J Anesth (1996) 10:204–210

Journal of
Anesthesia

Comparative hemodynamic effects of hypotension induced by CGRP and PGE_1 in dogs

SHOHEI TAKEDA, YUTAKA INADA, KUMIKO MATSUI, and TERUAKI TOMARU

Department of Anesthesiology, Showa University Fujigaoka Hospital, 1-30 Fujigaoka, Aoba-ku, Yokohama 227, Japan

Abstract: Calcitonin gene-related peptide (CGRP) produces vasodilation, hypotension, and tachycardia. We compared the hemodynamic effects of CGRP-induced hypotension with the effects of prostaglandin E_1 (PGE_1), which is currently used as a hypotensive agent during anesthesia. Eighteen mongrel dogs were anesthetized with pentobarbital (25 mg·kg^{-1}), and 0.87% halothane in oxygen (1MAC). Measurements of hemodynamic variables were made before, during, and after induced hypotension. The mean arterial pressure (MAP) was lowered to 60 mmHg by the infusion of either CGRP ($n = 10$) or PGE_1 ($n = 8$). This decrease in MAP was appoximately 50% of the baseline value. The CGRP- and PGE_1-induced hypotension resulted in 61% and 51% maximum reductions ($P < 0.01$, respectively) in systemic vascular resistance associated with a significant increase in stroke volume index; the two treatments, however produced inconsistent changes in cardiac index (CI). With CGRP, a maximum increase of 144% ($P < 0.01$) in CI was observed during induced hypotension. In contrast, PGE_1-induced hypotension caused no significant changes in CI throughout the observation period. Left ventricular maximum dP/dt decreased ($P < 0.01$) during the hypotensive period with PGE_1, whereas it remained unchanged during CGRP-induced hypotension. The different results for changes in CI and cardiac contractility during the CGRP- and PGE_1-induced hypotension were probably due to differences in ventricular filling pressure. Hypotension induced by PGE_1 was associated with a significant decrease in heart rate (HR), whereas CGRP did not affect HR. This study shows that both CGRP and PGE_1 are effective in decreasing afterload and in inducing hypotension; the results suggest that CGRP is a useful vasodilator for inducing hypotension during halothane anesthesia.

Key words: CGRP (calcitonin gene-related peptide), PGE_1 (prostaglandin E_1), Induced hypotension, Systemic hemodynamics

Address correspondence to: S. Takeda

Received for publication on November 10, 1995; accepted on March 26, 1996

[1] This study was presented, in part, at the Annual Meeting of the American Society of Anesthesiologists, October, 1993, Washington DC, and at the 41st Annual Meeting of the Japan Society of Anesthesiology, April, 1994, Tokyo

[2] This study was supported by a Grant-in-Aid (No 04807115) for Scientific Research (C) from the Ministry of Education, Science, Sports, and Culture, Japan

Introduction

Induced hypotension is used in surgery to reduce the risks associated with homologous blood transfusion and to provide a better operative field. Medical costs are also reduced, as the treatment for complication due to blood transfusion. Commonly used hypotensive drugs, including nitroprusside, trimethaphan, nitroglycerin, and adenosine triphosphate may have side effects related to their pharmacological characteristics. To date, hypotensive drugs used in surgery are not ideal, because of side effects such as cyanide toxicity, reflex tachycardia, tissue hypoperfusion, prolonged hypotension, cerebral vasodilation, and renal vasoconstriction.

Calcitonin gene-related peptide (CGRP), administered intravenously, has been shown to cause vasodilation and hypotension associated with positive chronotropic and inotropic activity [1–3]. It has been suggested that this tachycardia may be partly due to a reflex sympathetic stimulation in alert humans [4,5] and in animals [6]. Both in vitro and in vivo it has been demonstrated that the vasodilatory action of CGRP is at least 1000 times more potent than that of acetylcholine (Ach), adenosine triphosphate (ATP), adenosine diphosphate (ADP), adenosine, 5-hydroxytryptamine (5-HT), and substance P, and 10–100 times more potent than that of the synthetic β-adrenergic stimulant isoprenaline [7]. CGRP is, possibly, the most potent endogenous vasodilator to have

been studied in humans to date [8]. We have reported recently that CGRP produces a decrease in mean arterial pressure in a dose-dependent fashion by reducing systemic vascular resistance, and that CGRP-induced reflex tachycardia was suppressed by halothane anesthesia in dogs [9]. This hemodynamic profile suggests that CGRP may play a valuable therapeutic role in the perioperative period in inducing hypotension and in controlling hypertension during surgery.

The objectives of this study were to investigate and compare the hemodynamic effects of CGRP-induced hypotension with these effects of prostaglandin E_1 (PGE_1), an agent currently used intraoperatively to decrease blood pressure [10]. We performed the study in halothane-anesthetized dogs.

Methods

All experimental procedures and the protocols for this study were approved by the Animal Experiment Ethics Committee of Showa University Fujigaoka Hospital. Eighteen healthy adult mongrel dogs of either sex, weighing between 11 and 18 kg (14.4 ± 2.4 kg, mean ± SD) were fasted overnight and anesthetized with sodium pentobarbital (25 mg·kg^{-1}), given intravenously. Tracheal intubation was carried out and the animals were mechanically ventilated with a Harvard ventilator to maintain normocapnia (end-expiratory carbon dioxide concentration monitored to maintain $FECO_2$ in the 38 ± 5 mmHg range). Anesthesia was maintained with 1.0 MAC halothane (0.87%), via an Ohmeda Vaporizer (BOC Health Care; Wilddlesham, UK), using oxygen as a carrier gas, at a flow of 3–5 l·min^{-1} throughout the experimental period. End-tidal halothane and CO_2 concentrations were monitored continuously by an infrared analyzer (Capnomac Ultima; Datex, Helsinki, Finland).

Instrumentation

Cannulae were installed by a cutdown into the left femoral artery for continuous systemic blood pressure (SBP) monitoring and blood sampling, and into the right femoral vein for drug administration; normal saline was infused at a rate of 7 ml·kg^{-1}·h^{-1} together with the infusion of the hypotensive drugs. A 7-F flow-directed pulmonary catheter (Swan-Ganz thermodilution catheter; Baxter Healthcare Corporation, Irvine, Calif.) was advanced into a pulmonary artery via the right external jugular vein and positioned by means of pressure monitoring in a branch of the pulmonary artery for the measurements of right atrial pressure (RAP), mean pulmonary artery pressure (MPAP), pulmonary capillary wedge pressure (PCWP), and cardiac output (CO).

CO was measured in triplicate, by the thermodilution technique; we used a cardiac output computer (model MTC6210; Nihon Kohden, Tokyo, Japan) and injected 5 ml of ice-cold, temperature monitored, normal saline into the right atrium at end-expiration. Cardiac index (CI), stroke volume index (SVI), systemic vascular resistance (SVR), and pulmonary vascular resistance (PVR) were calculated by standard formulae. CI and SVI were calculated as cardiac output and stroke volume divided by the body surface area, respectively. SVR was calculated as $(MAP - RAP) \cdot CO^{-1} \times 80$, and PVR as $(MPAP - PCWP) \cdot CO^{-1} \times 80$. Mean arterial pressure (MAP) was determined by electronic integration.

A 7-F pigtailed catheter (Softip Catheter; Schneider Inc., Minneapollis, Minn.), passed into the left ventricle via cutdown of the right femoral artery, was used for measurement of left intraventricular pressure (LVP). Left ventricular maximum dP/dt (LV dP/dt_{max}) was electrically derived from the left ventricular pressure wave signal via an electronic differentiator (model EQ601G; Nihon Kohden). Heart rate (HR), calculated from lead II of the electrocardiogram (ECG) via a cardiotachometer (model AT601G; Nihon Kohden), was continuously monitored. Body temperature, monitored by a thermistor attached to the pulmonary artery catheter, was maintained at 37.0 ± 1.0°C with electric heating pads and lamps.

Each pressure monitoring catheter was connected to a pressure transducer (Uniflow; Baxter Healthcare Corporation). SBP, ECG, LVP, and LV dP/dt_{max} were monitored continuously on a polygraph (model RM 6200; Nihon Kohden) and recorded with an eight-channel pen recorder (model VM-640G; Nihon Kohden).

Experimental protocol

The 18 dogs were divided into two groups: the CGRP group (n = 10) received a 0.001% solution of CGRP (CGRP dissolved in 0.1% bovine serum albumin in normal saline). The PGE_1 group (n = 8) received a 0.005% solution of PGE_1 (PGE_1 dissolved in normal saline).

After the completion of surgical preparations, the animals were observed for approximately 60 min to allow hemodynamic variables (SBP, MPAP, and HR) to stabilize. Measurements of baseline values were then obtained before infusion of the hypotensive drugs began. After the baseline measurements had been made, MAP was reduced to 60 mmHg for a 60-min hypotensive period by the infusion of CGRP or PGE_1. The solution of CGRP and PGE_1 was infused into

the left femoral vein with an infusion pump (model STG-521; Terumo, Tokyo, Japan). Measurements of hemodynamic variables were taken 30 and 60 min after the induction of hypotension, and 10 and 30 min after the termination of drugs infusion. Des-1-Ala, des-α-amino chicken CGRP, provided by Asahi Chemical Industry Co., Ltd (Tokyo, Japan) was used for the study.

Statistical analysis

Values are expressed as means ± SD. Intragroup differences were analyzed by two-way analysis of variance from repeated measurements of the same variables, followed by Dunnett's test when appropriate. Intergroup differences were analyzed by Student's unpaired *t*-test if the *F* test was significant. A probability value less than 0.05 was considered statistically significant.

Table 1. Baseline values of MAP, HR, CI, SVI, MPAP, PCWP, SVR, PVR, and LV dP/dt_{max} in CGRP and PGE_1 groups

	CGRP group (n = 10)	PGE_1 group (n = 8)
MAP (mmHg)	114 ± 13	118 ± 15
HR (bpm)	156 ± 30	172 ± 35
CI ($l \cdot min^{-1} \cdot m^{-2}$)	2.9 ± 0.8	2.8 ± 0.5
SVI ($ml \cdot beat^{-1} \cdot m^{-2}$)	19 ± 7	17 ± 5
MPAP (mmHg)	16 ± 6	16 ± 4
PCWP (mmHg)	10 ± 4	10 ± 2
SVR ($dynes \cdot s \cdot cm^{-5}$)	4839 ± 1634	5013 ± 1250
PVR ($dynes \cdot s \cdot cm^{-5}$)	268 ± 137	270 ± 118
LV dP/dt_{max} ($mmHg \cdot s^{-1}$)	3200 ± 639	3275 ± 631

Values are means ± SD.
CGRP, calcitonin gene-related peptide; PGE_1, prostaglandin E_1; MAP, mean arterial pressure; HR, heart rate; CI, cardiac index; SVI, stroke volume index; MPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance; LV dP/dt_{max}, left ventricular maximum dP/dt.

Results

There were no significant differences in the baseline values of systemic hemodynamics between the CGRP and the PGE_1 groups (Table 1).

Hypotension was readily induced and maintained by CGRP or PGE_1 at the desired MAP, with no observed differences in tolerance. The doses of CGRP and PGE_1 were increased in a step-wise fashion until the desired MAP was attained. A hypotensive steady state of MAP at 60 mmHg was achieved within 8.9 ± 5.1 min in the CGRP group and within 10.8 ± 7.8 min in the PGE_1 group. The mean doses of CGRP and PGE_1 required to maintain MAP at 60 mmHg for a 60-min hypotensive period were 0.50 ± 0.43 $\mu g \cdot kg^{-1} \cdot min^{-1}$, and 2.57 ± 1.55 $\mu g \cdot kg^{-1} \cdot min^{-1}$, respectively.

MAP decreased from baseline values of 114 ± 13 mmHg in the CGRP group and from 118 ± 15 mmHg in the PGE_1 group to 60 mmHg ($P < 0.01$) at the end of the 60-min hypotensive period. Within 30 min after termination of drug infusion, MAP gradually tended to return towards the baseline values but this change in MAP was significantly lower when compared to baseline values in either group. Further, MAP was significantly lower in the CGRP group than the PGE_1 group both 10 min and 30 min after the induced hypotensive period had ended (Fig. 1a).

In the PGE_1 group, HR decreased from the baseline value of 172 ± 35 beats per min to 150 ± 41 beats per min ($P < 0.01$) at 30 min and 155 ± 45 beats per min ($P < 0.01$) at 60 min during the induced hypotension. On the other hand, HR remained unchanged throughout the course of observation in the CGRP group (Fig. 1b).

CGRP caused an increase in CI from baseline values of 2.9 ± 0.8 to 3.4 ± 0.6 ($P < 0.05$) and 4.0 ± 0.7 ($P < 0.01$) $l \cdot min^{-1} \cdot m^{-2}$ at 30 and 60 min, respectively, during induced hypotension, and increased CI values to 4.0 ±

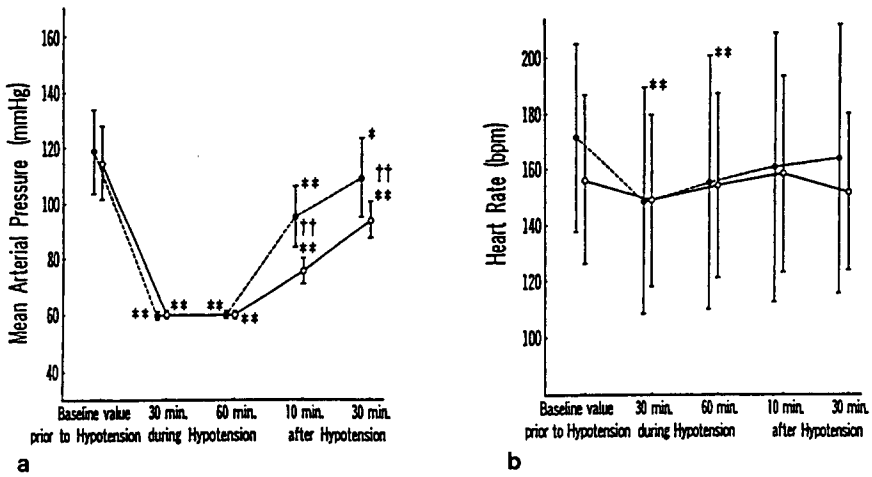
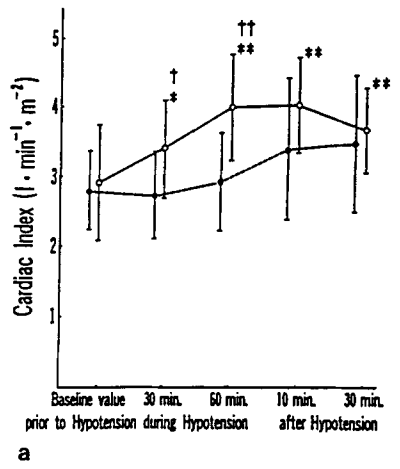


Fig. 1a,b. Effect of calcitonin gene-related peptide (*CGRP*; circles; n = 10) and prostaglandin E_1 (PGE_1; *dots*; n = 8) induced hypotension on **a** mean arterial pressure and **b** heart rate in halothane-anesthetized dogs. $^{*}P < 0.05$; $^{**}P < 0.01$ significantly different compared with baseline values; $^{+}P < 0.05$; $^{++}P < 0.01$ significantly different compared with both CGRP and PGE_1 (These values were compared at predetermined identical times). Values are means ± SD



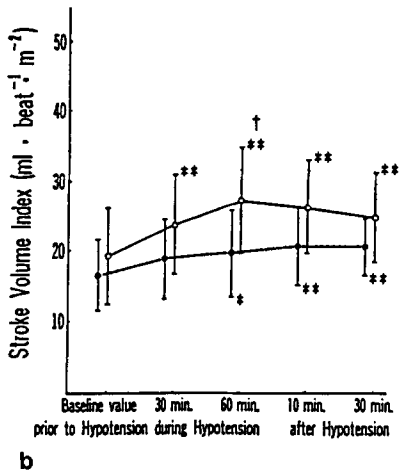
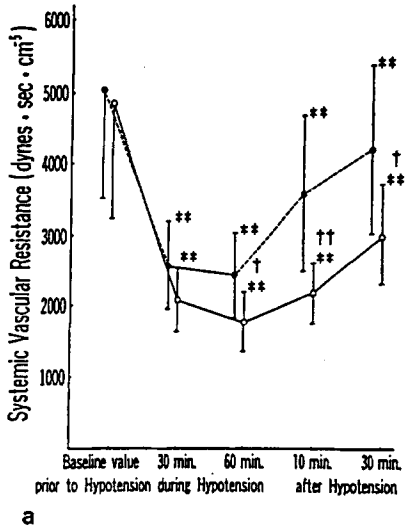


Fig. 2a,b. Effect of CGRP (n = 10) and PGE_1 (n = 8) induced hypotension on **a** cardiac index and **b** stroke volume index in halothane-anesthetized dogs. $*P < 0.05$; $**P < 0.01$ significantly different compared with baseline values; $^{+}P < 0.05$; $^{++}P < 0.01$ significantly different compared with both CGRP and PGE_1 (These values were compared at predetermined identical times). Values are means ± SD. *Symbols*, As in *Fig. 1*



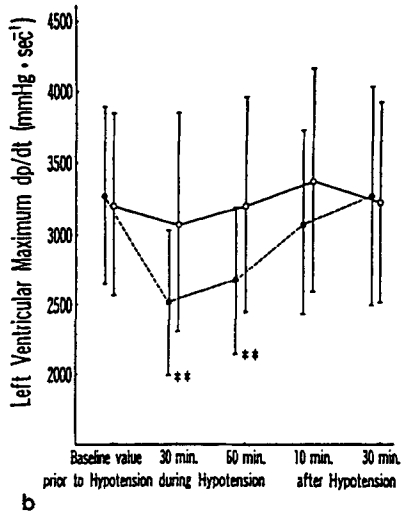
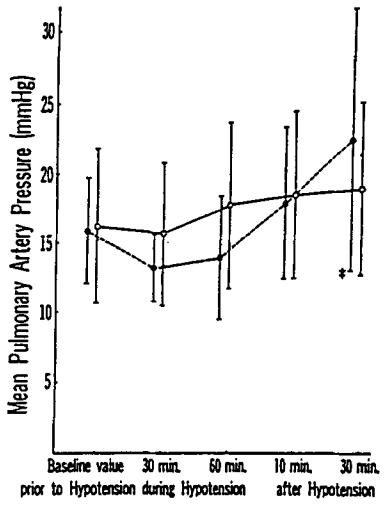


Fig. 3a,b. Effect of CGRP (n = 10) and PGE_1 (n = 8) induced hypotension on **a** systemic vascular resistance and **b** left ventricular maximum dP/dt in halothane-anesthetized dogs. $*P < 0.05$; $**P < 0.01$ significantly different compared with baseline values; $^{+}P < 0.05$; $^{++}P < 0.01$ significantly different compared with both CGRP and PGE_1 (These values were compared at predetermined identical times). Values are means ± SD. *Symbols*, As in *Fig. 1*



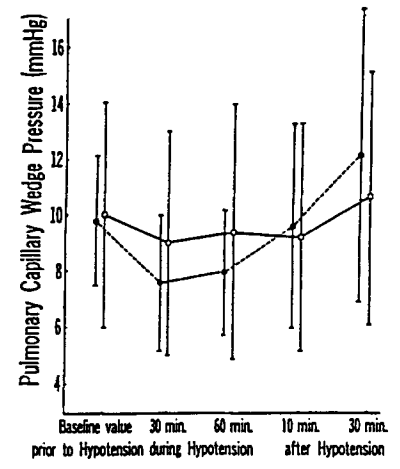


Fig. 4a,b. Effect of CGRP (n = 10) and PGE_1 (n = 8) induced hypotension on **a** mean pulmonary artery pressure and **b** pulmonary capillary wedge pressure in halothane-anesthetized dogs. $*P < 0.05$, significantly different compared with baseline values (These values were compared at predetermined identical times). Values are means ± SD *Symbols*. As in *Fig. 1*

0.6 ($P < 0.01$) and 3.6 ± 0.5 ($P < 0.01$) $l \cdot min^{-1} \cdot m^{-1}$ at 10 and 30 min, respectively, after the end of the induced hypotension. SVI in the CGRP group increased from baseline values of 19 ± 7 $ml \cdot beat^{-1} \cdot m^{-2}$ to a maximum of 27 ± 8 $ml \cdot beat^{-1} \cdot m^{-2}$ at the end of the 60-min hypotensive period, and then decreased, although still remaining at more than the baseline values, after termination of infusion (Fig. 2b). In the PGE_1 group, in contrast, CI remained unchanged throughout the course of observations, although SVI increased significantly after 60 min of PGE_1-induced hypotension, and plateaued at approximately, 120% of baseline values for up to 30 min after termination of infusion (Fig. 2a,b). CI was significantly higher in the CGRP group compared with the PGE_1 group after 60 min of the induced hypotension. SVI was also significantly higher in the CGRP group than in the PGE_1 group at this time (Fig. 2b).

SVR declined in the CGRP group from baseline values of 4839 ± 1634 $dynes \cdot s \cdot cm^{-5}$ to a nadir of 1748 ± 409 ($P < 0.01$) $dynes \cdot s \cdot cm^{-5}$ at 60 min of the hypotensive period. In the PGE_1 group, SVR declined from baseline values of 5013 ± 1250 $dynes \cdot s \cdot cm^{-5}$ to a nadir of 2412 ± 590 ($P < 0.01$) $dynes \cdot s \cdot cm^{-5}$ at 60 min of the hypotensive period. SVR was significantly lower in the CGRP group than in the PGE_1 group at 60 min of the hypotensive period and after termination of infusion (Fig. 3a).

LV dP/dt_{max} decreased from baseline values of 3275 ± 631 $mmHg \cdot s^{-1}$ to 2512 ± 511 $mmHg \cdot s^{-1}$ ($P < 0.01$) at 30 min and to 2675 ± 523 $mmHg \cdot s^{-1}$ ($P < 0.01$) at 60 min during induced hypotension in the PGE_1 group. In contrast, in the CGRP group, LV dP/dt_{max} remained unchanged throughout the course of observations (Fig. 3b). MPAP and PCWP in the PGE_1 group decreased but at levels that were not statistically significant. Throughout the induced hypotension. In contrast, these values remained unchanged in the CGRP group (Fig. 4a,b).

Discussion

The results of this study demonstrated that the hypotension induced by both CGRP and PGE_1 was due to a significant reduction in SVR. However, the CGRP-induced hypotension was associated with a significant increase in CI, whereas the PGE_1-induced hypotension was not.

The differences between CGRP and PGE_1 in their effects on CI may reflect the venodilation with decreased venous return evoked by PGE_1. The hemodynamic changes that occurred during PGE_1-induced hypotension were associated with decreases in both MPAP and PCWP. However, neither of these variables were changed during CGRP-induced hypotension. This may reflect differences in the sites of vasodilatory action of the two agents within the arterial and venous vascular beds. Studies of trinitroglycerin (TNG)- and PGE_1-induced hypotension by Liang et al. [11] demonstrated that PGE_1 and TNG had a similar effect in increasing venous capacitance during moderate hypotension (MAP 70 mmHg); however, the increase in venous capacitance evoked by PGE_1 was less than that produced by TNG at doses required to produce profound hypotension (MAP 50 mmHg). The venodilator effects we observed during PGE_1-induced hypotension were consistent with those reported earlier, showing that PGE_1 dilated venules and arterioles in the microcirculation studies [12] and that, in pentobarbital anesthetized dogs, PGE_1 increased venous capacitance [13].

These results suggest that CGRP behaves as an arteriolar vasodilator, whereas PGE_1 is a vasodilator of both the arteriolar and the venous system.

Ventricular filling pressures remained unchanged during CGRP-induced hypotension. This lower venodilation compared to that produced by PGE_1 may contribute to the better maintenance of venous return and the increase in cardiac output seen with CGRP, since venous return is one of the major mechanisms regulating cardiac output.

The increased CI observed in the CGRP-induced hypotension may be explained by the increase in SVI resulting from the reduction in SVR and by the maintenance of venous return due to the unchanged ventricular filling pressures.

The results of the present study showed that the hypotension induced by CGRP was not associated with a significant change in HR, whereas PGE_1-induced hypotension was associated with a significant decrease in HR. It has been demonstrated that the administration of CGRP increases HR in alert humans [4,5] and in animals [6], this increase being mediated by reflex sympathetic stimulation occurring as a consequence of the decreased arterial blood pressure. In contrast to the findings in the alert condition, in the present study, we found that reflex tachycardia did not occur during CGRP-induced hypotension, even though the MAP decreased significantly in the halothane-anesthetized dogs. These contradictory results may be due to the effects of halothane anesthesia. Halothane reduces cardiac contractile force and decreases HR, leading to a decrease in arterial blood pressure. Indeed, halothane suppresses activity at all levels of the baroreflex arc [14]. Halothane also decreases the rate of spontaneous discharge of slow action potentials in sinoatrial nodal tissue and prolongs atrial ventricular conduction [15]. Therefore, it is possible that a direct negative chronotropic effect of halothane on the heart could counteract the tachycardiac effect of CGRP.

Similarly to CGRP, it has also been reported that the administration of PGE_1 provoked an increase in HR in

alert humans [16] and in pentobarbital-anesthetized dogs [13,17]. This increase in HR elicited by PGE_1 seems to be mediated by the reflex sympathetic stimulation in response to the decrease in arterial blood pressure [13]. However, the chronotropic response to PGE_1 is complex; HR was reported to be increased [10] and as not changed [11,18–21] significantly during PGE_1-induced hypotension. These inconsistent results may be due to different experimental conditions, such as dosages of PGE_1, the anesthetics used, the different animal species, and the magnitude of hypotension. Our present study showed a significant decrease in HR during the PGE_1-induced hypotension, in contrast to the lack of significant change in HR in PGE_1-induced hypotension reported in the studies cited above [11,18–21].

The precise mechanisms responsible for this decrease in HR during the PGE_1-induced hypotension have not been identified. However, two possible mechanisms may be involved in these cardiac effects. In the present study, MPAP and PCWP were sightly reduced during the PGE_1-induced hypotension. These changes may have contributed to the observed decrease in venous return. It is accepted that changes in the regulation of HR may be related to changes in the volume of venous return to the right atrium. In this regard, it has been pointed out that genetic modification of the Bainbridge reflex appears to be of major importance in dogs [22]. It is possible that right atrial stretch receptors responding to the reduction in venous return may have contributed to the decrease in HR during the PGE_1-induced hypotension. Consequently, the effects of PGE_1 on capacitance vessels may be of physiological importance.

As seen in studies in anesthetized dogs, prostaglandin E_2 (PGE_2) [23,24] and prostaglandin I_2 (PGI_2) [25] stimulate cardiac receptors, stimulating firing in the chemosensitive endings of nonmyelinated vagal afferent nerves in the left ventricle. The stimulation of cardiac receptors by prostaglandin compounds results in hypotension and bradycardia. The bradycardiac effects we found in the PGE_1-induced hypotension are in agreement with the findings of the study by Roux et al. [26], who employed left atrial injections of high-dose PGE_1. The systemic administration of high doses of PGE_1 in our present study may have produced local concentrations sufficient to activate cardiac receptors, this phenomenon being responsible for the decrease in HR during PGE_1-induced hypotension.

The results of the present study indicate that, during the infusion of CGRP or PGE_1, the CGRP- and PGE_1-induced hypotension did not evoke undesirable reflex sympathetic activity such as reflex tachycardia. This lack of reflex tachycardia during the CGRP- and PGE_1-induced hypotension contrasts with the effect observed nitroprusside-induced hypotension during halothane anesthesia [27].

The onset of hypotension was similar in the CGRP and PGE_1 groups. The desired MAP of 60 mmHg was maintained without reflex tachycardia or signs of acute tachyphylaxis. However, at 10 and 30 min after discontinuation of the drugs there were significant hemodynamic differences between the CGRP and PGE_1 groups. MAP and SVR were significantly lower in the CGRP group than in the PGE_1 group after termination of infusion. The hemodynamic changes after CGRP infusion produced persistent hypotension and vasodilation, the effect of CGRP being less evanescent than that of PGE_1. Thus, the results of the present study suggest that because of the lack of prompt recovery from CGRP-induced hypotension after termination of infusion, CGRP may not be a desirable vasodilator.

In conclusion, CGRP and PGE_1, at appropriate infusion rates, are effective in decreasing afterload and in achieving induced hypotension. The hemodynamic profile of CGRP—induced hypotension shows potent vasodilatory action, increased cardiac output, and unchanged cardiac contractility during the period of profound hypotension. However, CGRP appears to bring about persistent hypotension and vasodilation. Further studies are needed to evaluate whether this agent can be used clinically.

Acknowledgments. The authors gratefully acknowledge Professor Carl Lynch III, Department of Anesthesiology, University of Virginia, Health Sciences Center, VA for his valuable comments and Mrs. Yoshie Hirakawa for her excellent secretarial assistance.

References

1. Fisher LA, Kikkawa DO, Rivier JE, Amara SG, Evans RM, Rosenfeld MG, Vale WW, Brown MR (1983) Stimulation of noradrenergic sympathetic outflow by calcitonin gene-related peptide. Nature 305:534–536
2. Marshall I, Al-Kazwini SJ, Roberts PM, Shepperson NB, Adams M, Craig RK (1986) Cardiovascular effects of human and rat CGRP compared in the rat and other species. Eur J Pharmacol 123:207–216
3. DiPette DJ, Schwarzenberger K, Kerr N, Holland OB (1987) Systemic and regional hemodynamic effects of calcitonin gene-related peptide. Hypertens 9[Suppl III]:III142–III146
4. Franco-Cereceda A, Gennari C, Nami R, Agnusdei D, Pernow J, Lundberg JM, Fisher JA (1987) Cardiovascular effects of calcitonin gene-related peptides I and II in man. Circ Res 60:393–397
5. Gennari C, Fischer JA (1985) Cardiovascular action of calcitonin gene-related peptide in humans. Calcif Tissue Int 37:581–584
6. Wang BC, Bie P, Leadley Jr RJ, Goetz KL (1989) Cardiovascular effects of calcitonin gene-related peptide in conscious dogs. Am J Physiol 257 (Regulatory Integrative Comp Physiol 26): R726–R731
7. Brain SD, Williams TJ, Tippins JR, Morris HR, MacIntyre I (1985) Calcitonin gene-related peptide is a potent vasodilator. Nature 313:54–56
8. Struthers AD, Brown MJ, Macdonald DWR, Beacham JL, Stevenson JC, Morris HR, MacIntyre I (1986) Human calcitonin

generelated peptide: A potent endogenous vasodilator in man. Clin Sci 70:389–393
9. Takeda S, Inada Y, Matsui K, Tomaru T (1996) Halothane anesthesia suppresses reflex tachycardia caused by CGRP in dogs. J Anesth 10:58–62
10. Hoka S, Yoshitake J, Dan K, Goto Y, Honda N, Morioka T, Muteki T, Okuda Y, Shigematsu A, Takasaki M, Totoki T, Yoshimura N (1993) Intra-operative blood pressure control by prostaglandin E_1 in patients with hypertension and ischemic heart disease. J Anesth 7:173–183
11. Liang J, Hoka S, Okamoto H, Kawasaki T, Yoshitake J (1993) Changes in venous capacitance during prostaglandin E_1-induced hypotension; Comparisons with trinitroglycerin. J Anesth 7:303–307
12. Weiner R, Kaley G (1969) Influence of prostaglandin E_1 on the terminal vascular bed. Am J Physiol 217:563–566
13. Nakano J, McCurdy JR (1967) Cardiovascular effects of prostaglandin E_1. J Pharmacol Exp Ther 156:538–547
14. Seagard JL, Hopp FA, Donegan JH, Kalbfleisch JH, Kampine JP (1982) Halothane and the carotid sinus reflex: Evidence for multiple sites of action. Anesthesiology 57:191–202
15. Lynch III C, Vogel S, Sperelakis N (1981) Halothane depression of myocardial slow action potentials. Anesthesiology 55:360–368.
16. Bergström S, Carlson LA, Ekelund L-G, Orö L (1965) Cardiovascular and metabolic response to infusion of prostaglandin E_1 and to simultaneous infusions of noradrenaline and prostaglandin E_1 in man. Acta Physiol Scand 64:332–339
17. Carlson LA, Orö L (1966) Effect of prostaglandin E_1 on blood pressure and heart rate in the dog. Prostaglandin and related factors. Acta Physiol Scand 67:89–99
18. Goto F, Otani E, Kato S, Fujita T (1982) Prostaglandin E_1 as a hypotensive drug during general anaesthesia. Anaesthesia 37: 530–535
19. Abe K, Demizu A, Kamada K, Morimoto T, Sakaki T, Yoshiya I (1991) Local cerebral blood flow with prostaglandin E_1 or trimethaphan during cerebral aneurysm clip ligation. Can J Anaesth 38:831–836
20. Abe K, Demizu A, Yoshiya I (1992) Effect of prostaglandin E_1-induced hypotension on carbon dioxide reactivity and local cerebral blood flow after subarachnoid haemorrhage. Br J Anaesth 68:268–271
21. Hoka S, Sato M, Okamoto H, Arimura H, Yoshitake J (1992) Effects of prostaglandin E_1 on left ventricular performance in dogs; Comparisons with trinitroglycerin and adenosine triphosphate. J Anesth 6:45–50
22. Boettcher DH, Zimpfer M, Vatner SF (1982) Phylogenesis of the Bainbrige reflex. Am J Physiol 242 (Regulatory Integrative Comp Physiol 11):R244–R246
23. Hintze TH, Kaley G (1984) Ventricular receptors activated following myocardial prostaglandin synthesis initiate reflex hypotension, reduction in heart rate, and redistribution of cardiac output in the dogs. Circ Res 54:239–247
24. Panzenbeck MJ, Tan W, Hajdu MA, Cornish KG, Zucker IH (1989) PGE_2 and arachidonate inhibit the baroreflex in conscious dogs via cardiac receptors. Am J Physiol 256 (Heart Circ Physiol 25):H999–H1005
25. Hintze TH, Martin EG, Messina EJ, Kaley G (1979) Prostacyclin (PGI_2) elicits reflex bradycardia in dogs: Evidence for vagal mediation. Proc Soc Exp Biol Med 162:96–100
26. Roux S, Latour JG, Thérou P, Clozel JP, Bourassa MG (1984) Prostaglandin E_1 increases myocardial contractility in the conscious dog. Can J Physiol Pharmacol 62:1505–1510
27. Bloor BC, Fukunaga AF, Ma C, Flacke WE, Ritter J, Van Etten A, Olewine S (1985) Myocardial hemodynamics during induced hypotension: A comparison between sodium nitroprusside and adenosine triphosphate. Anesthesiology 63:517–525