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The effect of CGRP-induced hypotension on organ blood flow during halothane anesthesia in dogs: a comparison with trimetaphan

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Abstract

Purpose. Calcitonin gene-related peptide (CGRP) is an endogenous 37-amino-acid peptide which is a powerful vasodilator of the splanchnic circulation. To elucidate the effects of CGRP-induced hypotension on the organ blood flow, we compared the renal, hepatic, and pancreatic organ flows of CGRP-induced hypotension with those of trimetaphan (TMP) in halothane-anesthetized dogs.

Methods. Systemic hemodynamics and organ blood flow were determined in 18 mongrel dogs allocated to one of two groups: CGRP group ($n = 10$) and TMP group ($n = 8$). CGRP or TMP was infused at a rate sufficient to decrease the mean arterial pressure (MAP) to near 60 mmHg from the baseline values for a 60 min-hypotensive period. Organ blood flow was measured using the hydrogen clearance technique.

Results. The decrease in MAP was approximately 50% of baseline values ($P < 0.01$). The hypotension induced by either CGRP or TMP was associated with a reduction ($P < 0.01$) in systemic vascular resistance in both groups. Cardiac index (CI) in the CGRP group did not change significantly throughout the experiment. On the other hand, CI decreased at 30 min ($P < 0.01$) and 60 min ($P < 0.01$) during the hypotensive period in the TMP group. No changes were observed in renal, hepatic, and pancreatic blood flows in the CGRP group. Renal blood flow in the TMP group did not change significantly throughout the experiment. In contrast, hepatic blood flow resulted in a significant decrease ($P < 0.01$) during TMP-induced hypotension. Pancreatic blood flow decreased during the hypotensive period ($P < 0.01$) and at 30 min ($P < 0.05$) after termination of TMP.

Conclusion. These findings show that CGRP does not adversely affect renal, hepatic, and pancreatic organ blood flows even in the presence of profound hypotension in halothane-anesthetized dogs. The results of this study suggest that CGRP may preserve organ blood flow during induced hypotension.

Key words: Calcitonin gene-related peptide (CGRP), Trimetaphan, Induced hypotension, Organ blood flow, Halothane anesthesia

Introduction

Calcitonin gene-related peptide (CGRP) has been shown to cause vasodilation, hypotension, and tachycardia, suggesting that tachycardia elicited by CGRP may be partly due to reflex sympathetic stimulation in alert humans [1,2] and animals [3]. We have reported recently that CGRP-induced reflex tachycardia could be suppressed by halothane anesthesia in dogs [4]. 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 with volatile anesthetics. More recently, it has been suggested that the hemodynamic profile of CGRP-induced hypotension may be a useful vasodilator during halothane anesthesia [5]. Although CGRP is a powerful vasodilator of splanchnic circulation [6], the safe use of CGRP-induced hypotension essentially requires an understanding of organ blood flow responses during hypotension with CGRP. On the other hand, trimetaphan (TMP)-induced hypotension may alter organ blood flow, and it has been reported that splanchnic organs may be at risk due to ischemic damage [7].

To elucidate the effects of CGRP-induced hypotension on renal, hepatic, and pancreatic organ blood flows, we compared the systemic hemodynamics and the

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organ blood flows of CGRP-induced hypotension with those of TMP in halothane-anesthetized dogs.

Materials and methods

All experimental procedures and the protocols for this study were approved by the Animal Experiment Ethics Committee, Showa University Fujigaoka Hospital. Eighteen healthy adult, mongrel dogs of either sex, weighing between 12 and 27 kg (16.6 ± 4.3 kg, mean ± SD) were fasted overnight and anesthetized with sodium pentobarbital (25 mg·kg^{-1}), given intravenously. After tracheal intubation, the animals were mechanically ventilated with a Harvard ventilator to maintain normocapnia. Anesthesia was maintained with 1.0 minimum alveolar concentrations (MAC) halothane (0.87%) via an Ohmeda vaporizer (BOC Health Care, Windlesham, UK) using oxygen as a carrier gas at a flow of 3–5 l·min^{-1} over the experimental period. End-tidal halothane and CO_2 concentrations were continuously measured by an infrared analyzer (Capnomac Ultima, Datex, Helsinki, Finland).

Instrumentation

Cannulas were placed in a cutdown into the left femoral artery for continuous systemic blood pressure (SBP) monitoring and blood sampling, and into the right femoral vein for the administration of maintenance fluid (normal saline at 7 ml·kg^{-1}·h^{-1}) and drugs as required. A 7-F flow-directed pulmonary catheter (Swan-Ganz thermodilution catheter, Baxter Health Care, Irvine, CA, USA) was advanced into the pulmonary artery via cutdown of 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), pulmonary artery pressure (PAP), pulmonary capillary wedge pressure (PCWP), and cardiac output (CO). CO was measured in triplicate, using the thermodilution technique; we used a cardiac output computer (MTC6210, Nihon Kohden, Tokyo, Japan) and injected 5 ml ice-cold, temperature monitored, normal saline into the right atrium at end-expiration. Heart rate (HR), calculated from lead II of the electrocardiogram (ECG) using a cardiotachometer (AT601G, Nihon Kohden), which was continuously monitored. Body temperature, monitored by a thermistor attached to the pulmonary artery catheter, was maintained at 37.0 ± 1.0°C by electric heating pads and lamps. Each pressure monitoring catheter was connected to a pressure transducer (Uniflow, Baxter). SBP and ECG were monitored continuously on a polygraph (RM6200, Nihon Kohden) and recorded using an eight-channel pen recorder (VM-640G, Nihon Kohden). The dogs were fixed supine during the measurements and the zero reference was leveled at the midchest. Both mean arterial pressure (MAP) and mean pulmonary artery pressure (MPAP) were determined electronically. Cardiac index (CI) and systemic vascular resistance (SVR) were calculated using standard formulae. CI was calculated as cardiac output divided by the body surface area (BSA). (The BSA of dogs was calculated as 0.112 × body weight$^{2/3}$). SVR was calculated as (MAP-RAP)·CO^{-1} × 80.

Following these preparations, the dogs were incised with a midline laparotomy, and the liver, pancreas, and left kidney were carefully isolated. Platinum electrodes (Standard needle type 100 μm diameter, UHE-100, Unique Medical, Tokyo, Japan) were placed in the left lobe of the liver, the body of the pancreas, and the cortex of the left kidney, respectively. These platinum electrodes were introduced to a depth of 3–6 mm from the surface of these organs, respectively. Three reference electrodes of renal, hepatic, and pancreatic platinum electrodes were used silver/silver chloride electrodes (Plate type UHE-001, Unique Medical) which placed subcutaneously in the animal's flank close to the kidney, liver, and pancreas, respectively. After the completion of these procedures, the abdomen was closed. The platinum electrodes were connected to hydrogen detection systems (Digital UH meter MHG-D1, Unique Medical), and recorders (Desk recorder U-288, Unique Medical). Measurements of the organ blood flows were performed in the following manner, using the hydrogen clearance methods as originally reported by Aukland et al. [8] and adapted for the using in dogs by Griffiths et al. [9].

Hydrogen gas, at approximately 10%, was added to the inspired gas for one min to the extent of near saturation in the tissue, at which time the hydrogen gas inhalation was terminated. After the cessation of hydrogen inhalation, the 'washout' curve of hydrogen was recorded through an appropriate amplifier unit (MHG-D1U, Unique Medical). This curve was transposed on semi-logarithmic paper and half time ($T_{1/2}$) was measured. When the clearances were mono-exponential, the organ blood flows were calculated from the formula:

$$\text{Flow} = \lambda \frac{0.693}{T_{1/2}} \text{ ml·g}^{-1}\text{·min}^{-1}$$

λ (tissue/blood partition coefficient) was taken to be 1. When the clearance curves were bi-exponential, flow in the fast and slow compartments was calculated by the formula of the Height–Area method. This method is according to Zienler's theory.

$$\text{Flow} = \frac{\lambda(C_{io} - C_i(t_1))}{\int_0^{t_1} C_i(t)dt} = \frac{H}{A}\ \text{ml}\cdot 100\,\text{g}^{-1}\cdot\text{min}^{-1}$$

Where C_i is hydrogen concentration in tissue, C_{io} is hydrogen concentration in tissue when clearance starts, and t is time (min). In the present study, the digital UH meter measured both mono-exponentials and bi-exponentials by using a simultaneous computer system program.

Experimental protocols

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 TMP group (n = 8) received a 0.1% solution of TMP (TMP 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 of hemodynamic variables and the organ blood flows were then obtained before infusion of the hypotensive drugs. After baseline measurements had been made, MAP was reduced to 60 mmHg for a 60-min hypotensive period by the infusion of CGRP or TMP. Measurements were taken 30 and 60 min after the induction of hypotension, and 30 min after the termination of drug infusion. The CGRP and TMP solutions was infused into the left femoral vein with an infusion pump (STG-521, Terumo, Tokyo, Japan). Des-1-Ala, des-α-amino chicken CGRP (Asali Chemical Industry, Tokyo, Japan) was used for the present study.

Statistical analysis

Values are expressed as mean ± SD. Intragroup differences were analyzed by a two-way analysis of variance from repeated measurements of the same variables followed by the Dunnett's test where appropriate. Intergroup differences of values in each of the phases (baseline, during, and after hypotension) between the CGRP and TMP groups were analyzed by Student's unpaired t-test when the F-test was significant. $P < 0.05$ was considered statistically significant.

Results

The changes in hemodynamic variables of the CGRP and TMP groups are shown in Table 1. There were no significant differences in baseline values of systemic hemodynamics including MAP, HR, CI, MPAP, PCWP, and SVR between the CGRP and TMP groups.

MAP decreased from baseline values of 110 ± 12 mmHg and 103 ± 9 mmHg in the CGRP and TMP groups to near 60 mmHg ($P < 0.01$) during the 60-min

Table 1. Changes in hemodynamic variables of the CGRP and TMP groups

		During hypotension		After hypotension
	Baseline values	30 min	60 min	30 min
MAP (mmHg)				
CGRP	110 ± 12	61 ± 1**	61 ± 1**	91 ± 6**
TMP	103 ± 9	60 ± 0.4**	60 ± 0.4**	92 ± 9**
HR (beats·min^{-1})				
CGRP	147 ± 16	142 ± 18	147 ± 20	144 ± 22
TMP	147 ± 19	126 ± 17**	120 ± 15**	136 ± 24
CI (l·min^{-1}·m^{-2})				
CGRP	3.1 ± 0.4	3.2 ± 0.6	3.4 ± 0.7	3.3 ± 0.7
TMP	2.9 ± 0.8	2.1 ± 0.3**++	2.1 ± 0.3**++	2.5 ± 0.4++
MPAP (mmHg)				
CGRP	17 ± 6	15 ± 6**	16 ± 6	17 ± 6
TMP	16 ± 2	14 ± 2*	13 ± 3**	16 ± 3
PCWP (mmHg)				
CGRP	11 ± 4	9 ± 4**	9 ± 4**	10 ± 4
TMP	10 ± 2	8 ± 1**	8 ± 2**	9 ± 2
SVR (dynes·s·cm^{-5})				
CGRP	4219 ± 1132	2217 ± 571**	2044 ± 585**	3259 ± 1010**
TMP	3332 ± 589	2628 ± 409**	2671 ± 417**	3399 ± 710

Values are expressed as mean ± SD.
MAP, mean arterial pressure; HR, heart rate; CI, cardiac index; MPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; SVR, systemic vascular resistance.
* $P < 0.05$, ** $P < 0.01$ compared with baseline values; ++ $P < 0.01$ compared with both the CGRP and TMP groups (these values were compared at predetermined identical times).

hypotensive period, respectively. Within 30 min after termination of drug infusion, MAP resulted in a significant decrease ($P < 0.01$) in both groups. CI and HR in the CGRP group did not change significantly during and after induced hypotension. In contrast, HR in the TMP group resulted in a significant decrease ($P < 0.01$) during induced hypotension. CI in the TMP group decreased from baseline values of 2.9 ± 0.8 l·min^{-1}·m^{-2} to a nadir of 2.1 ± 0.3 l·min^{-1}·m^{-2} ($P < 0.01$) for the 60-min hypotensive period. CI was significantly lower ($P < 0.01$) in the TMP group than in the CGRP group during and after induced hypotension. MPAP and PCWP decreased significantly during the hypotensive period in both groups. SVR in the CGRP group reduced from baseline values of 4219 ± 1132 dynes·s·cm^{-5} to a nadir of 2044 ± 585 dynes·s·cm^{-5} ($P < 0.01$) at 60 min of the hypotensive period followed by a significant reduction ($P < 0.01$) below baseline values after termination of infusion. SVR in the TMP group reduced from baseline values of 3332 ± 589 dynes·s·cm^{-5} to a nadir 2628 ± 409 dynes·s·cm^{-5} ($P < 0.01$) at 30 min of the hypotensive period, but it returned to baseline values after induced hypotension.

The changes in organ blood flows determined by the hydrogen clearance method in the CGRP and TMP groups are shown in Table 2. There were no significant differeces in the baseline values obtained from both groups. No changes were observed in renal, hepatic, and pancreatic blood flows measured in the CGRP group throughout the experiment. CGRP-induced hypotension did not affect splanchnic organ blood flow adversely even though the MAP decreased significantly. In the TMP group, renal blood flow did not change significantly throughout the experiment. Hepatic blood flow resulted in a significant decrease ($P < 0.01$) during induced hypotension. Pancreatic blood flow decreased from baseline values of 34 ± 7 ml·min^{-1}·100 g^{-1} to a nadir of 28 ± 6 ml·min^{-1}·100 g^{-1} ($P < 0.01$) during the 60-min hypotensive period followed by a significant decrease ($P < 0.05$) below baseline values after termination of infusion.

Discussion

The results of the present study demonstrate that hypotension induced by CGRP produced a potent vasodilator of renal, hepatic, and pancreatic organ vasculature, whereas hypotension induced by TMP was accompanied by significant reductions in hepatic and pancreatic blood flows.

The present study revealed that hypotension induced by either CGRP or TMP affected renal autoregulation only minimally, since renal blood flow was maintained despite a significant decrease in the MAP. CGRP has been reported to induce a dose-dependent increase in renal blood flow and a dose-dependent decrease in renal vascular resistance [10,11]. Further, it has been shown that intrarenal infusion of CGRP in anesthetized dogs at nonhypotensive doses increases renal blood flow and glomerular filtration [12]. CGRP also relaxes glomerular mesangial cells and increases the glomerular filtration rate and filtration fractions [13]. Moreover, nerve fibers containing immunoreactive CGRP have been identified in the renal vessels [14], suggesting that endogenous CGRP may act locally to regulate renal vascular tone. Even under pathological conditions, Bergman et al. [15] reported that CGRP preserves renal function in experimental acute renal failure despite decreases in the MAP. Li et al. [16] also showed that CGRP has protective action on ischemic-reperfusion renal injury by decreasing lipid peroxidation of membranes. Both studies suggested that CGRP may be a beneficial agent for the therapy of acute renal failure.

Table 2. Changes in organ blood flows of the CGRP and TMP groups

		During hypotension		After hypotension
	Baseline values	30 min	60 min	30 min
RBF (ml·min^{-1}·100 g^{-1})				
CGRP	93 ± 39	87 ± 47	87 ± 51	87 ± 39
TMP	118 ± 14	106 ± 19	101 ± 15	110 ± 12
HBF (ml·min^{-1}·100 g^{-1})				
CGRP	63 ± 43	60 ± 36	60 ± 35	75 ± 38
TMP	71 ± 6	59 ± 8**	56 ± 7**	67 ± 6
PBF (ml·min^{-1}·100 g^{-1})				
CGRP	31 ± 16	32 ± 19	33 ± 20	32 ± 19
TMP	34 ± 7	28 ± 6**	28 ± 6**	32 ± 7*

Values are expressed as mean ± SD.
RBF, renal blood flow; HBF, hepatic blood flow; PBF, pancreatic blood flow.
*$P < 0.05$, **$P < 0.01$ compared with baseline values.

CGRP has been reported to normalize renal plasma flow and glomerular filtration rates which were reduced in response to a bolus administration of the vasoconstrictor endothelin-1 [17]. These findings indicate that CGRP is a potent renal vasodilator under both normal and pathological conditions as well as under situations involving induced hypotension with sustained hypotension. No change in renal blood flow with TMP was not consistent with the results of an earlier study which reported that TMP-induced hypotension produced a decrease in renal blood flow [18]. On the other hand, it has been reported that TMP-induced hypotension preserves the renal cortical and medullary oxygenation, and it is suggested that TMP is a hypotensive agent safe for the kidney [19]. Our results suggest that the renal cortical blood flow induced by either CGRP or TMP may be at least maintained, even when CGRP or TMP is infused at a rate of reducing the MAP to 60 mmHg.

Compared with the kidney, the liver has a limited ability to autoregulate its blood flow in the presence of hypotension so that a decrease in systemic arterial pressure leads to a decrease in hepatic arterial flow [20]. It is well known that a decrease in hepatic arterial flow is usually accompanied by an increase in portal venous flow through a hepatic arterial response [21]. In disagreement with an earlier study in the rhesus monkey [22], a reduction in hepatic blood flow resulted during TMP infusion in the present study. Trimetaphan also has been reported to decrease mesenteric blood flow and increase mesenteric vascular resistance in dogs [7,18], possibly contributing directly to the liver and gut ischemia. Contrary to trimetaphan-induced hypotension, the present study demonstrates that CGRP-induced hypotension does not appear to significantly affect hepatic blood flow, probably because a decrease in hepatic arterial flow is compensated by an increase in portal venous flow. It has been reported that CGRP produces splanchnic vasodilation in the conscious rat [6,23]. The blood vessels in the gastrointestinal tract [24] and the liver [25] have been demonstrated to be innervated with CGRP-immunoreactive fibers. It appears that high levels of CGRP immunoreactivity in the splanchnic organ blood vessels are well in accordance with responsiveness of the vasculature to the vasodilatory action of CGRP. Recently, Fletcher et al. [26] have reported that CGRP is vasodilatory in the renal and hepatic vascular bed, that is, the infusion of CGRP ($10\,pmol \cdot kg^{-1} \cdot min^{-1}$) in the conscious sheep has been shown to maintain renal and hepatic flow despite a marked reduction in perfusion pressure.

In the present study, blood flow to the pancreas was well maintained during CGRP-induced hypotension. In contrast, TMP-induced hypotension resulted in significant reductions in pancreatic blood flow, most likely as a result of a cardiac depression, during and after induced hypotension. Therefore, the unchanged flow to the pancreas observed during CGRP infusion is likely to be a result of a vasodilatory mechanism of the pancreatic vasculature, which dilates the celiac artery and superior mesenteric artery in response to CGRP infusion. On the other hand, CGRP has been reported to induce a specific decline in total pancreatic blood flow with only minor effects on other splanchnic organs in spontaneously hypertensive rats [27]. CGRP also has been reported to cause a decrease in both total pancreas and islet blood flow concurrent with a decrease in duodenal and colonic blood flow in Sprague-Dawley rats [28]. The discrepancy between the earlier studies and the present one regarding the pancreatic blood flow may arise due to different experimental conditions such as animal species selected, the dosage of CGRP, and the anesthetic used. Effects of CGRP on the pancreatic blood flow remain to be further elucidated.

In conclusion, this study shows that CGRP is a potent vasodilator of renal, hepatic, pancreatic organ vasculature in halothane-anesthetized dogs and that blood flow to the splanchnic organs are maintained even when CGRP is infused at a rate capable of reducing the MAP to 60 mmHg. The results of this study suggest that CGRP may preserve organ blood flow during induced hypotension.

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