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ORIGINAL PAPER

Acupoint dependence of depressor and bradycardic responses elicited by manual acupuncture stimulation in humans

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Abstract

The cardiovascular effects of the autonomic nervous system (ANS) are modulated by inputs from peripheral sensors and other brain regions. However, it currently remains unknown whether the manual acupuncture (MA) stimulation of different acupuncture points evokes different responses by the heart and vasculature, a phenomenon known as "site specificity". Sixty healthy subjects were randomly divided into a control group and MA stimulation groups at the lower leg, ear, abdomen, and forearm. MA was performed at 1 Hz for 2 min. A depressor response was observed only in the lower leg stimulation group, in which mean blood pressure significantly decreased from 83.4 ± 10.1 to 80.9 ± 11.7 mmHg ($p < 0.003$). A bradycardic response was elicited in all MA stimulation groups. There was no significant differences in the magnitude of the bradycardic response between groups. MA-induced cardiovascular responses, which may be mediated by the modulation of ANS, differ depending on acupuncture points.

Keywords Acupuncture · Blood pressure · Heart rate

Introduction

Acupuncture is an alternative non-pharmacological modality for the treatment of cardiovascular diseases with autonomic dysfunctions. We recently reported that electroacupuncture at the Ximen acupuncture point (acupoint) (WHO; PC4) elicited significant depressor and bradycardic responses [1]. The stimulation frequency of 1 Hz was optimal for inducing these cardiovascular responses. Nishijo et al. [2] also demonstrated that manual acupuncture (MA) at the PC4 acupoint for 30–60 s induced a bradycardic response, and pharmacological autonomic blockade abolished the heart rate response. MA or an electroacupuncture stimulation may activate somatic afferents [3] and affect cardiovascular regulatory function by modulating the autonomic nervous system (ANS).

According to the traditional acupuncture theory, the cardiovascular effects of acupuncture are site specific. For example, Tjen-A-Looi et al. [4] examined six sets of acupoints in anesthetized cats and demonstrated that electroacupuncture at the acupoints overlying the median nerve most effectively inhibited sympathoexcitation evoked by a chemosensitive afferent stimulation of the gallbladder. Gao et al. [5] also demonstrated that a MA stimulation of the ear had a more significant inhibitory effect on mean arterial pressure and heart rate than that of the lower leg and forearm. Uchida et al. [6] examined the effects on cerebral blood flow and mean arterial blood pressure of an acupuncture stimulation delivered to various areas, such as the brain

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stem and cervical, thoracic, lumbar and sacral segments. The findings obtained showed that the acupuncture stimulation delivered to the brain stem and cervical and lumbar segments increased mean arterial pressure, while that delivered to the thoracic segment decreased it. Uchida et al. [7] also reported that an acupuncture-like stimulation of the forelimb, chest, abdomen, or hindlimb decreased heart rate in anesthetized rats. No significant differences were noted in the magnitude or time course of heart rate responses between the areas of stimulation. In humans, Kurono et al. [8] found that an acupuncture stimulation called "the epifascial stimulation" (the needle is inserted perpendicular to the depth of the fascia without penetrating it and is pulled out immediately) at the Danzhong acupoint (WHO; CV17), but not the Zhongting acupoint (WHO; CV16), decreased heart rate and increased the power of the high-frequency component of heart rate variability. Minagawa et al. [9] also reported the site-specific, organ-selective effect of an epifascial acupuncture stimulation.

Although the majority of previous studies examined either blood pressure or heart rate responses to an acupuncture stimulation, blood pressure and heart rate may respond differently to an acupuncture stimulation [10]. Although the heart is governed by the vagal and sympathetic systems, the vasculature is mainly regulated by the sympathetic system. The blood pressure response may reflect the effects of acupuncture on the vasculature because vascular properties, not ventricular properties, predominantly contribute to blood pressure regulation [11]. To the best of our knowledge, the site specificity of MA for blood pressure and heart rate responses has not yet been systematically examined in humans. Therefore, the aim of the present study was to test the hypothesis that a MA stimulation to the ear, forearm, abdomen, and lower leg, which belong to different segments of the body and were previously reported to be the effective acupoints for cardiovascular responses, evokes different effects on blood pressure and heart rate. A clearer understanding of the acupoint specificity of cardiovascular effects will promote the potential use of acupuncture for the treatment of cardiovascular diseases with autonomic dysfunction.

Methods

Subject and experimental protocols

Sixty healthy volunteers (35 men and 25 women) participated in the present study. Subjects were randomly assigned to one of the following groups: the control group ($N=11$) and MA stimulation groups at the lower leg ($N=15$), ear ($N=10$), abdomen ($N=14$), and forearm ($N=10$). Subjects were requested to remain calm in a resting supine position for approximately 10 min to achieve a stable cardiovascular status before the trial. Disposable electrocardiogram (ECG) electrodes were then attached to the chest to monitor heart rate via a three-lead ECG telemeter (BSM-7201, Nihon Kohden Co., Tokyo, Japan). Mean blood pressure was recorded continuously from the left arm using an automatic blood pressure monitoring device with tonometry (BP-608, Omron Colin Co., Ltd., Tokyo, Japan) [1]. This device utilizes state-of-the-art multisensor array technology to detect pulse waves from the radial artery. Before each trial, blood pressure was calibrated using arterial pulse waves obtained by an oscillometric method from the ipsilateral brachial artery.

In the control group, subjects did not receive any MA stimulation and remained in the resting supine position for a given period. In the MA stimulation groups, hemodynamics were recorded for the 60 s (pre-stimulation period) of a 10-min rest period. Each subject then received a MA stimulation for 2 min on the right side. A stainless-steel acupuncture needle (diameter, 0.16 mm; length, 40 mm; CE0123, Seirin) was inserted into a target acupoint to a depth of 5 mm. In the lower leg stimulation group, the acupoint was Zusanli (WHO; ST 36) overlying the deep peroneal nerve and tibialis anterior muscle [4, 12–14]. In the ear stimulation group, the acupoint was at the cavum concha of the ear, which is mainly innervated by parasympathetic fibers [15, 16]. In the abdomen stimulation group, the acupoint was Tianshu (WHO; ST25), which is located just beside the navel. In the forearm stimulation group, the acupoint was Shousanli (WHO; LI10), which is located at intramuscular spaces on the radial side of the dorsal forearm. The acupuncture needle was moved up and down by approximately 5 mm at a frequency of 1 Hz during the MA stimulation. Immediately after the trial, subjects were asked whether they experienced dull pain or discomfort.

Data analysis

Mean blood pressure and heart rate were sampled at 200 Hz and stored on a laboratory computer system. In the MA stimulation groups, mean blood pressure and heart rate values were averaged for the pre-stimulation period (the last 60 s of the 10-min rest period) and the MA stimulation period (2 min). In the control group, mean blood pressure and heart rate values were calculated for the periods corresponding to the MA stimulation groups.

Statistical analysis

All data are expressed as the mean ± standard deviation. Age, height, weight, baseline hemodynamics, and the magnitude of the cardiovascular responses elicited by the MA stimulation were compared among groups using a one-way analysis of variance (ANOVA). In each group, changes in mean blood pressure and heart rate values elicited by the

MA stimulation were examined using a paired *t* test. A *p* value less than 0.05 was considered to be significant.

Results

Subject characteristics and baseline hemodynamics were not significantly different between groups, as shown in Table 1. All subjects completed the MA stimulation trial without pain or discomfort.

Figure 1a shows a representative time series of mean blood pressure. Mean blood pressure in the control group fluctuated, but did not increase or decrease over time. Mean blood pressure in the lower leg stimulation group started to decrease after the initiation of MA and remained decreased during MA. This depressor response was not obvious in the ear, abdomen, or forearm stimulation group. Figure 1b summarizes mean blood pressure values averaged for the pre-stimulation period (− 1 to 0 min) and for the MA stimulation period (0–2 min). Mean blood pressure significantly decreased only in the lower leg stimulation group (− 2.5 ± 2.7 mmHg, $p < 0.003$)

Figure 2a shows a representative time series of heart rate. Heart rate in the control group fluctuated, but did not increase or decrease over time. Heart rate decreased immediately after the initiation of MA in all stimulation groups. Although heart rate in the lower leg and forearm stimulation groups showed some recovery toward the pre-stimulation level, the bradycardic effect was significant when heart rate was averaged for the MA stimulation period. Figure 2b summarizes heart rate values averaged for the pre-stimulation period (− 1 to 0 min) and for the MA stimulation period (0–2 min). Heart rate was significantly lower during the MA stimulation period than during the pre-stimulation period in all stimulation groups. The magnitude of bradycardic responses did not significantly differ between the MA stimulation groups in a one-way ANOVA (2.6 ± 2.4, 3.6 ± 3.9, 4.5 ± 2.5, and 3.4 ± 3.5 beats/min in the lower leg, ear, abdomen, and forearm stimulation groups, respectively).

Discussion

We herein demonstrated that the MA stimulation at different acupoints evoked different mean blood pressure and heart rate responses in humans. A significant depressor response was observed only in the lower leg stimulation group (the ST36 acupoint). On the other hand, significant bradycardic responses were observed in all target acupoints. The present study is the first to provide systematic information on acupoint specificity for MA-induced cardiovascular responses in humans.

Effects of the acupuncture stimulation on cardiovascular responses through autonomic modulation

Acupuncture causes diverse cardiovascular responses. Nishijo et al. [2] observed that MA at the PC4 acupoint elicited a bradycardic response in humans. We also previously demonstrated that electroacupuncture at the PC4 acupoint produced bradycardic and depressor responses [1]. In a recent human study, Kimura et al. [12] reported that a 15-min acupuncture needle placement at the ST36 acupoint without additional needle manipulation induced a reduction in mean blood pressure. In an animal study, Michikami et al. [13] found a sustained decrease in arterial blood pressure during electroacupuncture at the ST36 acupoint in anesthetized rabbits. Yamamoto et al. [14] demonstrated that MA and electroacupuncture at the ST36 acupoint both elicited depressor and bradycardic responses in anesthetized rats. The depressor response observed in the lower leg stimulation group is consistent with previous findings.

Table 1 Number of subjects, subject characteristics, and beaseline hemodynamics in each group

	Group 1	Group 2	Group 3	Group 4	Group 5
Groups	Control	Lower leg	Ear	Abdominal	Forearm
N	11 (8 males, 3 females)	15 (11 males, 4 females)	10 (6 males, 4 females)	14 (6 males, 8 females)	10 (4 males, 6 females)
Years	21.7 ± 1.7	20.9 ± 0.7	26.1 ± 7.0	24.3 ± 6.4	22.6 ± 6.1
Height (cm)	168.9 ± 8.3	169.4 ± 6.5	169.2 ± 8.9	167.0 ± 9.5	165.5 ± 9.0
Weight (kg)	61.7 ± 13.8	58.5 ± 9.0	59.6 ± 8.6	59.6 ± 10.2	55.9 ± 15.1
No stimulation HR (beats/min)	61.0 ± 8.0	63.1 ± 10.6	66.4 ± 10.0	66.2 ± 11.1	62.9 ± 7.8
No stimulation MBP (mrnHg)	78.1 ± 7.5	83.4 ± 10.1	90.8 ± 16.3	86.4 ± 7.5	76.9 ± 8.8

Mean values are the means and standard deviations for all subjects

N number of subjects, *HR* heart rate, *MBP* mean blood pressure

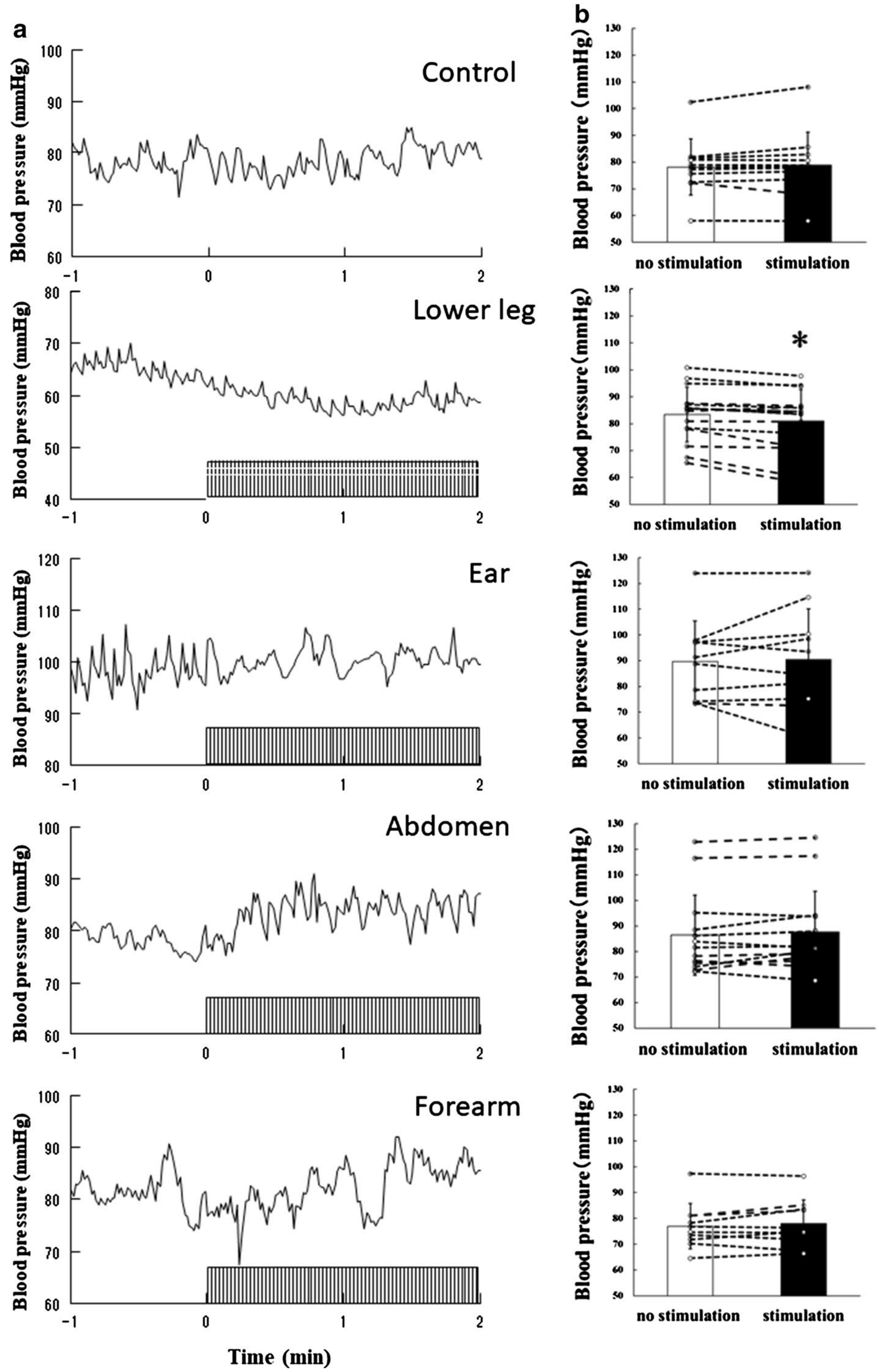

Fig. 1 **a** Representative traces of blood pressure responses obtained from the control group and manual acupuncture stimulation groups at the lower leg, ear, abdomen, and forearm. Stripe bars denote the duration of the acupuncture stimulation. **b** Blood pressure averaged during the pre-stimulation baseline period (− 1 to 0 min) and the acupuncture stimulation period (0–2 min). Values are the mean ± standard deviation. *$p < 0.05$ by the paired *t* test

Although the mechanisms underlying the depressor and bradycardic responses induced by the acupuncture stimulation have not yet been elucidated in detail, reflex autonomic modulation rather than a direct peripheral effect may contribute to the cardiovascular responses observed. Nishijo et al. [2] suggested that the MA-elicited bradycardic response was mediated by both an increase in cardiac vagal activity and a decrease in sympathetic nerve activity because the response was attenuated by sequential autonomic blockade with atropine and propranolol. Haker et al. [15] used a power spectral analysis of heart rate variability and documented changes in sympathetic and vagal activities during the acupuncture stimulation at the ear and hand acupoints. In the study by Kimura et al. [12], acupuncture at the ST36 acupoint elicited a depressor response, but did not show significant changes in muscle sympathetic nerve activity.

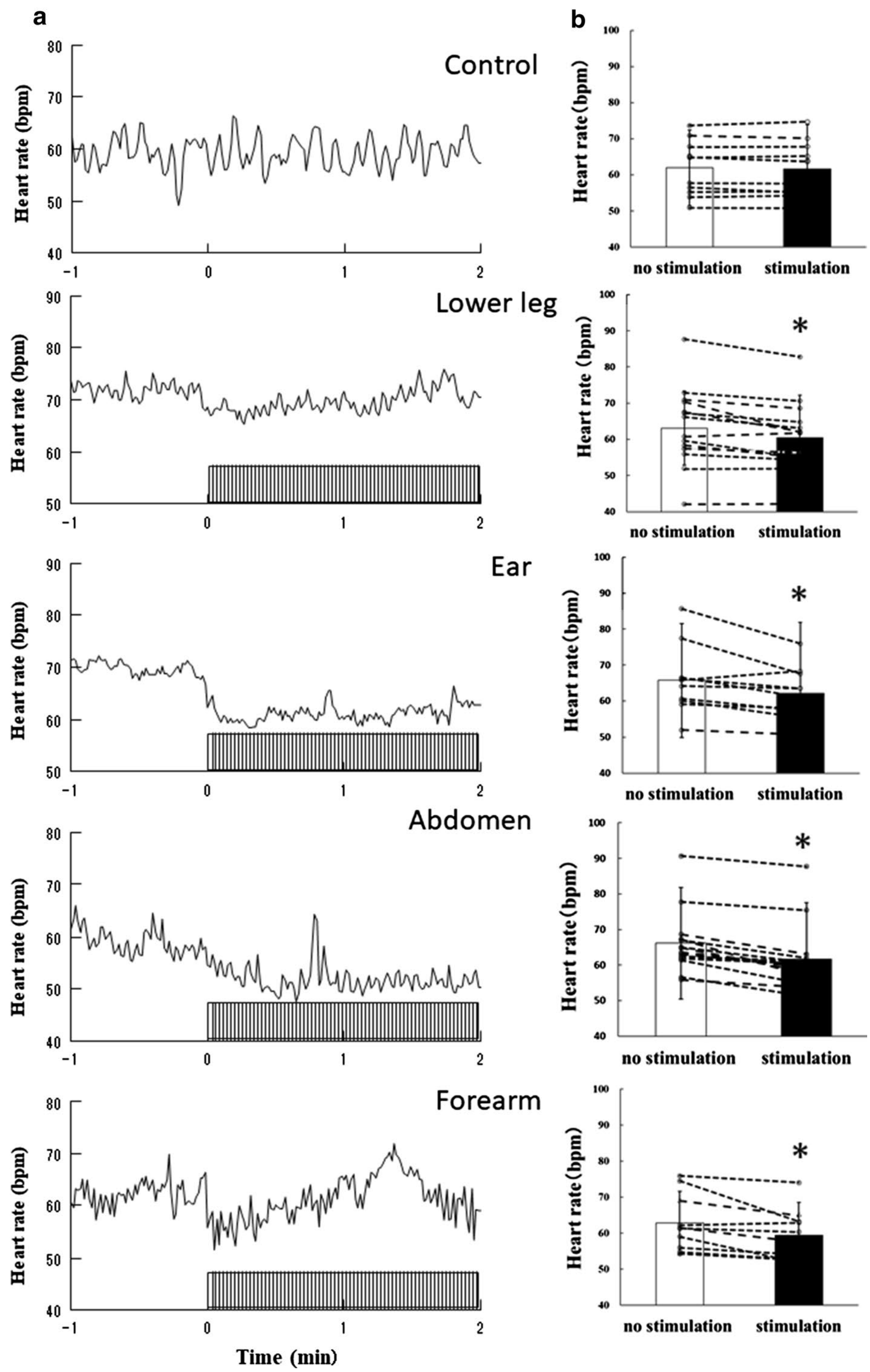

Fig. 2 **a** Representative traces of heart rate responses obtained from the control group and acupuncture stimulation groups at the lower leg, ear, abdomen, and forearm. Stripe bars denote the duration of the acupuncture stimulation. **b** Heart rate averaged during the pre-stimulation baseline period (− 1 to 0 min) and the acupuncture stimulation period (0–2 min). Values are the mean ± standard deviation. *$p < 0.05$ by the paired *t* test

They suggest that acupuncture attenuates the activity of the sympathetic nerves that supply non-muscular beds. This interpretation is supported by the observation that renal sympathetic nerve activity was reduced during electroacupuncture-induced hypotension in anesthetized cats [10]. Cardiac sympathetic nerve activity is also suppressed during electroacupuncture-induced hypotension in anesthetized rabbits [13]. Regarding the pathway mediating the heart rate response to an acupuncture-like stimulation, Uchida et al. [7] demonstrated that interventions of cardiac sympathectomy, high spinal transection, or the infusion of the $GABA_A$ receptor antagonist bicuculline into the cisterna magna were all effective for disrupting reflex bradycardia. These findings suggest that GABAergic neurons in the brainstem play a key role in the heart rate response to the acupuncture-like stimulation.

Acupoint-specific cardiovascular effects by the acupuncture stimulation

Tjen-A-Looi et al. [4] examined acupoint specificity for the effects of electroacupuncture on the pressor response induced by a chemosensitive afferent stimulation of the gallbladder with bradykinin in anesthetized cats. They found a prolonged reduction in the pressor response after electroacupuncture at the Jiangshi-Neiquan acupoints (WHO; PC5-PC6, overlying the median nerve) and Shousanli-Quchi acupoints (WHO; LI10-LI11, overlying the deep radial nerve), shorter-lasting reductions in the pressor reflex after electroacupuncture at the Hegu-Lique acupoints (WHO; LI4-LI7, overlying branches of the median nerve and superficial radial nerve) and Zusanli-Shangjuxu acupoints (WHO; ST36-ST37, overlying the deep peroneal nerve), and no significant attenuation of the pressor reflex after electroacupuncture at the Pianli-Wenlui acupoints (WHO; LI6-LI7) and Youngquan-Zhiyin acupoints (WHO; K1-B67). In the present study, the MA stimulation elicited a significant depressor response only in the lower leg stimulation group (the ST36 acupoint), thereby confirming acupoint specificity for the MA-induced depressor response in humans. The lack of a depressor response in the forearm stimulation group was inconsistent with previous findings reported by Tjen-A-Looi et al. [4] and our group using electroacupuncture [1]. In the study by Tjen-A-Looi et al. [4] sympathoexcitation was induced by a chemosensitive afferent stimulation with bradykinin. Our previous study [1] examined subjects in a sitting position, which may have activated the sympathetic system more than the resting supine condition. Weaker sympathetic nerve activity under the resting supine condition may have contributed to the absence of a significant depressor response in the forearm stimulation group in the present study.

Uchida et al. [7] reported that the acupuncture-like stimulation at the forelimb, chest, abdomen, or hindlimb produced significant heart rate reductions in anesthetized rats. No significant differences were observed in the magnitude of heart rate changes between the areas of the acupuncture stimulation. The lack of significant acupoint specificity in the heart rate response is consistent with the present results. On the other hand, Kurono et al. [8] suggested the site specificity of the acupuncture-induced heart rate response in humans. In their study, an epifascial acupuncture stimulation at the Danzhong acupoint (WHO; CV17), located at the level of the 4th intercostal space, decreased heart rate. In contrast, an epifascial acupuncture stimulation at the Zhongting acupoint (WHO; CV16), located at the midpoint of the xiphisternal junction, had no significant effect on heart rate.

The inconsistency in cardiovascular responses elicited by acupuncture between different studies may be attributed to methodological differences in the stimulation: electroacupuncture [1, 3, 4, 10, 13, 14], acupuncture with immediate needle removal [8, 9], acupuncture with needle placement without additional manipulation [12], and acupuncture with intermittent needle manipulation [2, 3, 7, 14]. Even within the same method, stimulation parameters may significantly affect the observed responses. Bäcker et al. [17] performed MA on human subjects by twisting the acupuncture needle under high-frequency and low-amplitude (4–8 Hz and 0.5–2 rotations) and low-frequency and high-amplitude (1–2 Hz and 4–8 rotations) conditions. They showed that low-frequency and high-amplitude MA elicited a sustained decrease in blood pressure. Regarding the frequency of electroacupuncture, a low-frequency stimulation (2 Hz) was more effective than a high-frequency stimulation (40–100 Hz) at suppressing the reflex pressor response in anesthetized rats [3]. The optimal frequency of a hindlimb electrical stimulation was 5–10 Hz to evoke a depressor response in anesthetized cats [18]. In our previous human study, the optimal frequency was 1 Hz [1]. Factors such as intensity, pulse duration, and the insertion depth of the needle may influence the magnitude of cardiovascular responses to electroacupuncture. Differences in the acupuncture stimulation to either skin alone or muscle alone may also produce different effects on cardiovascular responses [19, 20]. Previous studies demonstrated that an acupuncture stimulation applied to the muscle alone produced depressor [19] and bradycardic [20] responses, while these responses were not induced by an acupuncture stimulation to the skin alone. Furthermore, the posture of subjects has been suggested to affect basal autonomic activity, which may, in turn, influence the magnitude of acupuncture-induced cardiovascular responses. Therefore, the collection of data in a systematic manner using a uniform stimulation method is required to elucidate the site specificity of acupuncture-induced cardiovascular responses.

Clinical perspectives

The modulation of autonomic nervous activity through a vagal nerve stimulation (VNS) has been tested as a new treatment strategy for chronic heart failure. Li et al. [21] showed that electrical cervical VNS significantly improved the survival of rats with chronic heart failure after myocardial infarction. However, cervical VNS requires the implantation of stimulation electrodes, which may hamper the routine clinical application of this modality. Cervical VNS also causes side effects, such as coughing, in some patients, which may have limited the intensity of VNS needed to produce a cardioprotective effect. Clinical trials on cervical VNS for chronic heart failure patients (NECTAR-HF and INOVATE-HF) failed to show definitive benefits [22, 23], whereas extended follow-up of the

ANTHEM-HF study demonstrated improvements in cardiac function and heart failure symptoms [24].

The difficulties associated with translating the results of the animal study to clinical practice may be partly due to an insufficient understanding of the treatment mechanisms of VNS. Nevertheless, correcting the autonomic balance remains an essential strategy for the treatment of cardiovascular diseases [13, 25]. Acupuncture, which does not require the implantation of stimulation electrodes, may be an alternative modality to modulate autonomic nervous activity. Li et al. [26] demonstrated that an electroacupuncture stimulation at the median nerve reduced reflex-regional myocardial ischemia in anesthetized cats. Ma et al. [27] showed that treating heart failure rats with electroacupuncture for 1 week markedly increased the left ventricular ejection fraction, reversed the enlargement of the left ventricle, and shrunk the infarct size. Lima et al. [28] reported improvements in hemodynamic parameters in heart failure rats by chronic electroacupuncture at the ST36 acupoint. In patients with coronary artery disease, Zamotrinsky et al. [16] demonstrated that VNS via an electrical ear stimulation prevented a decrease in the number of noradrenergic nerve plexuses in the atrial tissue. According to a recent human study by Yu et al. [29], a low-level tragus stimulation may be used to treat ischemia and reperfusion injury in patients with ST-segment elevation myocardial infarction. The present results provide an insight into the selection of acupoints for the treatment of cardiovascular diseases.

Among 4530 untreated hypertensive patients in the Framingham study, the risk of cardiovascular events increased with elevations in the resting heart rate [30]. However, Bangalore et al. [31] reported that slowing of the heart rate by beta-blockers was associated with an increased risk of cardiovascular events and death among hypertensive patients. Beta-blockers are no longer recommended as the first-line therapy for primary hypertension [32]. Non-selective beta-blockers may inhibit vascular smooth muscle relaxation mediated by beta$_2$-adrenergic receptors. This vasoconstrictive effect may be undesirable for hypertension when sympathetic outflow from the central nervous system is increased. Central sympathetic suppression may be required to treat some types of hypertension [33]. Flachskampf et al. [34] reported that an acupuncture treatment for 6 weeks significantly lowered mean 24-h ambulatory blood pressure, and suggested the potential of acupuncture as an alternative antihypertensive therapeutic option with no or minimal side effects. The present results suggest that an acupuncture stimulation at the lower leg is effective for the treatment of moderate hypertensive patients, possibly with no or minimal side effects.

Conclusions

Acupuncture stimulation-induced cardiovascular effects, which are modulated by the ANS, differ according to the stimulation of different acupoints. An acupuncture stimulation at the lower leg (the ST36 acupoint), which elicits depressor and bradycardic responses, may be effective for the treatment of hypertensive patients. Further systematic studies are warranted to establish acupuncture as an alternative non-pharmacological modality for the treatment of cardiovascular diseases with autonomic dysfunctions.

Author contributions HN and TM: designed the study, analyzed data, and drafted the manuscript; SU and EK: drafted the manuscript and acquired data; TK, HY, and MS: interpreted data and drafted the manuscript; HN, TK, SU, EK, HY, MS, and TM: edited and revised the manuscript and approved the final version.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval Experimental protocols were approved (No. 4) by the Ethics Committee of Morinomiya University of Medical Sciences. The present study was conducted in accordance with the 1964 Declaration of Helsinki and its later amendments.

Informed consent Written informed consent was obtained from all subjects after they were given full explanations of the objectives, methods, and potential risks of the study.

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