Medetomidine Suppresses Cardiac and Gastric Sympathetic Nerve Activities but Selectively Activates Cardiac Vagus Nerve

Shuji Shimizu, MD, PhD; Tsuyoshi Akiyama, MD, PhD; Toru Kawada, MD, PhD; Atsunori Kamiya, MD, PhD; Michael James Turner, PhD; Hiromi Yamamoto, MD, PhD; Toshiaki Shishido, MD, PhD; Mikiyasu Shirai, MD, PhD; Masaru Sugimachi, MD, PhD

Background: To identify a pharmacological agent that can selectively activate cardiac vagus nerve for potential use in vagal activation therapy against heart failure, the effects of medetomidine on autonomic nerve activities in both the heart and stomach were examined.

Methods and Results: In anesthetized rabbits, microdialysis probes were implanted into both the right atrial and gastric walls. Dialysate acetylcholine (ACh) and norepinephrine (NE) concentrations were measured by high-performance liquid chromatography. First, the effects of 100 μg/kg of intravenous medetomidine on vagal ACh and sympathetic NE releases were examined. Medetomidine significantly increased cardiac ACh release (4.7 ± 1.1 to 7.8 ± 0.9 nmol/L, P < 0.05), but suppressed gastric ACh release (8.0 ± 2.6 to 3.5 ± 1.5 nmol/L, P < 0.01). In contrast, medetomidine suppressed both cardiac and gastric NE releases. Second, the effects of medetomidine on ACh releases induced by electrical vagus nerve stimulation (VNS; 10 Hz) were examined. Electrical VNS significantly increased both cardiac (6.7 ± 1.2 to 14.8 ± 1.8 nmol/L, P < 0.01) and gastric (3.8 ± 0.8 to 181.3 ± 65.6 nmol/L, P < 0.01) ACh releases. Medetomidine did not alter the VNS-induced increases in ACh release.

Conclusions: Medetomidine suppresses both cardiac and gastric sympathetic nerve activities. In contrast, medetomidine activates cardiac vagus nerve but inhibits gastric vagal activity. Medetomidine might be one of the potential pharmacological agents for vagal activation therapy against heart failure without the risk of gastric adverse effects. (Circ J 2014; 78: 1405–1413)

Key Words: Acetylcholine; α2-adrenergic agonist; Norepinephrine; Sympathetic nerve activity; Vagus nerve activity
allows monitoring of ACh and NE releases as indices of organ-specific autonomic nerve activities. In the present study, we applied the microdialysis technique to both the heart and stomach of rabbits and examined the effects of medetomidine on organ-specific autonomic nerve activities.

**Methods**

**Surgical Preparation**
Animal care was provided in accordance with the *Guiding Principles for the Care and Use of Animals in the Field of Physiological Sciences* published by the Physiological Society of Japan. All protocols were approved by the Animal Subject Committee of the National Cerebral and Cardiovascular Center. Twenty-four Japanese white rabbits weighing 2.5–3.2 kg were used in this study. Anesthesia was initiated by an intravenous injection of pentobarbital sodium (50 mg/kg) via the marginal ear vein, and then maintained at an appropriate level by continuous intravenous infusion of α-chloralose and urethane (16 mg·kg⁻¹·h⁻¹ and 100 mg·kg⁻¹·h⁻¹, respectively). An adequate anesthesia level was confirmed by loss of the ear pinch response. The animals were intubated and ventilated mechanically with room air mixed with oxygen. The respiratory rate and tidal volume were set at 30 cycles/min and 15 ml/kg, respectively. Systemic arterial pressure was monitored by a catheter inserted into the femoral artery. Heparin sodium (10 IU·kg⁻¹·min⁻¹) was infused to prevent blood coagulation in the femoral artery. In a post-mortem examination, the right atrial lumen and the gastric cavity, as described in the *Dialysis Technique* section, were exposed through a midline cervical incision and sectioned to the right atrial myocardium near the sinoatrial node, which has the richest vagal innervation in the heart. Another dialysis probe was implanted into the anterior wall of the stomach because peristaltic movement was relatively smaller than the other part of the gastrointestinal tract. After implantation, these dialysis probes were perfused with Ringer’s solution (NaCl 147 mmol/L, KCl 4 mmol/L, CaCl₂ 3 mmol/L) alone for NE measurement, or with Ringer’s solution containing a cholinesterase inhibitor, eserine (100 μmol/L), for ACh measurement, at a speed of 2 μl/min using a microinjection pump (CMA/102; Carnegie Medicin, Stockholm, Sweden). Experimental protocols were started 2 h after implantation of the dialysis probes. The dead space between the dialysis membrane and the sample tube was taken into account at the beginning of each dialysate sampling. Four microliters of phosphate buffer (pH 3.5) was added to each sample tube before dialysate sampling, and each dialysate sampling period was set at 10 min (1 sample volume=40 μl). In the supplementary protocol, 8-μl of phosphate buffer was added to each sample tube, and each dialysate sampling period was set at 20 min (1 sample volume=40 μl). The dialysate ACh or NE concentration was analyzed by high-performance liquid chromatography, as described previously.

**Experimental Protocols**

**Protocol 1 (n=13)** We investigated the effects of intravenous medetomidine on both cardiac and gastric vagal ACh (n=7) and sympathetic NE (n=6) releases. First, 10-min baseline dialysate samples were collected under baseline conditions. Thereafter, 100 μg/kg of medetomidine, which has been shown to increase the cardiac dialysate ACh concentration, was injected intravenously via the femoral vein. After hemodynamic stabilization, dialysate samples were collected for 10 min (20 μl). Immediately after the second sampling, intravenous infusion of phenylephrine was started (4.3±0.7 μg·kg⁻¹·min⁻¹) to restore mean arterial pressure to the baseline level because a decrease in mean arterial pressure during the second sampling might have affected sympathetic and vagal outflows through the arterial baroreflex. After hemodynamic stabilization, dialysate samples were again collected for 10 min.

**Protocol 2 (n=6)** We investigated the effect of medetomidine on both cardiac and gastric ACh releases induced by electrical stimulation of bilateral cervical vagus nerves. Because there was a difference in vagal innervations between the right atrium and anterior wall of the stomach, bilateral vagus nerves were exposed through a midline cervical incision and sectioned at the neck region to perform a simultaneous stimulation to both the heart and stomach. A pair of bipolar stainless steel electrodes was attached to the efferent side of each vagus nerve. The nerves and electrodes were immobilized using a quick-curing silicone gel (Kwik-Sil; World Precision Instruments, Inc, FL, USA). After sampling the baseline dialysates, bilateral efferent vagus nerves were simultaneously stimulated at a frequency of 10 Hz using a digital stimulator (SEN-7203; Nihon Kohden, Japan). The pulse duration and amplitude of nerve stimulation were set at 1 ms and 10 V, respectively.

**Table.** Doses of Intravenous Phenylephrine Infusion Used to Maintain Mean Arterial Pressure at Baseline Level

<table>
<thead>
<tr>
<th>Phenylephrine (μg·kg⁻¹·min⁻¹)</th>
<th>Baseline after vagotomy</th>
<th>Bil. VNS</th>
<th>Medetomidine + Bil. VNS</th>
<th>Medetomidine + Bil. VNS + C6</th>
</tr>
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<tr>
<td>(n=6)</td>
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<tr>
<td>0</td>
<td>13.1±1.6</td>
<td>9.1±1.8</td>
<td>9.0±2.5</td>
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Bil. VNS, bilateral vagus nerve stimulation; C6, hexamethonium.
Cardioselective Vagal Activation of Medetomidine

Supplementary protocol (n=5) We investigated the effects of intravenous atipamezole, an α₂-adrenergic antagonist, on both medetomidine-induced cardiac and gastric vagal ACh and sympathetic NE responses. First, 20-min baseline dialysate samples were collected under baseline conditions. Thereafter, 100 μg/kg of medetomidine was injected intravenously via the femoral vein. After hemodynamic stabilization, dialysate samples were collected for 20 min (40 μl). Immediately after the second sampling, 2.5 mg/kg of atipamezole was injected intravenously. After hemodynamic stabilization, dialysate samples were again collected for 20 min.

Statistical Analysis
All data are presented as mean ± standard error. Heart rate and mean arterial pressure were compared by using one-way repeated measures analysis of variance (ANOVA) followed by a Holm’s test. After logarithmic transformation, dialysate ACh and NE concentrations were also compared by using one-way repeated measures ANOVA followed by a Holm’s test. In the supplementary protocol, after logarithmic transformation, dialysate ACh and NE concentrations were compared by using one-way repeated measures ANOVA followed by a Dunnett’s test against baseline values. Differences were con-

Figure 1. Effects of 100 μg/kg of medetomidine on heart rate (A) and mean arterial pressure (B) (n=13). All data are presented as mean ± SE. iv, intravenous injection. *P<0.01.
Results

Protocol 1
An intravenous injection of 100μg/kg of medetomidine significantly decreased the heart rate from 273±5bpm at baseline to 185±6bpm (P<0.01) (Figure 1A), and the mean arterial pressure from 87±3mmHg to 52±2mmHg (P<0.01) (Figure 1B). This dose of medetomidine significantly increased the cardiac dialysate ACh concentration from 4.7±1.1nmol/L at baseline to 7.8±0.9nmol/L (P<0.05), but decreased the gastric dialysate ACh concentration from 8.0±2.6nmol/L at baseline to 3.5±1.5nmol/L (P<0.01) (Figure 2A). The medetomidine injection significantly decreased the cardiac dialysate NE concentration from 244±36pmol/L at baseline to 111±16pmol/L (P<0.01) and also the gastric dialysate NE concentration from 196±64pmol/L at baseline to 58±27pmol/L (P<0.01) (Figure 2B).

After the medetomidine injection and dialysate sampling, infusion of phenylephrine restored the mean arterial pressure to the baseline level (90±3mmHg, not significant vs. baseline) and decreased the heart rate significantly (132±7bpm, P<0.01 vs. mediomidine alone) (Figures 1A, B). After the medetomidine injection, infusion of phenylephrine increased the cardiac dialysate ACh concentration to a significantly higher level than that of medetomidine alone (22.3±1.5nmol/L, P<0.01), but it did not change the cardiac and gastric dialysate NE concentration (3.5±1.1nmol/L, not significant vs. medetomidine alone) (Figure 2A). Infusion of phenylephrine subsequent to the medetomidine injection did not change the cardiac or gastric dialysate NE concentration (not significant vs. medetomidine alone), and both cardiac (106±17pmol/L, P<0.01 vs. baseline) and gastric dialysate NE concentrations (29±8pmol/L, P<0.01) were considered significant at P<0.05.
Cardioselective Vagal Activation of Medetomidine

Subsequent to the medetomidine injection under a 10-Hz vagal stimulation, an intravenous injection of 30 mg/kg hexamethonium bromide significantly reduced both the cardiac and gastric dialysate ACh concentrations (7.2±1.5 nmol/L and 9.7±2.7 nmol/L, respectively) (Figures 4A, B). However, the gastric dialysate ACh concentration remained higher than that of the baseline level (P<0.01 vs. baseline).

Protocol 2
The mean arterial pressure was maintained at the same level as that of the baseline by intravenous infusion of phenylephrine during VNS throughout the experiment (Figure 3A). Bilateral electrical VNS at a frequency of 10 Hz significantly decreased the heart rate from 265±10 bpm at baseline to 138±12 bpm (P<0.01) (Figure 3B). The 10-Hz VNS significantly increased the cardiac dialysate ACh concentration from 6.7±1.2 nmol/L at baseline to 14.8±1.8 nmol/L (P<0.01) (Figure 4A) and the gastric dialysate ACh concentration from 3.8±0.8 nmol/L at baseline to 181.3±65.6 nmol/L (P<0.01) (Figure 4B). Under a 10-Hz electrical VNS, injection of 100-μg/kg medetomidine did not alter the heart rate (146±14 bpm) (Figure 3B), and it did not affect the cardiac (13.6±2.2 nmol/L) or gastric (196.7±70.7 nmol/L) dialysate ACh concentration (Figures 4A, B).

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Supplementary Protocol
An intravenous injection of 100 μg/kg of medetomidine significantly increased the cardiac dialysate ACh concentration from 5.2±1.1 nmol/L at baseline to 8.4±1.4 nmol/L (P<0.01), but decreased the gastric dialysate ACh concentration from 6.4±1.8 nmol/L at baseline to 3.6±1.0 nmol/L (P<0.01) (Figure 5A). The medetomidine injection signifi-
Effects of Medetomidine on Vagal ACh Releases

The present study demonstrated that electrical stimulation of bilateral cervical vagus nerves at a frequency of 10 Hz significantly increased both the cardiac and gastric ACh releases. This result suggests that electrical stimulation of cervical vagus nerves might activate the whole vagal system. However, the extent of vagal activation might differ in various organs. Although baseline dialysate ACh concentrations in the heart and in the stomach did not differ (6.7±1.2 nmol/L and 3.8±0.8 nmol/L, respectively; not significant as found by an unpaired t-test), the dialysate ACh concentration during 10-Hz VNS was 12-times higher in the stomach (181.3±65.6 nmol/L) than that in the heart (14.8±1.8 nmol/L) (P<0.01 by an unpaired t-test). This difference in magnitude of a dialysate ACh response might reflect a difference in density of vagal innervation between the heart and stomach.

Discussion

Simultaneous monitoring of both the cardiac and gastric vagal ACh and sympathetic NE releases demonstrated that medetomidine enhanced cardiac ACh release but suppressed gastric ACh release to the stomach. In contrast, medetomidine significantly decreased the cardiac dialysate NE concentration from 472±88 pmol/L at baseline to 266±47 pmol/L (P<0.05) and also the gastric dialysate NE concentration from 381±116 pmol/L at baseline to 130±29 pmol/L (P<0.05) (Figure 5B). An intravenous injection of 2.5 mg/kg of atipamezole restored both the cardiac and gastric dialysate ACh concentrations to the baseline levels (6.0±1.2 and 7.6±2.6 nmol/L, respectively) (Figure 5A). Atipamezole also restored both the cardiac and gastric dialysate NE concentrations to the baseline levels (436±102 and 385±130 pmol/L, respectively) (Figure 5B).

Effects of Medetomidine on Vagal ACh Releases

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Cardioselective Vagal Activation of Medetomidine

reflects ACh release from postganglionic vagus nerve endings, and the peripheral effects of medetomidine on nerve endings should be small. Furthermore, the supplementary protocol demonstrated that medetomidine-induced vagal ACh responses in both the heart and stomach were almost completely diminished by an $\alpha_2$-adrenergic antagonist, atipamezole. Therefore, we think that medetomidine-induced vagal activation mainly depends on its central $\alpha_2$-adrenergic action.

In protocol 1, restoring the mean arterial pressure to baseline level using phenylephrine enhanced medetomidine-induced cardiac ACh release. As we have already demonstrated that medetomidine enhances cardiac ACh release through modulation of the baroreflex control, this vagotonic effect of medetomidine on the heart should be dependent on the baroreflex response. Robertson and Leslie showed that $\alpha_2$-adrenergic receptors are densely distributed in the nucleus tractus solitaries (NTS), where baroreceptor afferent nerves terminate. Grutu et al.

and the stomach. In clinical settings, although weaker electrical VNS at a lower frequency and lower voltage compared to the present study is used, electrical VNS might cause unexpected vagal activation in non-target organs, resulting in adverse effects.

In contrast to electrical VNS, vagal response to medetomidine differs in the heart and in the stomach. In protocol 1, 100 $\mu$g/kg of medetomidine significantly increased the cardiac ACh release but suppressed the gastric ACh release. As shown in protocol 2, medetomidine scarcely affected VNS-induced cardiac and gastric ACh releases, suggesting that the effects of medetomidine on vagus ganglion and postganglionic vagus nerve terminals were small. Furthermore, hexamethonium, which blocks ganglionic transmission between preganglionic and postganglionic neurons, almost completely suppressed the VNS-induced ACh releases. This finding suggests that dialysate ACh concentration monitored by microdialysis mainly reflects ACh release from postganglionic vagus nerve endings, and the peripheral effects of medetomidine on nerve endings should be small. Furthermore, the supplementary protocol demonstrated that medetomidine-induced vagal ACh responses in both the heart and stomach were almost completely diminished by an $\alpha_2$-adrenergic antagonist, atipamezole. Therefore, we think that medetomidine-induced vagal activation mainly depends on its central $\alpha_2$-adrenergic action.

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demonstrated that presynaptic α2-adrenergic receptors in the nucleus ambiguus are involved in baroreflex bradycardia. Thus, medetomidine might act on the NTS and/or the nucleus ambiguus, and exert this vagotonic effect on the heart. In contrast, the vagolytic effect on the stomach might depend on other pathways. Robertson and Leslie reported that α2-adrenergic receptors are also distributed in the dorsal motor nucleus (DMN) of the vagus, which contains preganglionic neurons that control gastric motility and secretion. As dexmedetomidine has been shown to inhibit gastric emptying and gastrointestinal transit in healthy volunteers, medetomidine might act on the DMN and exert vagolytic effects on the stomach. Although further investigations are needed to elucidate the sites of medetomidine action, the organ-specific vagal responses to medetomidine might be associated with different actions of medetomidine on the nuclei.

**Effects of Medetomidine on Sympathetic Nerve Activities**

In protocol 1, 100 μg/kg of medetomidine significantly suppressed both the cardiac and gastric NE releases. Thus, medetomidine might suppress the whole sympathetic nerve activities. The rostral ventrolateral medulla (RVLM) is known to serve as an important site in mediating the hypotensive and sedative effects of α2-adrenergic agonist, clonidine. Furthermore, in the supplementary protocol, an α2-adrenergic antagonist, atipamezole, blocked this medetomidine-induced suppression of sympathetic NE releases. Thus, medetomidine might act on α2-adrenergic receptors in the RVLM and exert sympatholytic effects to both the heart and stomach.

Restoring the mean arterial pressure to baseline level by infusing phenylephrine scarcely affected medetomidine-induced suppression of NE release both in the heart and stomach. It is possible that 100 μg/kg of medetomidine has already suppressed sympathetic nerve activities to the lowest level, leaving no room for further baroreflex-induced sympathetic suppression. This strong sympatholytic effect might be useful for the treatment of CHF as described in the Clinical Implications section.

**Clinical Implications**

Electrical VNS has recently become a new therapeutic option for CHF. However, electrical VNS sometimes causes gastrointestinal adverse effects. Approximately 10% of patients receiving VNS therapy for epileptic seizures complain of nausea. Sanossian and Haut reported chronic diarrhea associated with VNS. As shown in protocol 2, electrical stimulation of the cervical vagus nerve increases both cardiac and gastric ACh releases, and the augmented gastric ACh release might cause nausea and diarrhea in clinical settings. Furthermore, in an animal study, Cho et al. reported that intermittent electrical stimulation of the left cervical vagus nerve induced a 100% incidence of hemorrhagic ulcers in the glandular mucosa of rat stomachs. Thus, hemorrhagic gastric ulcer might be one of the most serious adverse effects caused by electrical VNS therapy in CHF patients, because CHF patients often receive concomitant anti-coagulation therapy, anti-platelet therapy, or both.

Organ-specific vagal activation is one strategy to reduce the above-mentioned adverse effects. Bianchi et al. have reported that endocardial atioventricular vagal stimulation significantly reduces the ventricular rate acutely during atrial fibrillation in humans. Thus, selective cardiac electrical VNS might be one of the most suitable approaches for vagal activation therapy in CHF patients, if the treatment effects of VNS are exclusively mediated by efferent vagal activation.

Another approach of vagal activation therapy in CHF patients is to use pharmacological agents. An ACh esterase inhibitor is a candidate for pharmacological vagal activation therapy. Because ACh esterase degrades ACh immediately after its release, an ACh esterase inhibitor will block ACh degradation and increase ACh in the synaptic cleft. Kubo et al. have reported that donepezil, an ACh esterase inhibitor against Alzheimer’s disease, significantly decreased plasma brain natriuretic peptide levels in patients with subclinical CHF. However, an ACh esterase inhibitor might also cause gastrointestinal adverse effects. Nausea and diarrhea are the most common adverse events related to donepezil therapy, which is similar to that caused by electrical VNS therapy. To prevent these gastrointestinal adverse events, we have to identify a new agent that activates cardiac vagus nerve without stimulating vagal activity in the gastrointestinal tract. However, there is a paucity of information on pharmacological agents that selectively activate the cardiac vagus nerve, partly because of the difficulty in selectively monitoring organ-specific vagus nerve activities. The microdialysis technique enables us to monitor organ-specific vagus nerve activities. The present study demonstrated that medetomidine selectively increased cardiac ACh release without augmenting gastric ACh release, suggesting that medetomidine is able to activate cardiac vagus nerve without stimulating gastric vagal activity. Medetomidine might be a more suitable agent than ACh esterase inhibitors for the treatment of CHF patients, although further investigations are required to examine the effects of medetomidine on other organs.

The sympatholytic effect of medetomidine might also be favorable for cardiac and gastric protection. Because sustained sympathetic overdrive contributes to progressive left ventricular dysfunction and promotes progressive left ventricular remodeling in CHF patients, inhibition of the sympathetic nerve system has been the cornerstone of drug therapy for CHF. Thus, we might be able to use medetomidine as well as β blockers to modify the augmented sympathetic tone in CHF. As medetomidine (or dexmedetomidine) has also been used as an anesthetic agent, sedation with medetomidine (or dexmedetomidine) might be beneficial for the intensive care of CHF patients. Furthermore, sympathetic overdrive also causes mucosal vasconstriction and reduces the mucosal blood flow in the stomach, potentially leading to gastric ulcers. Because 50–100 μg/kg of dexmedetomidine has an antiulcerative effect equivalent to 25 mg/kg of famotidine, sedation with medetomidine (or dexmedetomidine) might exert a gastroprotective effect in CHF patients while simultaneously conferring cardioprotection. Conversely, the sedative action of medetomidine might render this agent unsuitable for outpatient treatment.

**Study Limitations**

First, because ACh is degraded by ACh esterase immediately after release, the addition of eserine into the perfusate is required for measuring the in vivo release of ACh. The presence of eserine around the microdialysis fiber could have affected ACh release in the vicinity of the fiber.

Second, in protocol 2, gastric dialysate ACh concentration after hexamethonium injection was slightly but significantly higher than the post-vagotomy baseline level. Thus, the gastric dialysate ACh concentration might partly reflect ACh release from preganglionic nerves.

Third, medetomidine is a chiral imidazole derivative. Although hemodynamic and gastric secretory responses to medetomidine are known to be abolished by an α2-adrenergic antagonist, atipamezole, there is room for a possibility that imidazole receptors might also be involved in the cardiac vagal activation by medetomidine.

Finally, we did not examine both cardiac and gastric functions.
in the present study. According to previous papers, medetomidine can affect both cardiac and gastric functions as follows. Flacke et al. reported that the peak of the first derivative of systolic left ventricular pressure declined after intravenous administration of dexmedetomidine in anesthetized dogs. Savola et al. reported that medetomidine inhibited basal gastric acid and fluid output in conscious rats in a dose-dependent manner while in anesthetized rats, no effect was observed when it was administered intravenously. We need further investigations including chronic experiments to evaluate the effects of medetomidine on both cardiac and gastric functions in CHF conditions.

Conclusions

In the present in vivo study involving rabbits, while medetomidine suppressed both the cardiac and gastric NE releases, it enhanced cardiac ACh release but suppressed gastric ACh release through central actions. Medetomidine might be one of the potential pharmacological agents for vagal activation therapy against heart failure patients without the risk of causing gastric adverse effects.

Acknowledgments

This study was supported by a Grant-in-Aid for Scientific Research (23390415, 23592319) promoted by the Ministry of Education, Culture, Sports, Science and Technology of Japan, and by a Medical Research Promotion Grant from the Takeda Science Foundation, Japan.

Conflict of Interest

None declared.

References