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Neural Reflex Hypotension Induced by Very Small Dose of Hypertonic NaCl Solution in Rats

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Abstract

Although the precise mechanisms of transient hypotension after intravenous infusion of hypertonic saline (HTS) are not yet clarified, a rapid infusion of HTS is widely used as the initial therapy of hypovolemia. We investigated the effect of the intravenous infusion of a small dose of 0.97-9.7% NaCl solutions in anesthetized rats. Intravenous infusion of HTS at a rate of 0.3 ml/kg/min for 1 min produced the transient hypotension lasting for several minutes. The depressor response to HTS was not abolished by bilateral cervical vagotomy. The HTS infusion into the femoral vein evoked the depressor response with a larger magnitude and a shorter latency than that into the aortic arch. While the arterial baroreceptor pressure was kept constant at the baseline level of systemic arterial pressure, HTS-induced hypotension was significantly augmented. The gain factor of the arterial baroreflex was reduced by intravenous HTS. Pretreatment with bretylium tosylate completely abolished the depressor response without affecting the baseline level of arterial pressure. These results suggest that the depressor response to the very small dose of intravenous HTS is the sympathosympathetic neural reflex with cardiopulmonary afferents and vasomotor efferents.

Key Words: arterial pressure, baroreflex, hypotension, osmolality

Introduction

It is well documented that the intravenous bolus injection of hypertonic saline (HTS) induces a transient hypotension in animals and humans (7, 9, 12-14, 23, 24). However, the underling mechanisms of the depressor response remain to be controversial. Muirhead *et al*. (9) reported that the rapid intravenous injection of a small volume (~1 ml/kg) of 10% HTS produced a transient hypotension lasting for several minutes. It was considered that the rapidly injected volume of HTS reached the coronary artery without sufficient dilution from admixture with blood or from fluid uptake in the lung and inhibited cardiac pumping function (9, 23, 24). Direct vascular effects of HTS, an increase in pulmonary vascular resistance, and a decrease in systemic vascular resistance were also suggested as a major mechanism for such a depressor response (14). However, it was reported that the rapid infusion of HTS elicited hypotension through a neural reflex with the afferent limb of pulmonary C-fibers of the vagus and the efferent limb of sympathetic

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adrenergic fibers. The incremental response of C-fiber firing to the intravenous HTS was recorded (12), and α-adrenoceptor blockade abolished the HTS-induced hypotension (13).

Although the precise mechanisms of the transient hypotension are not yet clarified, the intravenous infusion of 7.2-7.5% HTS at a rate of 1 ml/kg/min for 4-5 min is widely used as the initial therapy for hypovolemia (7, 8). Accumulating evidence indicates that such a treatment improves circulatory shock after the short-lasting hypotension (see Ref. 8, for recent review). Therefore, it is still more important to clarify the mechanisms of the transient hypotension. Here the authors reported that a slow infusion of a very small volume of 2-10% HTS at a rate of 0.3 ml/kg/min for 1 min produced a marked depressor response by 10-70 mmHg through a neural reflex mechanism.

Materials and Methods

Animal and Surgical Procedures

All experiments were performed in strict accordance with the Guiding Principles for the Care and Use of Animals in the Field of Physiological Sciences by the Physiological Society of P.R. China. Male Wistar rats weighing 280-330 g were used. The rat was first placed in a glass jar where it inspired a mixture of 2% halothane in oxygen-enriched air for 5-10 min. After the induction of anesthesia, an endotracheal tube was introduced orally, and the rat was ventilated artificially *via* a volume-controlled rodent respirator (Model 683; Harvard Apparatus, South Natick, MA, USA). The respiratory rate was controlled at 1.5 Hz. According to Ono *et al*. (11), anesthesia was maintained through the use of 1.2% halothane during surgical procedures and 0.6% halothane during data recording. Polyethylene tubing (PE-50; Becton Dickinson, Parsippany, NJ, USA) were placed in the right common carotid artery and both femoral veins. The tip of the intracarotid cannula was advanced in the aortic arch. Pancuronium bromide (0.8 mg/kg/h, I.V.) was administered to eliminate spontaneous muscle activity. Arterial blood gases were monitored with a blood gas analyzer (IL-13064; Instrumentation Laboratory, Lexington, MA, USA). Body temperature was maintained at 37°C with a heating pad. For the prevention of dehydration during experiments, physiologic, *i.e.*, 0.97%, saline was continuously infused at a rate of 5 ml/kg/h with a syringe pump (CFV-3200; Nihon Kohden, Tokyo, Japan). For measurement of systemic arterial pressure (SAP), a 2-Fr catheter-tip micromanometer (SPC-320; Millar Instruments, Houston, TX, USA) was placed in the aortic arch through the right femoral artery.

Experimental Protocols

Preliminary to the present study, the authors checked the reproducibility of the depressor response to intravenous HTS infusion, and then found that repeated infusion of more concentrated HTS at shorter intervals produced smaller responses. An interval of 2 h restored the sensitivity of SAP to intravenous HTS infusion. No significant difference in SAP responses to 9.7% NaCl solutions was found between the 2 trials repeated at intervals of 2 h (n = 10). Therefore, according to Nishida *et al*. (10), a maximum of two repeated measurements of SAP responses to HTS solutions were made at intervals of 2 h for any given rat.

Protocol 1: Effect of Different Concentrations of NaCl Solutions

Before bilateral cutting of vagi and aortic depressor nerves and isolation of both carotid sinuses, the following concentrations of NaCl solutions were infused into the femoral vein at a rate of 0.3 ml/kg/min for 1 min with syringe pump: 0.97%, 1.5%, 2%, 4%, 6% and 9.7%. For each rat, only one trial of HTS solutions was made 30 min after the control trial of the physiologic saline, *i.e.*, 0.97% NaCl solution.

In another set of rats (n = 5 for each concentration), before and at the end of infusion, and 2 h after infusion, 0.1 ml of arterial blood were collected through the carotid cannula for measurement of serum osmolality by freezing-point determination (model 110; Fiske Associates, Norwood, MA, USA).

Protocol 2: Comparison of Intravenous and Intraaortic Infusions

To evaluate the effect of different routes of HTS administration, the authors measured the SAP responses to intravenous and intraaortic infusion of 9.7% NaCl solutions at a rate of 0.3 ml/kg/min for 1 min. On each rat, the two infusion routes were tested in random order at intervals of 2 h. The magnitude and latency of the response were then analyzed.

Protocol 3: Effect of Vagotomy

To examine the effect of vagotomy on the HTS-induced hypotension, the SAP responses to the intravenous infusion of 9.7% NaCl solution were measured at a rate of 0.3 ml/kg/min for 1 min before and at 2 h after bilateral cervical vagotomy.

Protocol 4: Effects of Isolation of Carotid Sinuses and Baroreceptor Reflex

To investigate the effect of the arterial baroreflex

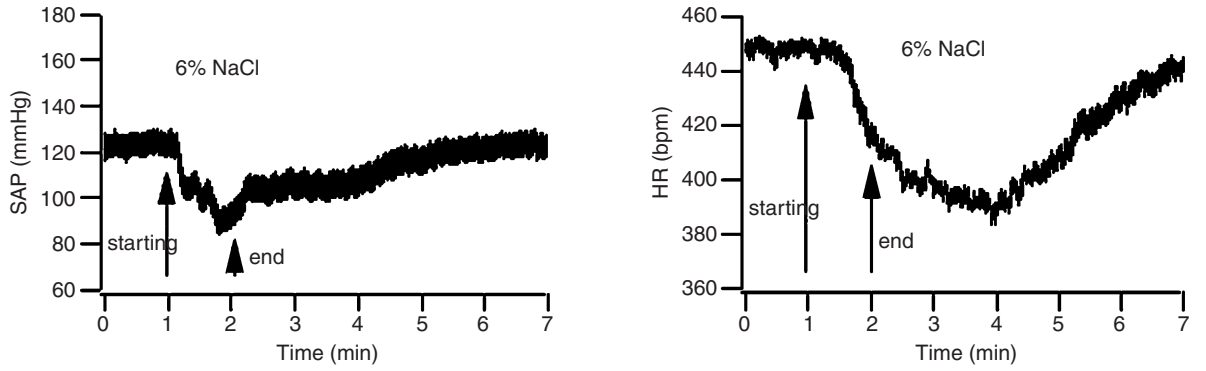

Fig. 1. A representative example of depressor responses to hypertonic saline (HTS). Approximately 10 sec after a start of the intravenous infusion of 6% HTS, a rapid fall in systemic artery pressure (SAP) and decrease in heart rate (HR) appeared and lasted for about 3 min.

on the HTS-induced hypotension, the SAP responses were measured under the closed- and open-loop conditions of the arterial baroreflex while intravenously infusing 9.7% NaCl solution at a rate of 0.3 ml/kg/min for 1 min. As described previously (17-19), on each rat, we could repeatedly alternate between open- and closed-loop conditions of the baroreflex even after surgical isolation of baroreceptor regions. Briefly, the external carotid artery was ligated at its root of the bifurcation of the common carotid artery, and then the internal carotid and pterygopalatine arteries were embolized with two ball bearings of 0.8 mm diameter (17). Two short polyethylene tubings (PE-50) were placed into both carotid sinuses and connected to a fluid-filled transducer (DX-200; Viggo-Spectramed, Singapore) and to a custom-made servo-controlled pump system based on an electromagnetic shaker and power amplifier (ARB-126; AR Brown, Osaka, Japan). A servo-controlled pump was used to impose various pressures on carotid sinus baroreceptor region. To reproduce the closed-loop conditions of the arterial baroreflex after isolation of carotid sinuses, the feedback loop was closed using with the servo-controlled pump system (17). A dedicated laboratory computer (PC-9821 Ap; NEC, Tokyo, Japan) in real time commanded the power amplifier to make carotid sinus baroreceptor pressure (BRP) identical with SAP by means of a digital-to-analog converter (DA 12-4-98; Contec, Osaka, Japan), while digitizing SAP at a rate of 2 kHz through a 12-bit analog-to-digital converter (AD12-16D-98H; Contec). Using this technique, the same pressure waveform was imposed as SAP on the carotid sinus baroreceptors in the frequency range up to 10 Hz. On the other hand, under the open-loop conditions, the BRP constant was kept at the same level as the operating SAP of the closed-loop system. For each rat, 2 trials of HTS infusions under the closed- and open-loop conditions of the arterial baroreflex were performed in random order at intervals of 2 h.

Protocol 5: Effect of Sympathetic Blokade

To examine whether the HTS-induced hypotension was mediated through sympathetic efferents, the SAP response in the vagotomized rat was measured under open-loop conditions of arterial baroreflex before and at 2 h after bretylium tosylate (12 mg/kg, I.V.), while intravenously infusing 9.7% NaCl solution at a rate of 0.3 ml/kg/min for 1 min. Carotid sinus BRP was kept constant at the baseline level of SAP. Bretylium tosylate is a bromobenzyl quaternary ammonium compound which selectively accumulates in sympathetic ganglia and their postganglionic adrenergic neurons where it inhibits norepinephrine release by depressing adrenergic nerve terminal excitability (2). Bretylium tosylate blocks the release of norepinephrine in response to neuron stimulation, but has less effect on the baseline level of SAP unlike ganglionic blockers such as trimethapan, hexamethonium, and chlorisondamine (15).

Data Analysis

The physiological data digitized at 100 Hz through the analog-to-digital converter were stored on a hard disk. The peak depressor response to HTS was defined as the difference between the baseline and minimum levels of SAP after HTS infusion. The baseline measurement was taken from the average for 1 min. The latency of the depressor response to HTS was defined as the lag time from the start of its infusion to the point of time at which SAP became lower than the mean-3 SD of the baseline SAP. The effect of different concentrations of HTS was examined by a one-way ANOVA. Differences in paired measurements under

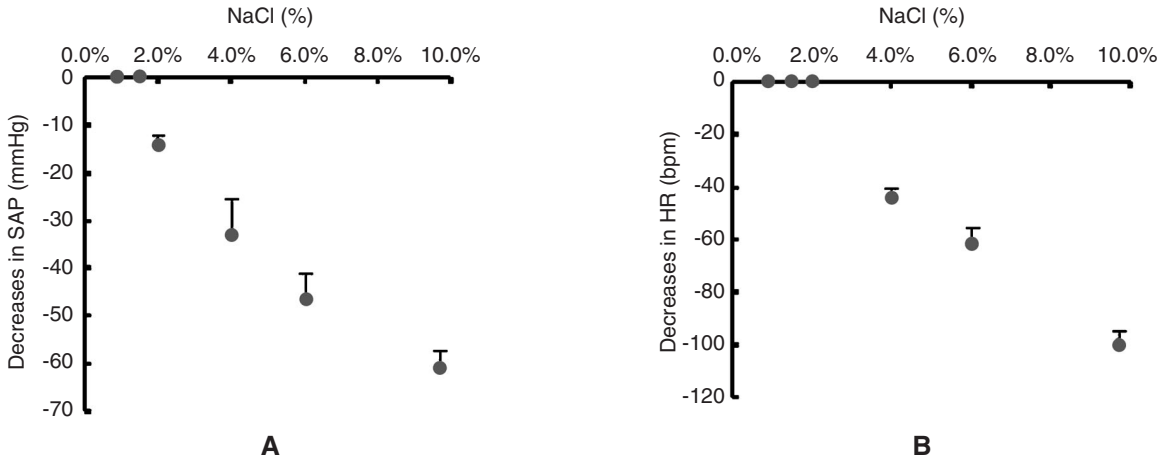

Fig. 2. The relationship between the magnitude of the depressor or bradycardium response and the concentration of HTS (n = 25 for 9.7% NaCl, n = 5 for each trial of HTS). A and B indicated that there was a threshold concentration of HTS for the depressor and bradycardiac response between 1.5% and 2%, and that the magnitude of response increased in a concentration-dependent manner.

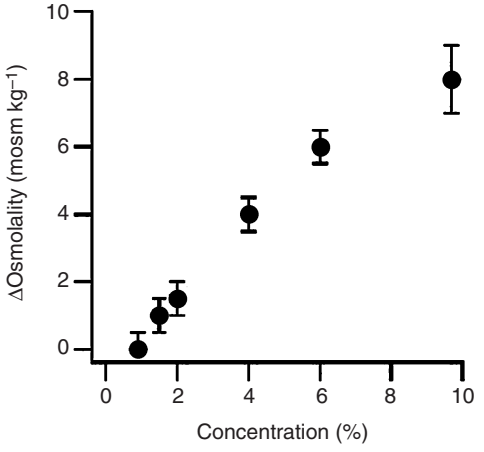

Fig. 3. The osmolality change to different concentrations of intravenous HTS in rats (n = 32). Intravenous infusions of 1.5%-9.7% HTS at a rate of 0.3 ml/kg/min for 1 min resulted in the increase in the osmolality of the arterial blood sampled at the ascending aorta by 1-8 mOsm/kg (n = 5 for each concentration). This increase in the osmolality disappeared 2 h after infusion.

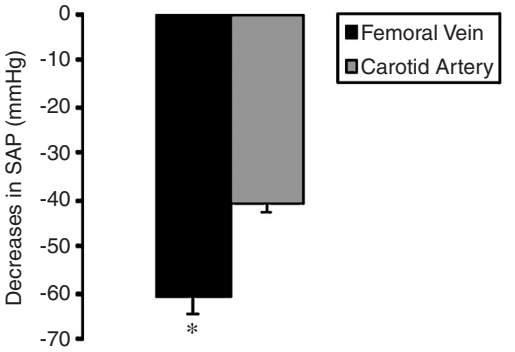

Fig. 4. The magnitude of the depressor response to intravenous and intraaortic 9.7% NaCl (n = 10). The magnitude of the depressor response to intravenous HTS was significantly larger than that to intraaortic HTS. Each bar is expressed as the means ± SD. *, $P < 0.05$ indicate a significant difference.

two conditions were tested by paired t-tests. Differences were considered significant at $P < 0.05$. Values are expressed as means ± SD.

Results

Effects of Different Concentrations of HTS

Shown in Fig. 1 is a representative example of depressor response of HTS. Approximately 10 sec after a start of the intravenous infusion of 6% HTS, a rapid fall in SAP and decrease in heart rate (HR) appeared and lasted for about 3 min. The relationship between the magnitude of the depressor and bradycardiac responses and the concentration of HTS indicated the following: [1] There was a threshold concentration of HTS for the depressor and bradycardiac responses between 1.5% and 2%; [2] The magnitude of response increased in a concentration-dependent manner (Fig. 2A and B, n = 25 for 0.97% NaCl, n = 5 for each trial of HTS). Intravenous infusions of 1.5%-9.7% HTS at a rate of 0.3 ml/kg/min for 1 min resulted in the increase in the osmolality of the arterial blood sampled at the ascending aorta by 1-8 mOsm/kg (Fig. 3, n = 5 for each concentration). This increase in the osmolality disappeared 2 h after infusion.

Depressor Responses to Intravenous and Inraaortic HTS

As illustrated in Fig. 4, the magnitude of the

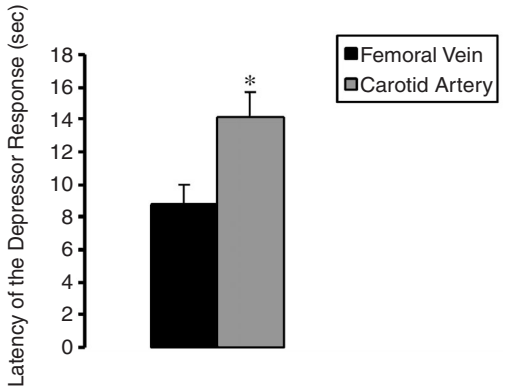

Fig. 5. The latency of the depressor response to intravenous and intraaortic 9.7% NaCl (n = 10). The latency of the depressor response to intravenous HTS was significantly shorter than that to intraaortic HTS (*, $P < 0.05$).

depressor response to intravenous HTS (9.7% NaCl) was significantly larger than that of the intraaortic HTS (ΔSAP, -52.7 ± 3.7 versus -40.4 ± 2.3 mmHg, n = 10, $P < 0.05$). The latency of the depressor response to intravenous HTS was significantly shorter than that of the intraaortic HTS (Fig. 5, 8.8 ± 1.2 versus 14.2 ± 1.5 sec, n = 10, $P < 0.05$).

Effect of Vagotomy

Vagotomy did not affect the baseline level of SAP or HR. Although vagotomy attenuated the bradycardiac response to intravenous HTS of 9.7% NaCl (ΔHR, -65 ± 5 versus -52 ± 8 beats/min, n = 10, $P < 0.05$), there was no significant effect of vagotomy on HTS-induced hypotension (ΔSAP, -50 ± 4.9 versus -49 ± 5.8 mmHg, n = 10).

Effects of Isolation of Carotid Sinuses and Carotid Sinus Baroreflex

Shown in Fig. 6 is a representative example of the responses of SAP to the intravenous infusion of 9.7% NaCl solution while BRP was controlled to be identical with SAP (shown on the left side) and while BRP was kept constant at the baseline level of SAP (shown on the right side). While carotid sinuses were vascularly isolated and carotid sinus baroreflex was functioning (see the Methods section for details), the intravenous infusion of 9.7% NaCl solution produced an SAP fall by 52.1 ± 5.7 mmHg (Fig. 7, n = 20). The depressor response to intravenous HTS became significantly larger (ΔSAP, -68.4 ± 5.8 mmHg, $P < 0.05$), while carotid sinus BRP was kept constant at the baseline level of SAP. There was no significant difference in the baseline level of SAP before the HTS infusion between the closed- and open-loop conditions.

Effect of Sympathetic Blockade

We tested the effect of HTS before and 2 h after administration of bretylium tosylate. Although a transient rise of SAP was found after the intravenous injection of bretylium tosylate, SAP gradually returned to the baseline level within 20 min. The pharmacological blockade of the sympathetic efferent limb completely abolished both depressor and bradycardiac responses to 9.7% HTS (ΔSAP, -49.8 ± 4.2 versus -0.4 ± 3.6 mmHg; ΔHR, -58 ± 9 versus -1 ± 3 beats/min, n = 8).

Discussion

The effects of intravenous HTS solutions have been studied for years. Apparently, two inconsistent hemodynamic responses to HTS are reported; hypotension (5, 7) versus hypertension (1, 16). The difference in experimental preparations, which is based on the difference in the objectives, may account for these disparate findings. In the fields of critical care medicine and anesthesiology, the transient hypotension after acute HTS infusion is a clinically important focus of interest (7, 8). On the other hand, in the fields of research in hypertension and fluid homeostasis, a sustained pressor response to chronic HTS infusion and ingestion attracts a great deal of attention (3, 4). In the present study, our interest was focused on the acute depressor response to intravenous HTS.

We demonstrated that the intravenous infusion of a small volume of HTS elicited the neurogenic depressor response with an efferent limb of sympathetic vasomotor nerves. Although a precise mechanism for the afferent limb of the reflex remains unclear, the vagal afferent systems such as cardiopulmonary receptors (12) and the central osmosensitive regions such as hypothalamic nuclei (5) appear not to participate in the reflex. The result of latency analysis suggests that the cardiopulmonary sympathetic afferent is a possible sensory mechanism for intravenous HTS-induced hypotension.

Depressor Response to HTS

Although many earlier studies examined the depressor response to bolus HTS infusion, it seems that unsystematic methods yielded inconsistent conclusions. Even fundamental characteristics of the depressor response such as the dose-response relationship were not fully documented. Therefore, as the first step, it would be important to describe such characteristics. The authors examined the relationship between the concentrations of HTS and

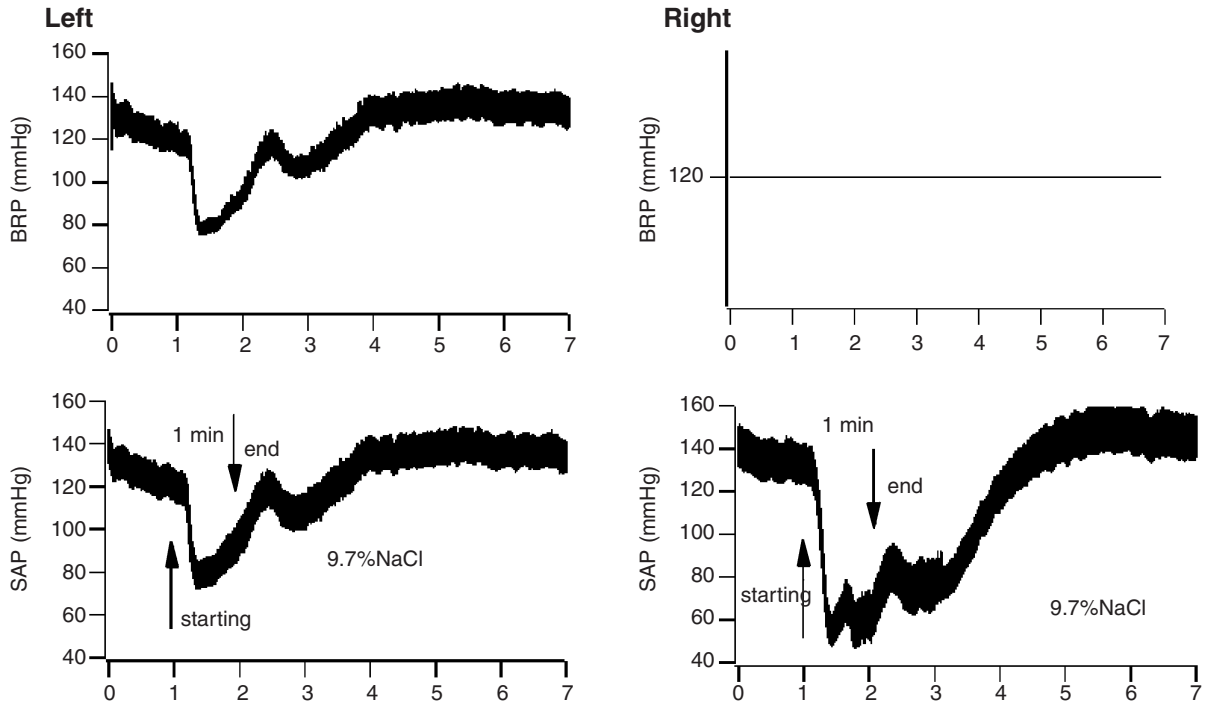

Fig. 6. A representative example of the responses of SAP to the intravenous infusion of 9.7% NaCl solution while carotid sinus baroreceptor pressure (BRP) was controlled to be identical with SAP, which was under closed-loop condition (shown on the left side) and while BRP was kept constant at the baseline SAP, which was under open-loop condition (shown on the right side).

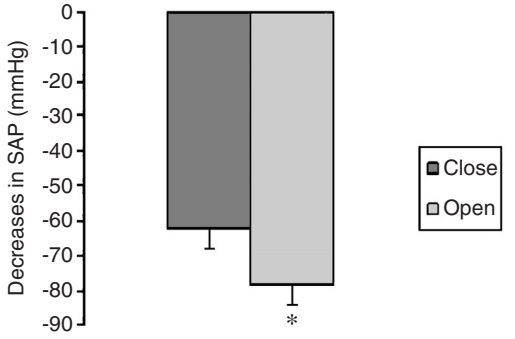

Fig. 7. There was significant difference (*, $P < 0.05$) in the responses of SAP to the intravenous infusion of 9.7% NaCl solution between the closed- and open-loop conditions ($n = 20$).

the depressor responses, while both the infusion rate and the total volume of solutions were fixed. Because rapid infusion of HTS could mask the depressor response with the incremental effect on cardiac output of an increase in preload, 0.3 ml/kg/min for the infusion rate and 0.3 ml/kg were selected for the total volume. Considering that the venous return of cardiac output of the anesthetized rat is about 100 ml/kg/min, it was assumed that the infusion of normal saline at this flow rate should have a negligible effect on preload. Therefore, the infusion protocol would be suitable for the purpose of the present study, *i.e.*, to clarify a mechanism for the transient depressor response to HTS.

To detect the peak increase in osmolality of arterial blood, the blood sample was taken from the ascending aorta immediately after HTS infusion. As shown in Fig. 3, the osmolality slightly increased in concentration-dependent fashion. Although Wildenthal *et al*. (23) showed that cardiac contractility was directly depressed by the increased osmolality (~400 mOsm/kg) of coronary arterial blood, the increase in osmolality produced by the present experimental protocols were too small to inhibit cardiac function.

Effect of Arterial Baroreflex

To quantitatively evaluate the raw effect of HTS on SAP, we addressed the effect of the arterial baroreflex. Because the arterial baroreflex masks or buffers the effect of HTS on SAP, the blockade of the arterial baroreflex function could reveal the raw effect of HTS. Several studies examined the effect of the arterial baroreflex by the comparison before and after baroreceptor deafferentation (5). However, as indicated by previous studies (18), such an approach is inappropriate for evaluation of the effect of the arterial baroreflex system deviate from its baseline, comparison

before and after baroreceptor deafferentation should manifest the effects of not only the arterial baroreflex but also the deviation of its operating point. On the other hand, in the present study, we could disrupt the arterial baroreflex function without altering its operating point at the baseline. From the result shown in Fig. 6, the total-loop gain factor of the arterial baroreflex was estimated using the following equation (18):

$$G = \frac{\Delta SAP_{open}}{\Delta SAP_{closed}} - 1$$

Where G is the gain factor, ΔSAP_{open} and ΔSAP_{closed} are the depressor responses to HTS under the open- and closed-loop conditions of the arterial baroreflex, respectively. Although the gain factor is estimated to be 0.3 in the present study, the gain factor was reported to be 2-2.5 in the previous study (17), where ΔSAP_{open} and ΔSAP_{closed} were the depressor responses to head-up tilting under the open- and closed-loop conditions. The differences in the estimated values suggest the possibility that HTS inhibits the arterial baroreflex. The action site of HTS to inhibit the arterial baroreflex is assumed not to be located in carotid sinuses, which were isolated in our experimental preparation.

Neural Reflex Hypotension

From the result of the pretreatment with bretylium tosylate, intravenous HTS is considered to initiate a neural reflex hypotension with an efferent limb of sympathetic vasomotor fibers. Several earlier studies also report that the depressor response to HTS is completely abolished by α-adrenergic blockade (13) or transaction of the cervical spinal cord (5). They suggest that the depressor response is mediated by a sympathoinhibitory reflex. However, the neural reflex shown by these studies appeared to be different from ours, because their reflex is significantly attenuated or completely abolished by cervical vagotomy and is not influenced by baroreceptor deafferentation.

In the present study, no effect of vagotomy on HTS-induced hypotension suggests no role of vagal afferents from the cardiopulmonary (12) or hepatoportal region (6). The central receptor responding to HTS (5) is an unlikely sensory mechanism, because intravenous HTS evoked the depressor response with a larger magnitude and a shorter latency than HTS infusion into the aortic arch. A plausible explanation for the lack of effect of vagotomy and for the larger magnitude and the shorter latency in the depressor response to intravenous HTS is that there is a sensory mechanism *via* sympathetic afferents for HTS between the vena and the left ventricle (22). A peripheral osmoreceptor-afferent pathway not going through the vagus but through the spinal cord is reported by Vallet *et al*. (21) and Stoppini and Baertschi (20). They show that the response of the hypothalamoneurohypophysial system to hepatoportal HTS administration is not abolished by bilateral cervical vagotomy but by the injection of lidocaine into the spinal cord at thoracic levels. Alhtough the authors cannot determine the receptor site from the present results, it is speculated that the depressor response to intravenous HTS is the sympathosympathetic neural reflex with sympathetic cardiopulmonary afferents and vasomotor efferents.

The bradycardiac responses to HTS were attenuated to be 80% after vagotomy; on the other hand, sympathetic blockade completely abolished the responses. Therefore, the main efferent pathway for the bradycardiac responses was also considered to be sympathetic efferents.

In summary, the effects of the intravenous infusions of 0.97%-9.7% NaCl solutions in anesthetized rats were examined in this study. Intravenous infusions of HTS produced the transient hypotension lasting for several min. The depressor response to HTS was not abolished by bilateral cervical vagotomy; intravenous HTS evoked the depressor response with a larger magnitude and a shorter latency than intraaortic HTS. Disruption of the arterial baroreflex augmented HTS-induced hypotension. The gain factor of the arterial baroreflex was reduced by HTS. Pretreatment with bretylium tosylate completely abolished the depressor response without affecting the baseline of SAP. These results suggest that the depressor response to intravenous HTS is the sympathosympathetic neural reflex with cardiopulmonary afferents and vasomotor efferents.

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References

1. Antunes, V.R., Yao, S.T., Pickering, A.E., Murphy, D. and Paton, J.E. A spinal vasopressinergic mechanism mediated by hyperosmolality-induced sympathoexcitation. *J. Physiol*. 576: 569-583, 2006.
2. Conway, J., Lauwers, P. and Hoobler, S.W. A sympathetic blocking agent, bretylium tosylate (Darenthin), in the treatment of hypertension. *J. Lab. Clin. Med*. 57: 199-205, 1961.
3. Frithiof, R., Mats, R., Johan, V., Stefan, E. and Hans, H. Comparison between the effects on hemodynamic responses of central and peripheral infusion of hypertonic NaCl during hemorrhage in conscious and isoflurane-anesthetized sheep. *Shock* 26: 77-86, 2006
4. Giusti-Paiva, A., Martinez, M.R., Bispo-Da-Silva, L.B., Salgado, M.C., Elias, L.L. and Antunes-Rodrigues, J. Vasopressin mediates the pressor effect of hypertonic saline solution in endotoxic shock. *Shock* 27: 416-421, 2007.

5. Holland, R.C., Sundsten, J.W. and Sawyer, C.H. Effects of intracarotid injections of hypertonic solutions on arterial pressure in the rabbit. *Circ. Res*. 7: 712-720, 1959.
6. Kabashi, M. and Adachi, A. Chemosensitivity of neurons in the dorsal motor nucleus of the vagus that responded to portal infusion of hypertonic saline in rats. *Brain Res. Bull*. 38: 11-15, 1995.
7. Kreimeier, U. and Messmer, K. Small-volume resuscitation: from experimental evidence to clinical routine. Advantages and disadvantages of hypertonic solutions. *Acta Anaesthesiol. Scand*. 46: 625-638, 2002.
8. Krausz, M.M. Initial of resuscitation of hemorrhagic shock. *World J. Emerg. Surg*. 27: 1-14, 2006.
9. Muirhead, E.E., Lackey, R.W., Bunde, C.A. and Hill, J.M. Transient hypotension following rapid intravenous injections of hypertonic solutions. *Am. J. Physiol*. 151: 516-524, 1947.
10. Nishida, Y., Sugimoto I., Morita, H., Murakami, H., Hosomi, H. and Bishop U.S. Suppression of renal sympathetic nerve activity during portal vein infusion of hypertonic saline. *Am. J. Physiol*. 274: R97-R103, 1998.
11. Ono, A., Kuwaki, T., Kumada, M. and Fujita, T. Differential central modulation of the baroreflex by salt loading in normotensive and spontaneously hypertensive rats. *Hypertension* 29: H326-H332, 1997.
12. Pisarri, T.E., Jonzon, A., Coleridge, H.M. and Coleridge, J.C. Intravenous injection of hypertonic NaCl solution stimulates pulmonary C-fibers in dogs. *Am. J. Physiol.* 260: H1522-H1530, 1991.
13. Rainzer, A.E., Costin, J.C., Croke, R.P., Bishop, J.B., Inglesby, T.V. and Skinner, N.S. Jr. Reflex, systemic and local hemodynamic alterations with experimental hyperosmolality. *Am. J. Physiol*. 224: 1327-1333, 1973.
14. Read, R.C., Johnson, J.A., Vick., J.A. and Meyer, M.W. Vascular effects of hypertonic solutions. *Circ. Res*. 8: 538-548, 1960.
15. Santajuliana, D., Hornfeldt, B.J. and Osborn, J.W. Use of ganglionic blockers to assess neurogenic pressor activity in conscious rats. *J. Pharmacol. Toxicol. Methods* 35: 45-54, 1996.
16. Sasaki, Y., Fujimura, M., Furukawa, M. and Kubo, T. Sensitivity of pressor response to central hypertonic saline is greatly enhanced even in pre-hypertensive spontaneously hypertensive rats. *Neurosci. Lett*. 399: 255-258, 2006.
17. Sato, T., Kawada, T., Inagaki, M., Shishido, T., Sugimachi, M. and Sunagawa, K. Dynamics of sympathetic baroreflex control of arterial pressure in rats. *Am. J. Physiol*. 285: R262-R270, 2003.
18. Sato, T., Kawada, T., Miyano, H., Shishido, T., Inagaki, M., Yoshimura, R., Tatewaki, T., Sugimachi, M., Alexander, J. Jr. and Sunagawa, K. New simple methods for isolating baroreceptor regions of carotid sinus and aortic depressor nerves in rats. *Am. J. Physiol*. 276: H326-H332, 1999.
19. Sato, T., Kawada, T., Sugimachi, M. and Sunagawa, K. Bionic technology revitalize native baroreflex function in rats with baroreflex failure. *Circulation* 106: 730-734, 2002.
20. Stoppini, L. and Baertschi, A.J. Activation of portal-hepatic osmoreceptors in rats: role of calcium, acetylcholine and cyclic AMP. *J. Auton. Nerv. Syst*. 11: 297-308, 1984.
21. Vallet, P.G. and Baertschi, A.J. Spinal afferents for peripheral osmoreceptors in the rat. *Brain Res*. 239: 271-274, 1982.
22. Wang, W.Z., Gao, L., Pan, Y.X., Zucker, I.H. and Wang, W. Differential effects of cardiac sympathetic afferent stimulation on neurons in the nucleus tractus solitarius. *Neurosci. Lett*. 409: 146-150, 2006.
23. Wildenthal, K., Mierzwiak, D.S. and Michell, J.H. Acute effects of increased serum osmolality on left ventricular performance. *Am. J. Physiol*. 216: 898-904, 1969.
24. Wildenthal, K., Skelton, C.L. and Coleman, H.N. Cardiac muscle mechanics in hyperosmotic solutions. *Am. J. Physiol.* 217: 302-306, 1969.