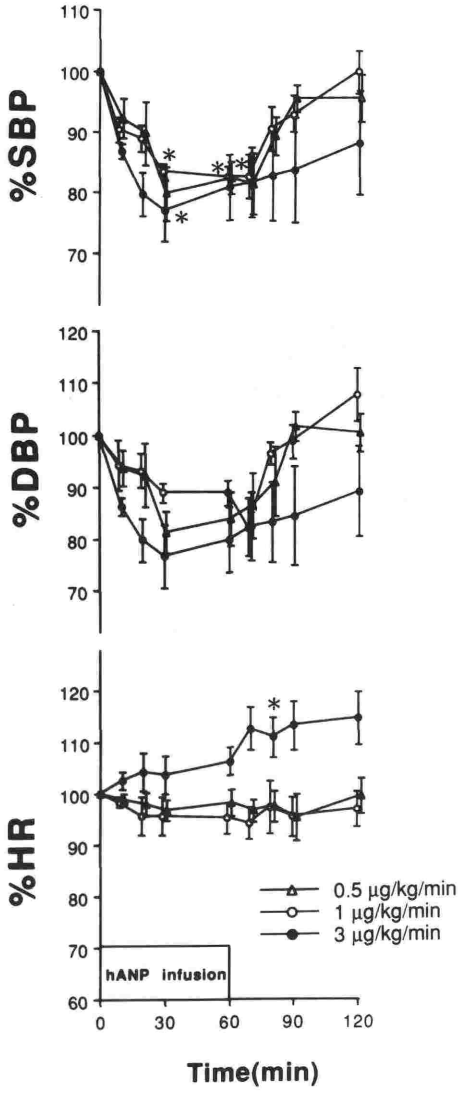

Fig 1. Time course of heart rate (HR), systolic blood pressure (SBP), and diastolic blood pressure (DBP). Open triagles, open circles, and filled circles represent Group 1 (0.5 μg/kg/min), Grous 2 (1 μg/kg/min), and Group 3 (3 μg/kg/min), respectively. Data are mean ± SEM (N=5). *P< 0.05 compared with baseline level.

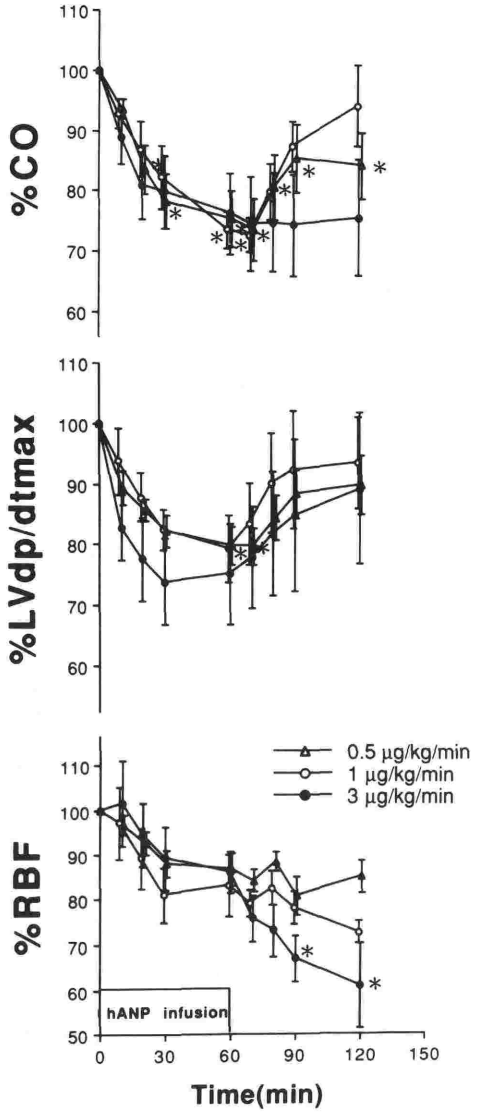

Fig 2. Time course of cardiac output (CO), LV dp/dt max, and renal blood flow (RBF). Open triagles, open circles, and filled circles represent Group 1 (0.5 μg/kg/min), Grous 2 (1 μg/kg/min), and Group 3 (3 μg/kg/min), respectively. Data are mean ± SEM. *P < 0.05 compared with baseline level.

Table 2 Changes in pulmonary capillary wedge pressure (PCWP), and %changes of systemic vascular resistance (SVR), and pulmonary vascular resistance (PVR).

PCWP (mmHg)	Group 1	Group 2	Group 3
hANP infusion			
0 min	6.8±1.2	7.5±2.2	6.5±1.5
10	6.0±0.8	5.5±1.7	4.8±1.8
20	4.8±1.2	5.8±1.3	4.3±1.1
30	5.0±1.0	5.0±1.0	4.8±1.5
60	4.4±1.0	6.5±1.3	4.3±1.5
recovery			
10 min	4.6±0.9	6.8±1.0	4.3±1.3
20	5.8±1.2	6.8±1.4	3.8±1.4
30	6.2±1.4	6.8±1.0	4.0±1.5
60	5.8±1.1	7.0±1.1	4.5±1.2
SVR (% of control)	Group 1	Group 2	Group 3
hANP infusion			
0 min	100	100	100
10	99±3	98±7	97±4
20	106±7	105±10	101±6
30	106±8	107±8	101±9
60	113±6	113±6	119±9
recovery			
10 min	114±10	110±5	116±10
20	114±9	111±5	120±12
30	115±13	107±4	122±13
60	117±9	109±10	128±9
PVR (% of control)	Group 1	Group 2	Group 3
hANP infusion			
0 min	100	100	100
10	91±10	129±14	160±20
20	114±8	140±60	215±42*
30	115±13	114±12	166±35
60	116±10	145±43	175±44
recovery			
10 min	100±10	147±36	184±35
20	105±20	106±6	171±40
30	92±13	118±18	192±47
60	97±7	102±9	192±47

Data are mean±SEM. *P<0.05 compared with baseline level.

Table 3. Changes in urine volume and creatinine clearance.

UV (ml/kg/hr)	N	baseline	hANP infusion	recovery
Group 1 (0.5 μg/kg/min)	5	3.5±0.8	8.2±1.7	4.6±1.1
Group 2 (1 μg/kg/min)	5	5.3±0.4	9.2±1.1*	2.5±0.5*
Group 3 (3 μg/kg/min)	5	5.9±0.7	11.3±2.8	4.7±3.3
Ccr (ml/kg/min)	N	baseline	hANP infusion	recovery
Group 1 (0.5 μg/kg/min)	4	7.6±3.4	5.4±0.4	2.8±0.7
Group 2 (1 μg/kg/min)	4	5.7±1.7	5.1±1.9	2.5±0.4
Group 3 (3 μg/kg/min)	5	5.4±1.4	2.7±0.6	1.6±0.7*

Data are mean±SEM. *P<0.05 compared with baseline level.

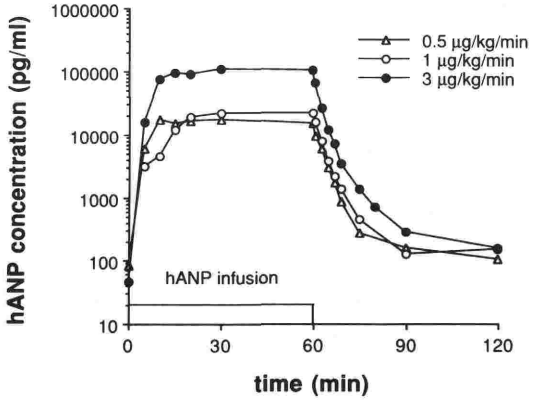

Fig 3. Plasma concentrations of hANP during and after hANP infusion. Open triangles, open circles, and filled circles represent Group 1 (0.5 μg/kg/min), Group 2 (1 μg/kg/min), and Group 3 (3 μg/kg/min), respectively. Data are mean (N=5).

tion[2] and baroreflex[6] cause hypotension. These mechanisms are unique and unlikely to lead reflex mediated tachycardia. However, hypotension was accompanied with a decrease of cardiac output in animals[4]. Accordingly in this study, the clinical usefulness of hANP-induced hypotension was investigated with beagles which were anesthetized with enflurane and nitrous oxide.

In this study, SBP was aimed to be lowered to 70% of the baseline value by hANP at first. But SBP decreased to only about 80% of the baseline value in all groups, which indicates hypotensive potency of

Table 4. Hematocrit and hormonal responses.

	baseline	30 min	60 min	120 min
Hematocrit (%)	36.4±0.6	39.5±1.4*	42.3±1.9*	40.1±2.6
Epinephrine (pg/ml)	55±38	263±177	348±272	330±234
Norepinephrine (pg/ml)	55±13	88±33	63±23	108±29
Renin (ng/ml/hr)	0.43±0.06	1.65±0.82	0.98±0.33	1.4±0.64
Angiotensin I (pg/ml)	121±28	738±446	333±143	609±302
Angiotensin II (pg/ml)	5.3±1.9	11±2.1	11.1±3.8	18.5±11.9
Aldosterone (pg/ml)	47±21	73±15	73±22	120±80

Data are mean±SEM(N=5). *P<0.05 compared with baseline level.

Table 5. Effect of hANP on action potential and contractile force of guinea-pig papillary muscles.

ng/ml	N	APD_{50}(ms)	APD_{90}(ms)	RMP(mV)	APA(mV)
0	6	157±41	199±39	−88.2±1.7	117±3.1
1	6	150±40	191±39	−87.4±2.3	119.1±1.9
10	6	156±42	197±40	−87.7±2.4	119.3±1.8
100	6	157±41	199±40	−87.4±2.1	120.1±1.7
1000	4	173±66	212±65	−85.4±1.4	120.2±2.6
ng/ml		CT(ms)	Vmax(V/s)	CF(mg)	
0		5.6±1.4	207±12	5.77±0.9	
1		6.5±1.9	2.5±8	6.18±1.22	
10		5.6±1.5	211±14	6.31±1.37	
100		6.2±1.6	206±14	6.42±1.49	
1000		5.6±2.2	191±13	4.68±1.56	

$APD_{50(90)}$, action potential duration at 50% (90%) repolarization; RMP, resting membrane potential; APA, action potential amplitude; CT, conduction time; Vmax, maximum rate of rise of 0 phase of action potential; CF, maximum contractile force. Data are mean ± SEM.

hANP is not enough for induced hypotension during inhalational anesthesia. It is unlike that subsequent infusion of hANP to achieve further reduction of SBP, because equilibrium of hANP plasma concentration is achieved. These findings are highly suggestive of a ceiling effect on blood pressure. Gradual recovery to the baseline value was observed after a discontinuation of hANP. But it lagged behind a rapid disappearance of plasma hANP. The hANP is different from other hypotensive drugs with this dissociation. These actions may limit clinical usefulness of hANP during general anesthesia.

HR remained unchanged during hANP infusion, which indicates that hANP suppresses reflex mediated tachycardia. It was reported that hANP did not alter the aortic nerve activity under induced hypotension nor hypertension[7]. And it is recognized that inhalational anesthetics inhibit baroreflex[8]. On the other hand, a vagal activation by hANP was indicated by the previous studies of Ackermann et al.[9] and Thoren et al.[10] This action

is very unique but may cause cardiovascular depressions.

PAP slightly decreased during infusion period (significantly in Group 1), whereas no decrease in PCWP. Previous researchers[11,12] pointed out that hANP increased capillary hydraulic conductivity followed by a volume shift from the intravascular to the extravascular compartment. A number of researchers[13-15] have reported that hANP increased the hematocrit level with a reduction of intravascular volume. The hematocrit levels in the present study are in accord with previous reports. It might be the major mechanism of a decrease of PAP. Residual hypotension after hANP discontinuation may account for this mechanism.

A reduction of CO was observed in all groups. This reduction was accompanied with a decrease of LV dp/dt max. Iwanaga et al.[16] reported that an intracoronary infusion of hANP did not alter myocardial contractility. Furthermore, the present study with isolated papillary muscles clearly eliminates the possibility of negative inotropic effects of hANP. These results may suggest important roles of other factors, such as regulation of autonomic nervous system and an interaction with volatile anesthetics, in the reduction of CO and LVdp/dtmax, though no evidence is presently available.

SVR remained unchanged, indicating no evidence of arterial vasodilatory effect of hANP. This finding may relate to relatively high infusion rate, which induces counterregulatory vasoconstriction[17]. This action is not useful for induced hypotension during anesthesia. Although we considered the possibile usefulness of a slow infusion rete, a slow onset of hypotension would restrict the advantage of lower dose than 0.5 μg/kg/min.

RBF decreased accompanied with CO. The renal hemodynamic effects of hANP are thought to be increases of glomerular filtration rate and natriuresis. This is explained by a redistribution of renal blood flow to the inner medulla[18]. Accordingly, we expected that hANP might unchange or improve renal functions in spite of induced hypotension. However, we observed no significant changes of Ccr during hANP infusion compared with baseline values. Because the blood concentrations of hANP are much over the physiological ranges, other factors such as reduced BP and CO might influence the results. As far as UV is concerned, hANP has no adverse effects, but rebound phenomena should be anticipated after discontinuation. Much lower doses would be beneficial for renal function[19].

In summary, although hANP did not change contractile property of isolated papillary muscles, a continuous infusion of hANP depresses BP and CO with no changes of vascular resistance in anesthetized beagles. Unexpectedly we observed no improvement on renal functions. These results do not show distinct advantage of hANP as a hypotensive agent during inhalational anesthesia.

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