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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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ABSTRACT

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/cm^2) 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 (SBP) < 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.

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

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

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.

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

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/cm^2 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 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.

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/cm^2 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.

Arterial stiffening is a feature of physiological vascular aging that is accelerated in type 2 diabetes and a variety of pathological conditions associated with increased cardiovascular risk [6]. Coronary plaques are more prevalent in well controlled asymptomatic patients with type 2 diabetes compared with healthy controls and independently associated with arterial stiffness [7]. The prevention of arterial stiffness therefore plays an important role in the management of type 2 diabetes.

The API is a novel noninvasive arterial stiffness indices, and is associated with known risk factors of cardiovascular diseases [8]. In the cross-sectional survey of 7248 Japanese adults (the mean age 45. 5 years) who underwent an annual medical checkup at a medical institution, the mean values of API were 25.1 [8]. In addition, multivariable linear regression analysis demonstrated that age, systolic BP, and BMI are independently associated with the API after adjustments, and that the API is correlated with the brachial-ankle pulse wave velocity (baPWV) [8,9].

Patients with type 2 diabetes and hypertension reportedly increases the sympathetic nerve activity [10,11]. The activity of the sympathetic nervous system is positively associated with peripheral resistance in men and women after menopause [12,13]. The ultrasound irradiation to the forearm for 10 min might therefore suppress the peripheral resistance by decreasing the sympathetic neural activity. We also cannot rule out potential mechanisms other than the sympathetic neural activity. Further studies will be needed to determine the mechanisms and to determine whether these acute benefits translate into sustained modification of the underlying disease.

In summary, these findings suggest that low-frequency (800 kHz) and low-intensity (25 mW/cm^2) ultrasound irradiation to the forearm for 10 min improves an index of arterial stiffness in subjects with hypertension and type 2 diabetes.

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

Variables	Control Baseline	Control 10 min	US treatment Baseline	US treatment 10 min
API	38.5 ± 1.9	36.8 ± 1.1	37.4 ± 0.7	32.9 ± 1.1*
SBP	153 ± 4	150 ± 4	153 ± 2	135 ± 3*
DBP	70 ± 2	69 ± 2	75 ± 2	71 ± 2
Pulse pressure	83 ± 3	81 ± 3	78 ± 2	64 ± 2*
Pulse rate	74 ± 2	73 ± 2	74 ± 2	69 ± 2*

US, ultrasound treatment; SBP, systolic blood pressure; DBP, diastolic blood pressure.
* P < 0.05.

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

Variables	Control Baseline	Control 10 min	US treatment Baseline	US treatment 10 min
API	34.6 ± 2.8	32.8 ± 1.3	36.5 ± 1.3	31.0 ± 1.4*
SBP	132 ± 4	131 ± 4	132 ± 2	125 ± 3*
DBP	69 ± 3	68 ± 3	67 ± 2	67 ± 2
Pulse pressure	63 ± 3	63 ± 3	65 ± 2	58 ± 2*
Pulse rate	76 ± 3	75 ± 3	70 ± 2	67 ± 2*

US, ultrasound treatment; SBP, systolic blood pressure; DBP, diastolic blood pressure.
* P < 0.05.

References

[1] J. Liao, J. Farmer, Arterial stiffness as a risk factor for coronary artery disease, Curr Atheroscler Rep 16 (2014) 387.
[2] H. Komine, Y. Asai, T. Yokoi, M. Yoshizawa, Non-invasive assessment of arterial stiffness using oscillometric blood pressure measurement, Biomed. Eng. Online 11 (2012) 6.
[3] R. Sasaki-Nakashima, T. Kino, L. Chen, H. Doi, S. Minegishi, K. Abe, et al., Successful prediction of cardiovascular risk by new non-invasive vascular indexes using suprasystolic cuff oscillometric waveform analysis, J. Cardiol. 69 (2017) 30–37.
[4] T. Ueda, S. Miura, Y. Suematsu, Y. Shiga, T. Kuwano, M. Sugihara, et al., Association of arterial pressure volume index with the presence of significantly stenosed coronary vessels, J. Clin. Med. Res. 8 (2016) 598–604.
[5] K. Nonogaki, T. Yamazaki, M. Murakami, N. Satoh, M. Hazama, K. Takeda, et al., Low-frequency and very low-intensity ultrasound decreases blood pressure in hypertensive subjects with type 2 diabetes, Int. J. Cardiol. 215 (2016) 147–149.
[6] A.N. Lyle, U. Raaz, Killing me unsoftly: causes and mechanisms of arterial stiffness, Arterioscler. Thromb. Vasc. Biol. 37 (2017) e1–e11.
[7] K.L. Funck, E. Laugesen, K. Overehus, J.M. Jesen, B.L. Norgaard, D. Dey, et al., Increased high-risk coronary plaque burden is associated with arterial stiffness in patients with type 2 diabetes without clinical signs of coronary artery disease: a computed tomography angiography study, J. Hypertens. 35 (2017) 1235–1243.
[8] M. Okamoto, F. Nakamura, T. Musha, Y. Kobayashi, Association between novel arterial stiffness indices and risk factors of cardiovascular disease, BMC Cardiovasc. Disord. 16 (2016) 211.
[9] S. Komatsu, H. Tomiyama, K. Kimura, C. Matsumoto, K. Shiina, A. Yamashita, Comparison of the clinical significance of single cuff-based arterial stiffness parameters with that of the commonly used parameters, J. Cardiol. 69 (2017) 678–683.
[10] A.J. Coats, J.M. Cruickshank, Hypertensive subjects with type-2 diabetes, the sympathetic nervous system, and treatment implications, Int. J. Cardiol. 174 (2014) 702–709.
[11] K. Masuo, H. Rakugi, T. Ogihara, Cardiovascular and renal complications of type 2 diabetes in obesity: role of sympathetic nerve activity and insulin resistance, Curr. Diabetes Rev. 6 (2010) 58–67.
[12] J.N. Barnes, E.C. Hart, T.B. Curry, Aging enhances autonomic support of blood pressure in women, Hypertension 63 (2014) 303–308.
[13] R.E. Harvey, J.N. Barmes, E.C. Hart, Influence of sympathetic nerve activity on aortic hemodynamics and pulse wave velocity in women, Am. J. Physiol. Heart Circ. Physiol. 312 (2017) H340–6.
[14] L.G. Shewan, A.J. Coats, Ethics in the authorship and publishing of scientific articles, Int. J. Cardiol. 144 (2010) 1–2.