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Low-frequency and low-intensity ultrasound increases cardiac parasympathetic neural activity and decreases clinic hypertension in elderly hypertensive subjects with type 2 diabetes

Katsunori Nonogaki [a,*], Mari Murakami [a], Tomoe Yamazaki [a], Naohiko Nonogaki [b]

[a] Department of Diabetes Technology, Tohoku University Graduate School of Biomedical Engineering, Japan
[b] Nonogaki Diabetic Clinic, Japan

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ABSTRACT

Background: The aims of the present study were to determine the effects of an ultrasound irradiation on clinic hypertension and the heart rate variability in elderly hypertensive subjects with type 2 diabetes.
Methods: We examined the effects of ultrasound (800 kHz, 25 mW/cm^2) applied to the forearm for 10 min on the autonomic nerve activity and the difference between BP at home and at a clinic visit in Japanese subjects with type 2 diabetes and hypertension.
Results: In 108 subjects who displayed systolic BP (SBP) >140 mm Hg at a clinic visit, 75 subjects (69%) had a mean SBP <135 mm Hg at home and 33 subjects (31%) had a mean SBP >135 mm Hg at home in the morning for 14 days. SBP, pulse rate, and pulse pressure in the ultrasound treatment group were significantly lower than the baseline values in these hypertensive subjects with type 2 diabetes, and lower than those of placebo controls independently of SBP at home. In 31 subjects who displayed systolic BP >140 mm Hg at a clinic, standard deviation of all RR intervals and the root mean square of successive differences were significantly higher in the ultrasound treatment group than the baseline values in these hypertensive subjects with type 2 diabetes, and lower than those of placebo controls.
Conclusions: The ultrasound treatment increases the cardiac parasympathetic neural activity and decreases the differences between SBP at home and at a clinic visit in elderly hypertensive subjects with type 2 diabetes.

Hypertension detected in the clinic in patients with type 2 diabetes could include white-coat hypertension (WCH), the white-coat effect (WCE) and uncontrolled hypertension. Type 2 diabetic subjects with WCH reportedly have an increased risk for microvascular complications such as diabetic retinopathy and nephropathy [1]. It remains difficult to differentiate WCH and/or WCE from uncontrolled hypertension at the clinic, and remains difficult to control them.

We previously reported that low-frequency and very low-intensity ultrasound irradiation to the forearm for 10 min or 20 min decreases measures of blood pressure (BP), pulse pressure, pulse rate, and an arterial pressure-volume index in hypertensive subjects with type 2 diabetes [2,3]. The effect of the ultrasound irradiation on the differences between the mean BP at home in the morning and BP obtained at a clinic visit, and mechanisms by which the ultrasound treatment decreases BP, however, remain unclear.

To determine the prevalence of clinic hypertension and the effect of the ultrasound irradiation in elder hypertensive subjects with type 2 diabetes, we examined the effects of low-frequency and low-intensity ultrasound (800 kHz, 25 mW/cm^2) applied to the forearm for 10 min on differences between the mean BP at home in the morning for 14 days and BP obtained at a clinic visit in Japanese elder subjects with type 2 diabetes and hypertension.

To determine the mechanisms, we examined the effect of an ultrasound applied to the forearm for 10 min on heart rate variability in Japanese elder subjects with type 2 diabetes and hypertension.

In the first study, BP and pulse rate were measured in 108 Japanese subjects (24 men and 84 women; mean age ± SE, 72 ± 2 years) with type 2 diabetes and hypertension (systolic BP >140 mm Hg at a clinic visit) at home in the morning for 14 days before a clinic visit (Fig. 1). The BP and pulse rate was measured before breakfast and after arising.

75 Japanese subjects (15 men and 60 women; mean age ± SE, 70 ± 1 years) with type 2 diabetes and hypertension (systolic BP >140 mm Hg at an office visit and mean systolic BP <135 mm Hg at home in the

* Corresponding author at: Department of Diabetes Technology, Tohoku University Graduate School of Biomedical Engineering, 6-6-11 Aoba, Aramakiaza, Aoba-ku, Sendai, Miyagi 980-8579, Japan.
E-mail addresses: katsu@trc.med.tohoku.ac.jp, knonogaki-tky@umin.ac.jp. (K. Nonogaki).

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morning for 14 days) were randomly assigned in a 2:1 ratio to undergo 800-kHz ultrasound irradiation or a sham procedure (Fig. 1).

33 Japanese subjects (9 men and 24 women; mean age ± SE, 74 ± 2 years) with type 2 diabetes and hypertension (systolic BP >140 mm Hg at an office visit and mean systolic BP >135 mm Hg at home in the morning for 14 days) were randomly assigned in a 2:1 ratio to undergo 800-kHz ultrasound irradiation or a sham procedure (Fig. 1).

In the second study, 31 Japanese subjects (7 men and 24 women; mean age ± SE, 69 ± 2 years) with type 2 diabetes and hypertension (SBP >140 mm Hg at an office visit) were randomly assigned in a 2:1 ratio to undergo 800-kHz ultrasound irradiation or a sham procedure (Fig. 1).

The subjects were treated with oral anti-diabetic agents and anti-hypertension agents, including irebesartan, candesartan, and valsartan, the selective angiotensin-1 subtype angiotensin II receptor antagonists (ARB), amlodipine, a long-acting calcium channel blocker, and/or atenolol, a beta1-adrenoceptor blocker. The weight and height of each of the subjects were recorded, and baseline BP and pulse rate were measured with the subject in a seated position. The BP and pulse rate were measured in the morning at the clinic.

The BP and pulse rate were monitored using a noninvasive monitor (HEM-7324c, Omron Inc., Japan). The ultrasound device was used as described previously [2,3].

The subjects underwent ultrasound irradiation applied to the forearm for 10 min at 800 kHz and 25 mW/cm^2 with 100% duty, or placebo irradiation. After treatment for 10 min, BP and pulse rate were again measured using a BP monitoring system. The heart rate variability was measured using an APG Heart rater SA-3000Plus (Tokyo Iken Co, Tokyo, Japan) as a noninvasive procedure to measure cardiac modulation by autonomic nervous activity.

All of the participants provided written informed consent to participate in this study, which was approved by the ethics committees of the Nonogaki Diabetic Clinic. The clinical studies were conducted in accordance with the institutional guidelines for clinical research at the Nonogaki Diabetes Clinic and Sendai Medical Welfare Association.

Comparisons between two groups were performed using Student's *t*-test. Comparisons among more than two groups were performed using analysis of variance with Bonferroni's correction for multiple comparisons. A P value of <0.05 was considered statistically significant.

Systolic BP (SBP) and pulse rate measured at a clinic visit were significantly higher than those measured at home in all subjects with hypertension and type 2 diabetes. Seventy-five subjects (69%) had a mean SBP <135 mm Hg at home, whereas thirty-tree subjects (31%) had a mean SBP >135 mm Hg. (Fig. 1).

Table 1A
Effects of 800-kHz ultrasound irradiation on the clinic hypertension in subjects with hypertension and type 2 diabetes who have the average SBP <135 mm Hg at home in the morning for 14 days.

Variables	Control	Control	US treatment	US treatment
	Baseline	10 min	Baseline	10 min
SBP	154 ± 1	154 ± 1	154 ± 2	136 ± 2*
DBP	78 ± 1	79 ± 1	81 ± 2	76 ± 2*
Pulse pressure	76 ± 1	75 ± 1	73 ± 2	60 ± 2*
Mean BP	116 ± 1	116 ± 1	117 ± 2	106 ± 2*
Pulse rate	73 ± 1	74 ± 1	72 ± 2	69 ± 2*

n = 25 for placebo controls (5 men and 20 women) and n = 50 for 800-kHz ultrasound irradiation group (10 men and 40 women), respectively. All subjects were treated with amlodipine and ARB (irebesartan (n = 28), valsartan (n = 28), candesartan (n = 19)). Fourteen subjects were treated with atenolol in addition to ARB and amlodipine.
US, ultrasound treatment; SBP, systolic blood pressure; DBP, diastolic blood pressure.
* P < 0.05.

Systolic and diastolic BP, pulse rate, and pulse pressure in the 800-kHz ultrasound treatment group were significantly lower than the baseline values in the hypertensive subjects with type 2 diabetes, who have the mean systolic BP <135 mm Hg in the morning at home for 14 days, and lower than those of placebo controls (Table 1A). The decreased SBP induced by treatment with the ultrasound irradiation at the clinic was significantly higher than the mean SBP measured at home.

In addition, SBP and pulse rate at clinic were significantly higher than those at home in the subjects with hypertension and type 2 diabetes, who have the mean SBP >135 mm Hg in the morning at home for 14 days, and lower than those of placebo controls (Table 1B). The decreased SBP induced by the ultrasound irradiation treatment at the clinic recovered to the mean SBP measured at home.

In 31 subjects who displayed SBP >140 mm Hg at a clinic visit, standard deviation of all RR intervals (SDNN) and the root mean square of successive differences (RMSSD) were significantly higher in the ultrasound treatment group than the baseline values in these hypertensive subjects with type 2 diabetes, and lower than those of placebo controls (Table 2).

There were no significant differences in age, body mass index (BMI), serum high-density lipoprotein-cholesterol (HDL-c), low-density

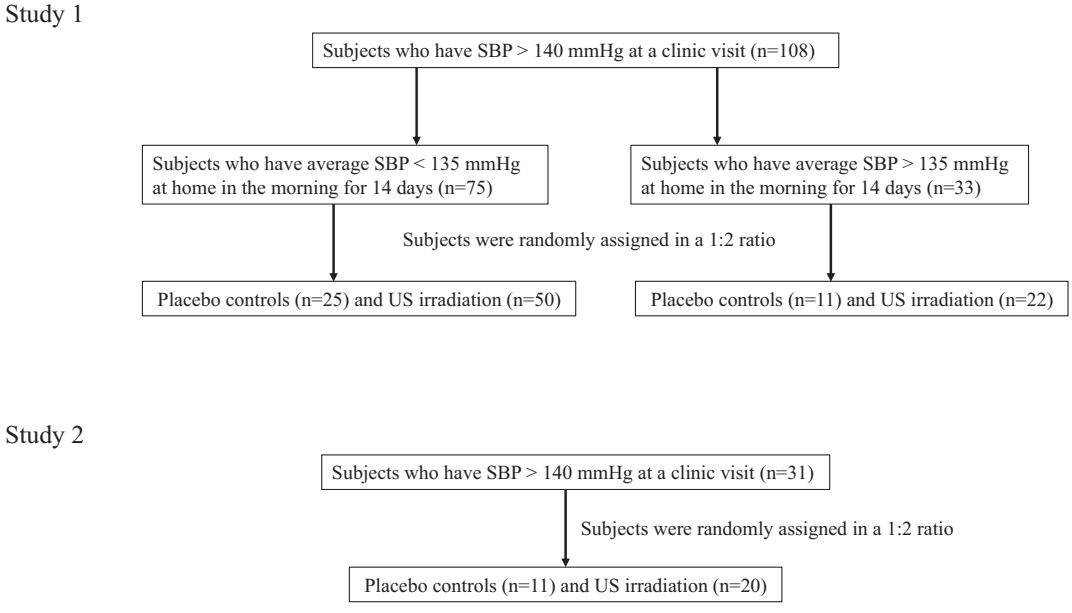

Fig. 1. A flow diagram outlining the randomization and groups.

Table 1B
Effects of 800-kHz ultrasound irradiation on clinic hypertension in subjects with hypertension and type 2 diabetes who have the mean SBP >135 mm Hg at home in the morning for 14 days.

Variables	Control	Control	US treatment	US treatment
	Baseline	10 min	Baseline	10 min
SBP	158 ± 3	158 ± 4	158 ± 3	140 ± 3*
DBP	75 ± 3	77 ± 5	78 ± 4	74 ± 2*
Pulse pressure	83 ± 3	81 ± 3	80 ± 3	66 ± 2*
Mean BP	117 ± 3	118 ± 4	118 ± 3	107 ± 2*
Pulse rate	76 ± 4	74 ± 3	74 ± 2	66 ± 2*

n = 11 for placebo controls (4 men and 7 women) and n = 22 for 800-kHz ultrasound irradiation group (5 men and 17 women), respectively. SBP, systolic blood pressure; DBP, diastolic blood pressure. All subjects were treated with amlodipine and ARB (irbesartan (n = 13), valsartan (n = 13), candesartan (n = 7)). Five subjects were treated with atenolol in addition to amlodipine and ARB.
* P < 0.05.

lipoprotein-cholesterol (LDL-c), triglyceride (TG), plasma glucose (PG), and HbA1c, systolic and diastolic BP, pulse rate, and pulse pressure between the placebo controls and the 800-kHz ultrasound treatment group (Supplementary Tables 1A, 1B and 2).

Hypertension in type 2 diabetic patients is a major risk factor for the onset and progress of diabetes complications and cardiovascular disease. Decreasing BP reportedly improves mortality and other clinical outcomes in type 2 diabetic patients with a baseline systolic pressure of 140 mm Hg and greater [4]. Although the BP goals for elderly patients remain inconclusive, BP treatment targeting a systolic BP of less than120 mm Hg in type 2 diabetic patients has recently been questioned [5,6]. Our results demonstrated that elder subjects with type 2 diabetes and hypertension likely have systolic WCE at a clinic visit. Treatment with ultrasound irradiation for 10 min might reduce WCE and improve clinic hypertension to a reasonable BP target in patients with type 2 diabetes without the additional use of anti-hypertensive agents.

Patients with type 2 diabetes and hypertension are reported to have increased sympathetic nerve activity [7,8]. The SDNN reflects total variability and carries the strongest prognostic information in heart disease [9]. The RMSSD correlates highly with high-frequency (HF) power, reflecting parasympathetic modulation [10]. Our results demonstrated that the ultrasound irradiation decreases the elevated SBP at a clinic by increasing cardiac parasympathetic neural activity in elderly hypertensive subjects with type 2 diabetes via novel afferent neural pathways from the forearm to the cardiovascular system. The ultrasound irradiation could be useful to determine whether the patients require the additional use of anti-hypertensive agents or not.

It remains unclear whether the ultrasound irradiation can impact directly or indirectly on the cardiac parasympathetic neural activity. We cannot rule out the possible involvement of a shifted baroreflex in the patients receiving the medications including ARB and amlodipine, which might modulate the effects of ultrasound irradiation.

In summary, these findings suggest that Japanese elderly hypertensive subjects with type 2 diabetes likely have elevated SBP at a clinic visit, and that low-frequency (800 kHz) and low-intensity (25 mW/cm^2) ultrasound irradiation to the forearm for 10 min is potentially useful to decrease the differences between SBP at home and at a clinic visit via increasing cardiac parasympathetic neural activity in elderly hypertensive subjects with type 2 diabetes.

Table 2
Effects of 800-kHz ultrasound irradiation on SDNN, RMSSD and clinic hypertension in subjects with hypertension and type 2 diabetes.

Variables	Control	Control	US treatment	US treatment
	Baseline	10 min	Baseline	10 min
SDNN	21.4 ± 2.2	22.1 ± 1.4	21.0 ± 1.2	26.1 ± 1.7*
RMSSD	13.3 ± 1.2	12.7 ± 1.4	14.6 ± 1.1	18.4 ± 1.6*
SBP	159 ± 3	156 ± 4	158 ± 2	135 ± 3*
DBP	79 ± 2	78 ± 2	80 ± 2	81 ± 2
Pulse pressure	80 ± 2	78 ± 3	78 ± 2	54 ± 2*
Pulse rate	73 ± 2	72 ± 2	73 ± 2	70 ± 2*

US, ultrasound treatment; SDNN, standard deviation of all RR intervals; RMSSD, the root mean square of successive differences; SBP, systolic blood pressure; DBP, diastolic blood pressure. n = 11 for placebo controls (1 men and 10 women) and n = 20 for 800-kHz ultrasound irradiation group (6 men and 14 women), respectively. All subjects were treated with amlodipine and ARB (irbesartan (n = 15), candesartan (n = 12), valsartan (n = 4)). Two subjects were treated with atenolol in addition to amlodipine and ARB.
* P < 0.05.

Conflict interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2018.04.002.

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