

## ORIGINAL ARTICLE

# Influence of meal intake on pulse wave indices in type 2 diabetes

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Augmentation index (AI), brachial–ankle pulse wave velocity (baPWV) and cardio-ankle vascular index (CAVI) are available for the assessment of arterial stiffness in clinical practices. However, influences of meal intake on these indices are still poorly understood. The aim of this study is to elucidate the effects of daily meal intake on pulse wave indices in patients with type 2 diabetes. We studied 17 patients with type 2 diabetes. AI was measured at fasting, 60 and 120 min after a commercial mixed meal (500 kcal) intake. The baPWV and CAVI were measured at fasting and 80–100 min after meal intake. All pulse indices decreased significantly after meal intake (AI,  $89.3 \pm 9.7\%$  to  $77.9 \pm 9.4\%$ ,  $82.0 \pm 8.4\%$ ,  $P < 0.001$ ; baPWV,  $1652 \pm 286$ – $1586 \pm 240$  cm s<sup>-1</sup>,  $P = 0.002$ ; CAVI,  $9.52 \pm 0.92$ – $9.20 \pm 0.89$ ,  $P = 0.037$ ).  $\Delta_{120}$  (value 120 min after meal intake–fasting value) AI correlated significantly with age, body weight,  $\Delta_{120}$  systolic blood pressure (SBP),  $\Delta_{120}$  diastolic blood pressure,  $\Delta_{120}$  pulse pressure,  $\Delta_{120}$  heart rate and fasting AI.  $\Delta$  (postprandial value–fasting value) baPWV correlated significantly with fasting baPWV,  $\Delta$  SBP,  $\Delta$  pulse pressure and HbA1c. In contrast,  $\Delta$  CAVI did not correlate with any clinical variables. In conclusion, postprandial decreases in AI, baPWV and CAVI can lead to underestimate arterial stiffness in patients with type 2 diabetes. Postprandial changes in AI and baPWV, but not CAVI, are associated with changes in hemodynamic variables after daily meal intake.

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**Keywords:** augmentation index; cardio-ankle vascular index; diabetes mellitus; postprandial change; pulse wave velocity

## INTRODUCTION

Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in patients with hypertension,<sup>1,2</sup> diabetes mellitus<sup>3</sup> and end-stage renal disease.<sup>4,5</sup> Aortic pulse wave velocity (PWV) has been widely used to assess arterial stiffness. However, measurements of aortic PWV are technically difficult because it necessitates the use of two oscillometric sensors positioned over the left common carotid artery and the left femoral artery. Recently, other indices such as the brachial–ankle PWV (baPWV) and the cardio-ankle vascular index (CAVI) have been developed in Japan as alternative parameters for arterial stiffness.<sup>6–8</sup> Earlier studies have shown that baPWV and CAVI reflect atherosclerosis.<sup>7–10</sup> In addition, the augmentation index (AI) of radial artery, which provides information on central blood pressure,<sup>11–13</sup> has been developed as arterial stiffness parameter.<sup>14,15</sup> AI has been also reported to be associated with severity of atherosclerosis and coronary risk factors.<sup>16,17</sup> Accordingly, AI, baPWV and CAVI have been used in routine examinations because of the convenience with which their measurements can be taken.

Diabetes mellitus is a major risk factor for atherosclerosis. In fact, patients with type 2 diabetes have been reported to have a two-

fold increased risk of cardiovascular mortality,<sup>18</sup> and accordingly, assessment of aortic stiffness has been widely accepted as an important parameter in risk stratification for patients with diabetes mellitus. However, clinical examinations are often performed in postprandial state as well as fasting state, especially in outpatient clinics. On the other hand, postprandial effects on these pulse wave indices are still poorly understood. Therefore, the aim of this study is to elucidate the effects of daily meal intake on these pulse wave indices in patients with type 2 diabetes.

## METHODS

### Study patients

We studied 17 patients with type 2 diabetes as diagnosed by the criteria of the American Diabetes Association.<sup>19</sup> Patients under insulin therapy or those who had suffered from heart failure (left ventricular ejection fraction <50%), atrial fibrillation, renal dysfunction (serum creatinine level >1.5 mg per 100 ml) or peripheral artery disease (ankle–brachial index <0.9) were excluded from this study. This study was performed in accordance with the Declaration of Helsinki (1989) of the World Medical Association and was approved by the ethics committee of National Hospital Organization Ehime Hospital. All subjects gave written informed consent to participate in this study.

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### Study protocol

After overnight fasting, all patients ingested a commercial mixed meal (CalorieMate 500 kcal: carbohydrate 51 g, fat 28 g, protein 10 g; Otsuka Pharmaceutical, Tokyo, Japan) with 300–500 ml of water within 15 min. Measurements of AI and blood samplings were performed during the fast, as well as 60 and 120 min after the meal intake. CAVI and baPWV were measured during the fast and 80–100 min after the meal intake. The administration of antihypertensive drugs was prohibited at least 24 h before the study. All medications that affect lipid metabolism were withheld for at least 72 h before the study. Patients were also advised not to take any antidiabetic drugs from the evening before the study until the study was completed.

### Measurement of radial AI

After 10 min of rest in a sitting position, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured at the right brachial artery. A pulse waveform of the left radial artery was recorded by an automated tonometric system (HEM-9000AI; Omron Healthcare, Kyoto, Japan). AI was calculated as follows:  $AI = (\text{second peak SBP} - \text{DBP}) / (\text{first peak SBP} - \text{DBP}) \times 100$  (%). This calculation was performed using a fourth-order differential equation for the radial arterial waveform. Detailed procedure about this device was reported in our earlier study.<sup>13</sup> The coefficients of variation for intra- and inter-observer measurements of AI were  $4.3 \pm 3.0$  and  $2.5 \pm 1.7\%$ , respectively.<sup>13</sup>

### Measurement of baPWV

The patients were placed in the supine position for at least 5 min, and then ECG and heart sound were monitored. Cuffs were wrapped around both upper arms and ankles. BaPWV was measured using an automatic waveform analyzer (form PWV/ABI, BP-203RPE II; Colin, Komaki, Japan) according to the following equation:  $baPWV = (D1 - D2) / T1$ , where  $D1$  is the distance from the heart to the ankle and  $D2$  is the distance from the heart to the right upper arm. These distances were calculated on the basis of the patient's height.  $T1$  is the time between the onset of the rise in the pulse volume record of the right upper arm and the onset of the rise in the pulse volume record of the left ankle. The average coefficient of variation for the measurement of baPWV was reported to be  $\leq 10.0\%$ .<sup>7</sup>

### Measurement of CAVI

After measurement of baPWV, CAVI was measured using an automatic vascular screening system (VaSera VS-1000; Fukuda Denshi, Tokyo, Japan). PWV was obtained by dividing the vascular length by the time it took for the pulse wave to propagate from the aortic valve to the ankle. SBP and DBP were measured at the brachial artery. The formula used to calculate CAVI is as follows:  $CAVI = a \{ (2\rho/\Delta P) \times \ln(SBP/DBP) PWV^2 \} + b$ , where  $\Delta P$  is  $SBP - DBP$ ,  $\rho$  is blood density, and  $a$  and  $b$  are scale conversion constants to match aortic PWV. The principle of CAVI was reported earlier.<sup>8</sup> This equation is derived from Bramwell–Hill's equation and the stiffness parameter  $\beta$ , and CAVI is adjusted for blood pressure based on the stiffness parameter  $\beta$ . Therefore, CAVI reflects the stiffness of the aorta, femoral artery and tibial artery as a whole, and theoretically, it is not affected by blood pressure. All these measurements and calculations were performed automatically in VaSera VS-1000. The average coefficient of variation for the measurement of CAVI was reported to be  $< 5.0\%$ .<sup>8</sup>

### Statistical analysis

All data are expressed as the mean  $\pm$  s.d. The paired Student's *t*-test or repeated measure analysis of variance was used to compare continuous data. Relations between continuous variables were analyzed by linear regression analysis. Stepwise multiple regression analysis was used to evaluate the independent determinants of  $\Delta$  (postprandial value–fasting value) AI and  $\Delta$  baPWV. All statistical analyses were performed using SPSS version 16.0J for Windows (SPSS Japan Inc., Tokyo, Japan) and a *P*-value  $< 0.05$  was considered statistically significant.

## RESULTS

### Patient characteristics

Table 1 shows the characteristics of the study patients. All patients were taking antidiabetic drugs, including pioglitazone (all patients),  $\alpha$ -glucosidase inhibitors (10 patients) and sulfonylurea (8 patients). Thirteen patients (76.5%) were taking antihypertensive drugs, including calcium antagonists (10 patients),  $\beta$ -blockers (7 patients) and angiotensin II receptor blockers/angiotensin-converting enzyme inhibitors (7 patients). Eight patients (47.1%) were taking statins, and one patient (5.9%) was a smoker at the time.

### Effect of meal intake on clinical variables

Table 2 shows the effects of meal intake on clinical variables. SBP, DBP and pulse pressure decreased significantly, whereas heart rate increased after meal intake. Glucose and insulin levels increased significantly after meal intake.

### Effect of meal intake on pulse wave indices

AI decreased significantly after meal intake ( $89.3 \pm 9.7\%$  to  $77.9 \pm 9.4\%$ ,  $82.0 \pm 8.4\%$ ;  $P < 0.001$ ) (Figure 1a). Both baPWV and

**Table 1** Baseline characteristics of patients with type 2 diabetes

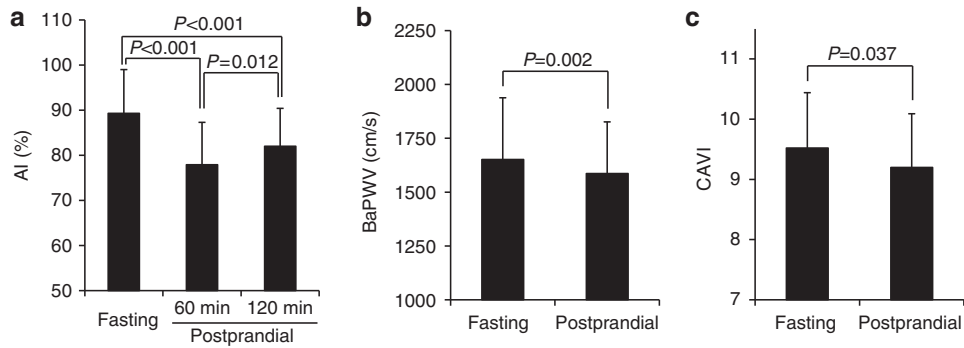
Variables	
<i>N</i> (male/female)	17 (10/7)
Age (years)	$66.8 \pm 4.8$
Body height (m)	$1.58 \pm 0.09$
Body weight (kg)	$58.4 \pm 7.8$
BMI ( $\text{kg m}^{-2}$ )	$23.3 \pm 3.0$
SBP (mm Hg)	$134.0 \pm 15.6$
DBP (mm Hg)	$69.3 \pm 9.2$
Pulse pressure (mm Hg)	$64.7 \pm 11.4$
Heart rate (beats per minute)	$63.2 \pm 8.5$
Fasting glucose (mg per 100 ml)	$116.4 \pm 16.3$
Fasting insulin ( $\mu\text{U ml}^{-1}$ )	$4.08 \pm 1.63$
HbA1c (%)	$5.97 \pm 0.62$
Total cholesterol (mg per 100 ml)	$205.4 \pm 28.1$
Triglyceride (mg per 100 ml)	$112.1 \pm 53.0$
HDL-C (mg per 100 ml)	$66.1 \pm 16.0$
Creatinine (mg per 100 ml)	$0.76 \pm 0.19$
AI (%)	$89.3 \pm 9.7$
BaPWV ( $\text{cm s}^{-1}$ )	$165.2 \pm 286$
CAVI	$9.52 \pm 0.92$

Abbreviations: AI, augmentation index; BaPWV, brachial-ankle pulse wave velocity; BMI, body mass index; CAVI, cardio-ankle vascular index; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein-cholesterol; SBP, systolic blood pressure.

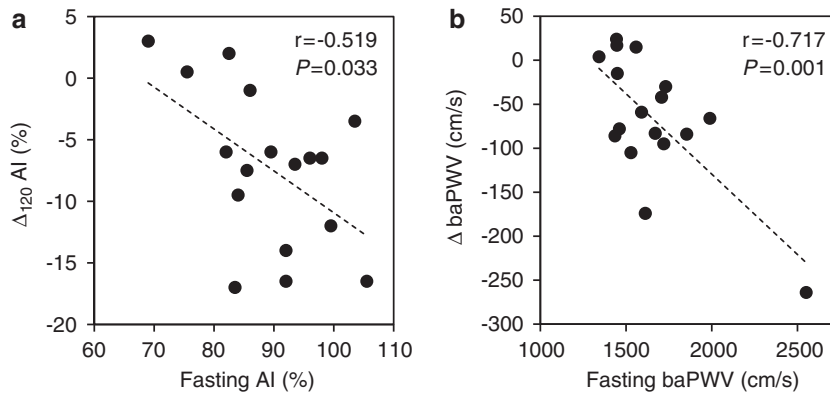
**Table 2** Postprandial changes in clinical variables in patients with type 2 diabetes

Variables	Fasting	Postprandial	
		60 min	120 min
SBP (mm Hg)	$134.0 \pm 15.6$	$122.2 \pm 14.4^*$	$123.2 \pm 13.4^*$
DBP (mm Hg)	$69.3 \pm 9.2$	$62.4 \pm 9.2^*$	$62.7 \pm 9.8^*$
Pulse pressure (mm Hg)	$64.7 \pm 11.4$	$59.9 \pm 10.0^*$	$60.5 \pm 9.8^*$
Heart rate (beats per minute)	$63.2 \pm 8.5$	$73.0 \pm 11.6^*$	$66.9 \pm 9.6^{\dagger}$
Glucose (mg per 100 ml)	$116.4 \pm 16.3$	$168.3 \pm 35.7^*$	$172.5 \pm 43.1^*$
Insulin ( $\mu\text{U ml}^{-1}$ )	$4.08 \pm 1.63$	$15.97 \pm 7.18^*$	$19.42 \pm 9.02^{\dagger}$

Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure. \* $P < 0.05$  vs. fasting;  $^{\dagger}P < 0.05$  vs. 60 min.



**Figure 1** Comparisons between fasting and postprandial values of AI (a), baPWV (b) and CAVI (c) in patients with type 2 diabetes.



**Figure 2** Relationships between the degree of postprandial changes and fasting values in AI (a) and baPWV (b) in patients with type 2 diabetes.

CAVI also decreased significantly after meal intake ( $1652 \pm 286 - 1586 \pm 240 \text{ cm s}^{-1}$ ;  $P=0.002$ ,  $9.52 \pm 0.92 - 9.20 \pm 0.89$ ;  $P=0.037$ , respectively) (Figures 1b and c). Positive linear correlations were observed between baPWV and CAVI in both fasting ( $r=0.676$ ,  $P=0.003$ ) and postprandial states ( $r=0.614$ ,  $P=0.009$ ). On the other hand, no significant association was observed between AI and other pulse wave indices. The percent change of AI from fasting to 60 and 120 min after meal intake was  $-12.6 \pm 8.3$  and  $-7.8 \pm 7.1\%$ , respectively. The percent change of baPWV and CAVI from fasting to postprandial state was  $-3.7 \pm 3.7$  and  $-3.2 \pm 5.9\%$ , respectively.

#### Correlation between $\Delta$ pulse wave indices and clinical variables

Linear regression analysis was performed to evaluate the relationship between  $\Delta$  pulse wave indices and clinical variables.  $\Delta_{60}$  (value 60 min after meal intake–fasting value) AI showed significant correlation between age ( $r=-0.706$ ,  $P=0.002$ ), body weight ( $r=0.533$ ,  $P=0.028$ ), HbA1c ( $r=-0.530$ ,  $P=0.029$ ) and  $\Delta_{60}$  SBP ( $r=0.528$ ,  $P=0.029$ ). In contrast,  $\Delta_{60}$  AI was not correlated with  $\Delta_{60}$  glucose ( $r=0.010$ ,  $P=0.971$ ) and  $\Delta_{60}$  insulin ( $r=0.202$ ,  $P=0.437$ ). Stepwise multiple regression analysis among these correlating variables revealed that age and HbA1c were the independent determinants of  $\Delta_{60}$  AI ( $F=13.9$ ,  $R^2=0.665$ ).  $\Delta_{120}$  (value 120 min after meal intake–fasting value) AI showed significant linear correlation between age ( $r=-0.620$ ,  $P=0.008$ ), body weight ( $r=0.604$ ,  $P=0.010$ ),  $\Delta_{120}$  SBP ( $r=0.725$ ,  $P=0.001$ ),  $\Delta_{120}$  DBP ( $r=0.656$ ,  $P=0.004$ ),  $\Delta_{120}$  pulse pressure ( $r=0.520$ ,  $P=0.033$ ),  $\Delta_{120}$  heart rate ( $r=-0.841$ ,  $P<0.001$ ) and fasting AI ( $r=-0.519$ ,  $P=0.033$ ) (Figure 2a).  $\Delta_{120}$  AI showed no significant correlation with  $\Delta_{120}$  glucose ( $r=0.106$ ,  $P=0.685$ ) and  $\Delta_{120}$  insulin ( $r=-0.411$ ,  $P=0.101$ ). Stepwise multiple regression analysis

showed that age,  $\Delta_{120}$  DBP and  $\Delta_{120}$  heart rate were the independent determinants of  $\Delta_{120}$  AI ( $F=29.3$ ,  $R^2=0.871$ ). In addition,  $\Delta$  baPWV was significantly correlated with HbA1c ( $r=-0.549$ ,  $P=0.023$ ),  $\Delta$  SBP ( $r=0.584$ ,  $P=0.014$ ),  $\Delta$  pulse pressure ( $r=0.623$ ,  $P=0.008$ ) and fasting baPWV ( $r=-0.717$ ,  $P=0.001$ ) (Figure 2b).  $\Delta$  baPWV was not correlated with  $\Delta_{60}$  glucose ( $r=-0.218$ ,  $P=0.401$ ),  $\Delta_{120}$  glucose ( $r=-0.312$ ,  $P=0.223$ ),  $\Delta_{60}$  insulin ( $r=0.345$ ,  $P=0.176$ ) and  $\Delta_{120}$  insulin ( $r=0.128$ ,  $P=0.625$ ). Stepwise multiple regression analysis showed that fasting baPWV and  $\Delta$  pulse pressure were the independent determinants of  $\Delta$  baPWV ( $F=17.0$ ,  $R^2=0.708$ ). In contrast, linear regression analysis showed no significant correlation between  $\Delta$  CAVI and any clinical variables.

#### DISCUSSION

The results of this study show that AI, baPWV and CAVI decreased significantly after meal intake in patients with type 2 diabetes.

Although the precise mechanisms behind the postprandial decreases in these indices are unclear, earlier studies have shown several changes after meal ingestion. Meal ingestion leads to biochemical and hormonal changes including secretion of gastric acid and gut peptides. Increased insulin acts as a vasodilator through generation of nitric oxide.<sup>20</sup> Splanchnic blood flow is enhanced by a variety of postprandial hemodynamic changes including an increase in heart rate, stroke volume and cardiac output.<sup>21,22</sup> Sympathetic nerve activity increases in response to food ingestion to maintain blood pressure in healthy persons.<sup>23</sup> On the other hand, an inadequate sympathetic response sometimes occurs in elderly persons and patients with autonomic neuropathy,<sup>24</sup> and results in a decrease in blood pressure.

Among these changes, our results indicate that hemodynamic changes have important functions in the decrease in AI and baPWV. In this study,  $\Delta$  baPWV is correlated with changes of hemodynamic variables such as  $\Delta$  SBP and  $\Delta$  pulse pressure.  $\Delta$  AI is also correlated with a variety of hemodynamic changes such as SBP, DBP, pulse pressure and heart rate. These results are consistent with earlier studies showing both baPWV and AI as dependent indices on hemodynamic variables such as blood pressure and heart rate.<sup>25–28</sup> On the other hand, in this study, the degree of postprandial changes in glucose and insulin levels were not correlated with  $\Delta$  baPWV and  $\Delta$  AI. This finding is also consistent with an earlier study showing decrease in AI under the insulin clamp technique, whereas no significant relation between  $\Delta$  AI and changes in glucose or insulin levels.<sup>29</sup> These results support the hypothesis that postprandial hemodynamic changes may affect baPWV and AI more directly than the other changes including biochemical, hormonal and autonomic changes.

With regard to postprandial changes in CAVI, we found no correlated clinical variable including postprandial hemodynamic changes. As CAVI was developed as an index of arterial stiffness without the influence of blood pressure,<sup>8,30–32</sup> postprandial hemodynamic effects may be limited for CAVI. Further investigation should be addressed to clarify the influence of biochemical, hormonal or autonomic factors in postprandial changes in CAVI.

The caloric value of the test meal used in this study was 500 kcal, an amount considered to provide appropriate energy for a daily meal. On the other hand, 28 g of fat occupied about 50% of total calorie intake. Berry *et al.* revealed impaired endothelial function after 50 g of high-fat diet.<sup>33</sup> In addition, they also showed different effects on postprandial endothelial function after stearic acid- or oleic acid-rich fat loading even though total calorie intake was similar in the two meals. Therefore, endothelial dysfunction may influence postprandial changes in arterial stiffness. However, our earlier study did not show significant changes in flow-mediated dilatation after 24 g of fat loading,<sup>34</sup> suggesting that the amount of fat loaded in this study has little influence on endothelial function. In addition, Raitakari *et al.* showed that high-fat (61 g; rich in saturated or monounsaturated fats) meal loading did not lead to endothelial dysfunction, as assessed by flow-mediated dilatation in the brachial artery, but it did induce vasodilatation and increased resting and post-ischemic-stimulated forearm blood flow.<sup>35</sup> Consequently, several issues are still in question; namely, the relationship between postprandial changes in arterial stiffness and endothelial function, the effects of different meal composition such as high-fat or carbohydrate meals on postprandial changes in arterial reactivity. Therefore, further investigation should be conducted to illuminate these unsolved issues. However, this study still carries a clear message that the pulse wave indices widely used in clinical practice significantly decrease after a daily meal intake in patients with type 2 diabetes, in spite of an ideal amount of calorie intake.

Our results showed that mean percent changes of baPWV and CAVI from fasting to postprandial state were  $-3$ – $4\%$ . These changes, on the whole, might be considered acceptable for the routine assessment of aortic stiffness in clinical practice. However, the maximal percent decreases of baPWV and CAVI reached  $-10.8$  and  $-14.1\%$ , respectively. In addition, mean percent change of AI showed a larger decrease during the postprandial state. Therefore, when assessing pulse wave indices, especially for AI in the postprandial state, caution should be taken not to underestimate arterial stiffness.

Patients with type 2 diabetes have an increased risk of atherosclerosis and cardiovascular mortality. On the other hand, postprandial hypotension has been observed in elderly patients with advanced

atherosclerosis<sup>24,36,37</sup> and in patients with autonomic neuropathy,<sup>24,38,39</sup> which are frequently seen among patients with diabetes. Unfortunately, we did not assess autonomic function such as heart rate variability. However, the degree of SBP reduction both 60 and 120 min after meal intake ( $11.8 \pm 9.8$  and  $10.8 \pm 10.3$  mm Hg, respectively) was much larger compared with our recent study, which used the same amount of CalorieMate<sup>13</sup> and with another study by Ahuja *et al.*<sup>40</sup> This might imply the presence of sympathetic nerve dysfunction in some of the patients with type 2 diabetes we studied.

Interestingly, our results revealed that the degree of postprandial changes in AI and baPWV correlated with those fasting levels. That is, in a case with advanced aortic stiffness, meal ingestion may result in larger hemodynamic changes and may contribute to larger decreases in AI and baPWV in patients with type 2 diabetes.

This study has several limitations. First, we cannot exclude the possibility that certain medications may affect these pulse indices. To reduce this limitation, however, we provided the withdrawal periods of antihypertensive and lipid-lowering agents. Second, because this study did not have healthy control subjects or patients without diabetes, it remains uncertain as to whether decrease of these pulse indices after meal intake would also be present in healthy persons or in patients without diabetes. Third, the study population was relatively small. However, our results are reasonable given that postprandial changes in AI and baPWV are dependent on hemodynamic changes, whereas CAVI is influenced less by hemodynamic changes.

In conclusion, AI, baPWV and CAVI significantly decreased after daily meal intake in patients with type 2 diabetes. Changes in AI and baPWV but not CAVI after meal intake were influenced by postprandial hemodynamic changes.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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