Cardiovascular Responses to Gastric Hypo-Osmolar Stimulation in Anesthetized Dogs

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Abstract We compared the cardiovascular response to the gastric infusion of distilled water (DI) with that to the gastric infusion of 0.9% saline (SI) and gastric ballooning with 37°C water (BA) through a gastric fistula in splenectomized mongrel dogs ($n=7$). DI, and SI amounting to 5% of body wt and the same volume of water were infused in approximately 20 s through the tube and responses in mean arterial pressure (MAP), CVP, heart rate (HR), and intra-esophageal pressure (EP) were monitored continuously. After DI, SI, and BA, the measured variables showed significant increases and attained maximal increases at about 2 min after the treatments. After DI, the maximum elevation in MAP was 21.3 ± 1.9 mmHg and 2 times higher than in SI and BA. The corresponding value in CVP was 5.0 ± 0.3 mmHg and 2–3 times higher than with SI and BA, and HR increased by 26.1 ± 3.0 beats/min showing 3 to 6 times larger increases compared with SI and BA. These gastro-cardiovascular reflexes were abolished after subdiaphragmatic truncal vagotomy. These findings suggest that both the mechanical and osmotic stimuli to the stomach induce cardiovascular reflexes and that the vagus is involved in the reflex.

Key words: cardiovascular reflex, gastric distension, hypo-osmolar stimuli, dog, vagotomy.

It was observed in humans more than sixty years before that food ingestion is followed by increases in heart rate, blood pressure, and cardiac output [1]. Cardiovascular reflexes initiated by events in the gastrointestinal tract have been suggested to be the cause of some physiological responses seen in humans but the mechanisms responsible for these events have not been identified yet [2]. There have been reports on the reflexes elicited by passive distension of the stomach [3–7]. Nosaka *et al.* [8] have also reported a cardiovascular response to gastric mechanoreceptors.

Recently, Itoh *et al.* found that dogs show a marked increase in central venous

pressure in association with drinking behavior and also that the responses were different between tap water and saline drinking [9]. Because this finding suggests the involvement of the osmoreceptor to the reflex, we compared the gastro-cardiovascular reflexes induced by the rapid gastric infusion of distilled water (DI) with that of 0.9% saline (SI) and gastric ballooning (BA) in seven anesthetized dogs. Arterial pressure (AP), central venous pressure (CVP), and heart rate (HR) were monitored continuously. Intra-esophageal pressure (EP) was monitored to confirm that the intragastric infusion did not leak to esophagus. The hematocrit (Hct) and total plasma protein concentration (TP) were used to measure the changes in their blood volume to exclude the effect of blood volume change on cardiovascular responses. The gastro-cardiovascular reflexes were studied before and after subdiaphragmatic trunkal vagotomy. The findings demonstrated that the cardiovascular responses were observed in response to changes in pressure and osmolality and that the reflexes were largely mediated by vagal afferents.

MATERIALS AND METHODS

Preparations of animals. Experiments were performed on 7 adult mongrel dogs of either sex, weighing 10.5 ± 0.3 kg (7.5–12.5 kg). The dogs were cared for and used in accordance with the guiding principles of the Physiological Society of Japan. Approximately 4 weeks before the experiment, each dog underwent splenectomy under sodium pentobarbital anesthesia (25 mg/kg, i.v.) to eliminate the mobilization of erythrocytes during the experiment.

Anesthesia was induced with ketamine hydrochloride (10 mg/kg body wt, i.m.) and maintained with 20% ethyl carbamate (urethane, 1.8 g/kg body wt, s.c.). Ethyl carbamate was used as the anesthetics because of its minimal depressant action on cardiovascular reflexes, and supplementary doses of the anesthetic (0.6 g/kg body wt, s.c.) were administered when fluctuation of AP was observed. The animals were intubated with a cuffed endotracheal tube and allowed to breathe spontaneously with 30% O₂–70% N₂.

Figure 1 shows the experimental schema. Each animal was surgically prepared with two gastric fistulae. One catheter was for infusion and the other was for gastric ballooning for which a latex balloon was attached at the end of the catheter. The catheters were inserted through a small incision in the fundus of the stomach after the stomach contents had been flushed out with isotonic saline. A purse string suture was run around the incision in the stomach wall, and the incision was closed by tying this onto the tubings. The muscle and skin layers were sutured to close the abdominal incision. The tubes for ballooning and infusion were connected to the drip infusion bags.

Two catheters were placed in the abdominal aorta via the femoral artery and in the superior caval vein via the jugular vein for measurement of AP and CVP, respectively. The catheters were connected to strain gauge transducers (GOULD, P23XL, U.S.A.). The zero reference was taken at the level of right atrium adjusted

Fig. 1. Diagram of preparation utilized for the determination of cardiovascular responses during gastric distension. AP, arterial pressure; CVP, central venous pressure; EP, intraesophageal pressure; A/D Conv., analog-digital converter; CPU, central processing unit. For details, see text.

to 60% of chest thickness [10]. Analysis was made on mean arterial pressure (MAP) and CVP as the changes from the control value. Instantaneous HR was computed by a cardiometer triggered by the AP signal.

A polyethylene tube with a small balloon was introduced into the lower esophagus to measure EP. The change in EP during the rapid gastric treatment was used as the index of esophageal regurgitation. Another catheter was also implanted in the femoral vein for blood sampling to measure Hct with the microcentrifugation method and TP with refractometry (Atago, Tokyo).

DI, SI, or BA were set to 5% body wt based on the results of the preliminary experiments in which the gastric treatments with more than 5% body wt elicited the maximum response in cardiovascular reflexes.

Experimental procedure. When steady readings of AP and CVP were obtained, the control blood at time zero was obtained, and each dog was given bolus

gastric infusions (37°C; 5% body wt) of DI, and SI, or BA with 37°C water (5% body wt) in random order. The infusion was performed within 15–20 s by raising the infusion bag to 2 m above the animal to give a stepwise change. All parameters, AP, CVP, HR, and EP, were monitored continuously throughout the experiment, transferred to a microcomputer endowed with A-D converter (SORD 243-V, Tokyo), and the mean values of the above measurements were calculated in every 30 s and stored in the microcomputer. The gastric treatments, DI, SI, or BA, were each repeated twice and the mean values were used for the analysis. After each measurement, the content of the stomach or water in the gastric balloon was aspirated and the volume was measured. About 10–30 min was allowed to ensure the stabilization of both AP, CVP, and HR before the next measurement.

Blood samples of about 0.5 ml were collected before and 10 and 30 min after the start of the gastric treatment for measurement of Hct and TP. The changes in the blood volume during and after ballooning and saline infusion were determined from the changes in Hct and those with distilled water were determined by the changes in Hct and TP [11].

Subdiaphragmatic vagotomy. In all animals, after the control responses with intact vagi (Intact Group) had been recorded, the abdominal wall was reopened, and the dorsal and ventral branches of the vagus were cut with scissors at as high as possible and below the diaphragm. Then the abdominal wall was closed again. After vagotomy, gastric treatments with DI, SI, and BA were repeated twice in all animals (Vagotomy Group). To evaluate the effects of vagotomy on the cardiovascular responses to each gastric treatment, the percent suppression of the maximum responses in each indices was defined as

$$\frac{(\text{response with intact vagi}) - (\text{response after vagotomy})}{(\text{response with intact vagi})} \times 100 (\%).$$

Analysis of data. All results of continuous measurements were smoothed by a moving average of 3 consecutive values and were used for analysis and graphical display. Values are represented as mean $\pm$ SEM ($n=7$). Results were analyzed with respect to the difference from the control value obtained as the mean of 5-min period prior to the gastric treatments (DI, SI, and BA). Three-way analysis of variance for repeated measures was used to determine the effects of gastric treatments and vagotomy on cardiovascular functions, and the effects of gastric treatments and vagotomy on gastric emptying of the gastric contents after DI or SI. Differences among the three groups at various times after each gastric treatment were determined with Tukey's minimum significant difference test [12]. The null hypothesis was rejected when $p < 0.05$, unless otherwise noted.

RESULTS

Figure 2 and Table 1 summarize the cardiovascular responses to the gastric distension in the intact vagi group as the differences from the pre-treatment control

Fig. 2. Cardiovascular responses in intact vagi group. Changes in mean arterial pressure (Δ MAP) (a), central venous pressure (Δ CVP) (b), heart rate (Δ HR) (c) (mean $\pm$ SE in 7 dogs) in response to rapid gastric infusion of distilled water (DI), 0.9% saline (SI), or gastric ballooning with intact vagi. A significant difference in Δ MAP between DI and SI was observed for 12 min after each treatment, in Δ CVP for 11 min after the gastric treatment, and in Δ HR at all data points.

Table 1. Maximal cardiovascular responses to the gastric ballooning, infusion of distilled water or saline.

	Intact vagi			After vagotomy		
	Balloon	Distilled	Saline	Balloon	Distilled	Saline
MAP (mmHg)	11.5±1.3	21.3±1.9*	9.5±1.6	-1.9±0.7 [†]	1.2±2.1 [†]	-1.9±1.6 [†]
CVP (mmHg)	1.8±0.5	5.0±0.3*	2.3±0.3	0.2±0.2	0.6±0.1 [†]	1.3±0.2
HR (beats/min)	4.3±1.1	26.1±3.0*	8.1±2.3	-6.4±0.8 [†]	2.5±2.7 [†]	3.8±1.7

Values are mean±SEM of 7 dogs. MAP, mean arterial pressure; CVP, central venous pressure; HR, heart rate. MAP attained the highest level within 5 min after the gastric treatments: *indicates significant difference from ballooning and also saline infusion ($p < 0.05$), and [†]denotes significant difference from intact vagi group ($p < 0.01$).

value. MAP increased sharply within 1 min after each gastric treatment, and then continued to increase up to 1.5–3.5 min (Fig. 2a). The maximal increase in each group ($n=7$) was 21.3±1.9 mmHg with DI, 9.5±1.6 mmHg with SI, and 11.5±1.3 mmHg with BA. Significant elevation above the control level was observed for 25.5 min with DI, for 30 min with SI, and for 15 min with BA. The increase in MAP with DI was significantly greater than that with SI for 12 min, and than that with BA for 12.5 min. Thereafter, the MAP decreased gradually to the control level in all groups. The responses to SI and BA were not different significantly with each other.

Increases in CVP were also observed after the gastric treatments (Fig. 2b), and the maximal increase was 5.0±0.3 mmHg with DI, 2.3±0.3 mmHg with SI, and 1.8±0.5 mmHg with BA. Significant elevation in CVP above the control level was detected for 12 min with DI, and for 3.5 min with both SI and BA. The response to DI was significantly higher than that to SI or BA for 11 min after the gastric distension. Then the CVP decreased gradually to the control level with DI, but decreased rapidly to the control level with SI and BA, the responses to SI and BA not being significantly different.

The maximal increase in HR was 26.1±3.0 beats/min with DI, 8.1±2.3 beats/min with SI, and 4.3±1.1 beats/min with BA. The HR was significantly higher than the control level from 1 to 30 min after DI, from 1 to 3 min after SI, and from 1.5 to 3 min after BA (Fig. 2c). Furthermore, the HR was decreased significantly below the control level from 8 to 30 min after SI, and from 10.5 to 30 min after BA. The response to DI was significantly higher than that to SI from 1.5 to 30 min after the gastric infusion, and significantly higher than that to BA from 1 to 30 min after treatment. The responses to SI and BA were different significantly with each other only at 0.5 min. A transient decrease, of 3.4 beats/min was observed immediately after BA and that of 3.9 beats/min was observed after DI, but no decrease was detected after SI. The responses to SI and BA were not significantly different between 1 min and 30 min after the gastric distension. The change in EP following the gastric treatment was neither detected nor significant compared with

Fig. 3. Cardiovascular responses after vagotomy. Changes in mean arterial pressure (Δ MAP) (a), central venous pressure (Δ CVP) (b), and heart rate (Δ HR) (c) (mean $\pm$ SEM in 7 dogs) in responses to rapid gastric infusion of distilled water (DI), 0.9% saline (SI), or gastric ballooning (BA) in the vagotomized group.

the pre-treatment value both in intact vagi and vagotomized dogs.

Effects of vagotomy on cardiovascular changes during gastric distension

Bilateral subdiaphragmatic truncal vagotomy was performed by successive cutting, and the responses to gastric infusion or gastric ballooning were studied (Fig. 3, Table 1). After vagotomy no appreciable changes in the baseline of MAP, CVP, and HR were observed.

Immediately after DI, the sharp and transient increase in MAP seen in the

intact vagi group was not observed in the vagotomy group, there being no significant change from the pre-treatment level. The change in MAP after SI was not detected for 7 min. After BA, the MAP decreased significantly below the control level from 1.5 to 2.5 min, with no significant changes being observed thereafter. After vagotomy, the sharp and transient increase in CVP seen just after the gastric treatment in the intact vagi group was not observed. After DI, CVP showed an increase with a peak response of 0.6 ± 0.1 mmHg, and significance above the control level was observed for 5 min after the DI treatment. Thereafter, CVP decreased gradually to the control level and the increase in CVP was significantly smaller than that in the intact vagi group up to 12 min after the gastric treatment. The changes in CVP occurring after SI was significantly smaller than that in the intact vagi group, and the peak increase in CVP after SI was 1.3 ± 0.2 mmHg. A significant increase above the control level was observed up to 25.5 min after the gastric treatment, and then CVP decreased gradually to the control level. Immediately after BA a significant increase in CVP above the control level was not detected, and after 24.5 min, CVP decreased significantly. The change in CVP after BA was significantly smaller for 3 min than that in the intact vagi group. HR increased immediately after DI, but the increase was not significant, and the change was smaller than that in the intact vagi group for 14 min after the gastric treatment. In the vagotomy group treated with SI, the HR showed an initial fall of -1.8 ± 2.4 beats/min, and with a subsequent rise. After 6 min of SI, the increase above the control level was significant. The HR response after BA showed an initial fall up to 14 min after the gastric treatment, and after 3 min of BA, the change in HR was significantly different from that in SI. Between 1.5 and 4 min following BA, the change in HR in the vagotomized group was significant from that in the intact vagi group.

Changes in blood volume

Table 2 summarizes the changes in blood volume during gastric treatments. No significant change in blood volume was detected at 10 min after the gastric treatments when marked cardiovascular reflexes had already been detected. At 30 min after the gastric treatments, the change in the blood volume from the preinfusion was not significant, although the increase in SI in the intact vagi group was significantly larger due to isotonic expansion of blood volume than that with BA. After vagotomy, significant differences were not observed among each gastric treatment.

The gastric emptying during the gastric treatments

The amount of fluid remaining after a 30-min gastric treatment was determined by recovering the gastric contents (Table 3). In the intact vagi groups, about 50% of infused fluid was recovered 30 min after both DI and SI, while in the vagotomy group, the amount of fluid recovered after 30 min was about 85%, which was significantly ($p < 0.05$) larger than that in the intact vagi group. No significant

Table 2. Changes in blood volume after gastric treatments.

	Δ Blood volume (%)	
	10 min	30 min
Intact vagi		
Balloon	0.14 ± 0.44	-0.03 ± 0.17
Distilled	-0.05 ± 0.25	0.43 ± 0.32
Saline	-0.15 ± 0.49	$1.30 \pm 0.45^*$
After vagotomy		
Balloon	0.25 ± 0.21	-0.23 ± 0.33
Distilled	0.36 ± 0.32	0.21 ± 0.19
Saline	0.27 ± 0.31	0.48 ± 0.27

Values are mean $\pm$ SEM in 7 dogs. *Significant differences from ballooning values with intact vagi ($p < 0.05$).

Table 3. The amount of fluid recovered 30 min after gastric treatment.

	DI (%)	SI (%)
Intact vagi	54.6 ± 3.4	49.0 ± 2.0
After vagotomy	$85.0 \pm 1.8^*$	$83.6 \pm 1.4^*$

Values are mean $\pm$ SEM (in %) of the fluid recovered 30 min after gastric infusion of distilled water (DI) or 0.9% saline (SI); number of rats in each group was 7. * $p < 0.05$ vs. intact vagi.

difference was observed between DI and SI in both the intact and vagotomized groups.

DISCUSSION

In the present study, gastric infusion or ballooning with fluid amounting to 5% of body wt were performed within a short period and the responses in MAP, CVP, and HR due to passive gastric distension were studied. We confirmed the reported cardiovascular responses to mechanical distension of gastric wall [3-8]. In addition, we found augmented cardiovascular responses with infusion of distilled water. As shown in Fig. 2 and Tabel 1, the responses in MAP, CVP, and HR obtained with SI and BA were similar, while those obtained with DI showed about a 2 times higher increase in MAP and 2-3 times higher CVP, and almost 3 to 6 times higher HR each with a longer time course, which suggests that the cardiovascular reflex is initiated with hypo-osmotic stimulus.

These cardiovascular responses were almost abolished by bilateral sub-diaphragmatic truncal vagotomy, which suggests that the reflexes generated by gastric mechanoreceptors and/or chemoreceptors are largely mediated by vagal afferents. In the vagotomized group, the percent suppression in MAP response was

$91 \pm 4\%$, and almost no response was detected after SI or BA. The CVP response was suppressed by $85 \pm 3\%$ with DI, $40 \pm 7\%$ with SI, and $86 \pm 3\%$ with BA, while HR response was suppressed by $83 \pm 6\%$ with DI, and $53 \pm 13\%$ with SI, but no response was detected for 18.5 min after BA in the vagotomized group. Gastric emptying determined by recovering the infused fluid after 30 min was reduced from 50 to 15% by the vagotomy, which might be attributed to the decreased gastric motility.

Because cardiovascular responses, especially that of CVP, are influenced by the change in blood volume, we determined the changes in blood volume occurring after the infusion of distilled water and saline, but no significant changes were detected although an increasing tendency was observed after saline infusion. Thus, the observed cardiovascular responses might be attributed to nervous reflexes.

Typical cardiovascular responses to viscerosensory excitation are primarily characterized by sympathetic excitement causing pressor response, tachycardia, increased myocardial contractility, and increase in systemic vascular resistance [4, 13–16]. Pittam *et al.* reported that the tachycardia is mediated by cardiac β -adrenoreceptor stimulation and that at least part of the pressor response is mediated by α -adrenergic vasoconstriction [17]. On the other hand, some investigators [18, 19] have reported the appearance of a depressor response to viscerosensory excitation. In our study, transient decreases in HR were detected in the heart rate of the initial phase of DI and BA in the intact vagi group and BA in the vagotomized group. In this connection, Ness and Gebhart showed that the direction of the cardiovascular expression was distinctly dependent on the condition of the animals [19], while the marked increases in HR observed after the transient decreases suggest that the stimuli used in this experiment were potent enough to stimulate cardiovascular responses. In addition, our findings in the vagotomized group show that viscerogenic cardiovascular reflexes are mediated by the vagus.

Previous studies showed that cardiovascular responses to mechanical or chemical stimulation to the stomach [4, 15] and gallbladder [20] are mediated by splanchnic afferents. Various receptor types also exist in the mesentery [21]. Gastric mechanoreceptors connected with both vagus and splanchnic afferent fibers were characterized by Nijjima [22]. His findings suggested that gastric mechanoreceptors connected with vagus afferents exist throughout the wall and respond exactly to low distension pressure, whereas those connected with splanchnic afferents are probably located on the serosal surface and require a higher distension pressure for their excitement. This suggests that vagus afferents deliver a sensation that signals the degree of the fullness of the stomach, whereas splanchnic afferents send a signal of gastric overdistension. Furthermore, the receptor responsible for hypo-osmotic stimuli should be identified. It should also be clarified whether the cardiovascular reflex is provoked by the gastric hypo-osmotic stimulus alone or gastric distension is required to activate the reflex.

Cardiovascular responses detected in the present study were regarded as within physiological ranges, because dogs are known to consume almost the same amount

of water required to restore their body fluid deficit within a few minutes, and are thereby referred to as rapid drinkers [23]. In addition, humans usually consume food or fluid amounting to 5% of body wt. Such hydraulic and osmotic stimulations may cause responses that occur during natural activation of gastric receptors. The cardiovascular reflexes occurring with passive gastric distension, observed in the present study, is similar to the hemodynamic changes following food ingestion. Ingested material might distend the gastric wall, thereby activating reflexes that affect the cardiovascular system. Such an effect could provide a possible explanation for the mechanism of postprandial angina in patients with coronary artery disease, because an increase in arterial blood pressure and myocardial contractility would augment myocardial oxygen demands in the face of a limited coronary blood supply [24, 25]. At the same time, this cardiovascular response might be related with the control of drinking behavior. Itoh *et al.* [9] found in dogs that CVP was elevated by about 6 mmHg during drinking behavior. After the cessation of initial drinking, CVP decreased gradually and drinking was observed again when CVP was lowered to about 4 mmHg. Thus, we conclude that the cardiovascular responses induced by ingestion of hypo-osmotic solution is very important in controlling cardiovascular integrity and also in body fluid homeostasis.

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