Low-frequency and low-intensity ultrasound irradiation to the forearm improves an index of arterial stiffness in subjects with type 2 diabetes and hypertension

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A B S T R A C T

Objectives: The arterial pressure-volume index (API) is a non-invasive assessment of arterial stiffness, and is suggested as a useful predictor of future cardiovascular events. The aim of the present study was to determine the effects of low-frequency and low-intensity ultrasound applied to the forearm for 10 min on the API in Japanese subjects with type 2 diabetes and hypertension.

Methods: We examined the effects of low-frequency and low-intensity ultrasound (800 kHz, 25 mW/cm²) applied to the forearm for 10 min on the API, blood pressure (BP) and pulse rate in 40 Japanese subjects (13 men and 27 women; mean age ± SE, 70 ± 2 years) with type 2 diabetes and hypertension, who had the API > 30 and systolic BP > 140 mmHg at a clinic visit. We also examined the effects of the ultrasound irradiation for 10 min on the API, BP and pulse rate in 33 Japanese subjects (11 men and 22 women; mean age ± SE, 65 ± 2 years) with type 2 diabetes and hypertension, who had the API > 30 and systolic BP > 140 mmHg.

Results: The API, systolic BP and pulse rate in the ultrasound treatment group was significantly lower than the baseline values in the subjects who had the API > 30 and either the baseline of systolic BP > 140 mmHg or systolic BP < 140 mmHg.

Conclusions: The low-frequency and low-intensity ultrasound irradiation to the forearm for 10 min might be useful as a preventive application for arterial stiffness in subjects with type 2 diabetes and hypertension.

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An arterial pressure-volume index (API) is reportedly a novel index of arterial stiffness [1]. The API is evaluated by assessing the curve between cuff pressure and arterial volume using oscillometric blood pressure measurement [2]. The API is reportedly associated with Framingham Cardiovascular Risk Score and the Suita Score [3] and the presence of significant coronary stenosis [4]. Thus, the API is suggested as a useful predictor of future cardiovascular events.

We previously reported that low-frequency (500 kHz and 800 kHz) and very low-intensity (25 mW/cm²) ultrasound irradiation to the forearm for 20 min at a 100% duty cycle decreased BP and pulse rate in hypertensive subjects with type 2 diabetes [5]. The noninvasive device-based approach for the prevention and/or the treatment of arterial stiffness in subjects with type 2 diabetes and hypertension, however, has not been evaluated. To determine the acute effect of the ultrasound irradiation for 10 min on the arterial stiffness, we examined the effect of the ultrasound (800 kHz, 25 mW/cm²) applied to the forearm for 10 min on the API in Japanese subjects with type 2 diabetes and hypertension.

In the first study, 40 Japanese subjects (13 men and 27 women; mean age ± SE, 70 ± 2 years) with type 2 diabetes and hypertension who had the API > 30 and systolic BP > 140 mm Hg at clinic visit were randomly assigned in a 1:1 ratio to undergo 800-kHz ultrasound irradiation or a sham procedure.

In the second study, 33 Japanese subjects (11 men and 22 women; mean age ± SE, 65 ± 3 years) with type 2 diabetes and hypertension who had the API > 30 and systolic BP < 140 mm Hg at clinic visit were randomly assigned in a 1:2 ratio to undergo 800-kHz ultrasound irradiation or a sham procedure.

The subjects were treated with oral anti-diabetic agents and anti-hypertension agents, including the selective angiotensin-1 subtype angiotensin II receptor antagonist amlopidine, 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 API, BP and pulse rate were measured with the subject in a seated position. The API, BP and pulse rate were measured in the morning and fasted conditions at the clinic.

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The API are measured oscillometrically at one-side of the upper arm, and in a sitting position similar to conventional measurements of BP. The API, BP and pulse rate were monitored using a noninvasive monitor (NAS-1000, NIHON KODEN, Japan). The ultrasound device was used as described previously [5].

The subjects underwent ultrasound irradiation applied to the forearm for 10 min at 800 kHz and 25 mW/cm² with 100% duty, or placebo irradiation. After treatment for 10 min, API, BP and pulse rate were again measured using NAS-1000.

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 Diabetic 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.

There were no significant differences in age, body mass index (BMI), serum high-density lipoprotein-cholesterol (HDL-c), low-density lipoprotein-cholesterol (LDL-c), triglyceride (TG), and HbA1c, systolic and diastolic BP, pulse rate, and pulse pressure between the placebo controls and the 800-kHz ultrasound treatment group (Tables 1A and 2A).

In the first study, the API, systolic and diastolic BP, and pulse rate in the 800-kHz ultrasound treatment group were significantly lower than the baseline values in the hypertensive subjects with type 2 diabetes, who have API > 30 and systolic BP > 140 mm Hg at the clinic, and the API, systolic BP and pulse rate in the 800-kHz ultrasound treatment group were significantly lower than those of placebo controls (Table 1B).

In the second study, the API, systolic BP and pulse rate in the 800-kHz ultrasound treatment group were significantly lower than the baseline values in the hypertensive subjects with type 2 diabetes, who have API > 30 and systolic BP < 140 mm Hg at the clinic, and systolic BP and pulse rate in the 800-kHz ultrasound treatment group were significantly lower than those of placebo controls (Table 2B). There were no sex-specific differences in responsiveness to the treatment in these studies. We detected no adverse effects on the human body after the 800-kHz ultrasound irradiation.

The results of the present study demonstrated that 800 kHz and 25 mW/cm² ultrasound irradiation to the forearm for 10 min with a 100% duty cycle significantly decreased the API compared with baseline in subjects who had the baseline of the API > 30 independently of the baselines of systolic BP.

### Table 1A
Profile of subjects with hypertension and type 2 diabetes who have the API > 30 and SBP > 140 mm Hg at the clinic.

| Variables | Control | US treatment |
|-----------|---------|-------------|
| Age (yr)  | 69 ± 2  | 70 ± 1      |
| BMI (kg/m²) | 23.6 ± 1.0 | 23.5 ± 0.9 |
| HDL-c (mg/dl) | 61 ± 4  | 58 ± 4      |
| LDL-c (mg/dl) | 113 ± 5  | 106 ± 5     |
| TG (mg/dl) | 116 ± 8 | 117 ± 8     |
| HbA1c (%) | 6.4 ± 0.1 | 6.5 ± 0.1   |

### Table 1B
Effects of 800-kHz ultrasound irradiation for 10 min on the API, BP and pulse rate.

| Variables | Control Baseline | US treatment Baseline | US treatment 10 min |
|-----------|------------------|-----------------------|---------------------|
| API       | 38.5 ± 1.9       | 36.8 ± 1.1            | 37.4 ± 0.7          |
| SBP       | 153 ± 4          | 150 ± 4               | 153 ± 2             |
| DBP       | 70 ± 2           | 69 ± 2                | 75 ± 2              |
| Pulse pressure | 83 ± 3       | 81 ± 3                | 78 ± 2              |
| Pulse rate | 74 ± 2           | 73 ± 2                | 74 ± 2              |

### Table 2A
Profile of subjects with hypertension and type 2 diabetes who have the API > 30 and SBP < 140 mm Hg at the clinic visit.

| Variables | Control | US treatment |
|-----------|---------|-------------|
| Age (yr)  | 64 ± 3  | 65 ± 2      |
| BMI (kg/m²) | 22.5 ± 1.1 | 23.5 ± 1.0 |
| HDL-c (mg/dl) | 65 ± 6  | 62 ± 3      |
| LDL-c (mg/dl) | 114 ± 3  | 110 ± 5     |
| TG (mg/dl) | 119 ± 9 | 119 ± 10    |
| HbA1c (%) | 6.0 ± 0.1 | 6.1 ± 0.1   |

### Table 2B
Effects of 800-kHz ultrasound irradiation for 10 min on the API, BP and pulse rate.

| Variables | Control Baseline | US treatment Baseline | US treatment 10 min |
|-----------|------------------|-----------------------|---------------------|
| API       | 34.6 ± 2.8       | 33.2 ± 1.3            | 36.5 ± 1.3          |
| SBP       | 132 ± 4          | 131 ± 4               | 132 ± 2             |
| DBP       | 69 ± 3           | 68 ± 3                | 67 ± 2              |
| Pulse pressure | 63 ± 3       | 63 ± 3                | 65 ± 2              |
| Pulse rate | 76 ± 3           | 75 ± 3                | 70 ± 2              |

### Conflict of interest
None.

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The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [14].

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