Relationships between the arterial velocity pulse index as a novel marker of atherosclerosis and biomarkers of cardiac or renal condition in patients with type 2 diabetes mellitus

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Abstract

Background The arterial velocity pulse index (AVI) has been explored as a novel marker of atherosclerosis using pulse wave analysis in the clinical setting. The aim of this study was to clarify the relationships between the AVI and biomarkers of cardiac or renal condition in patients with type 2 diabetes mellitus.

Methods In total, 301 outpatients with type 2 diabetes mellitus (116 males and 185 females; mean age $\pm$ standard deviation: 63 ± 12 years) without a history of cardiovascular events were enrolled in this study. The AVI and biomarkers of cardiac or renal condition were measured using a commercial device, and the relationships between the AVI and the biomarkers were examined.

Results The AVI was significantly associated with biomarkers of cardiac condition such as the blood levels of brain natriuretic peptide ($r = 0.29$, $P < 0.001$) and high-sensitivity cardiac troponin T (hs-cTnT) ($r = 0.48$, $P < 0.001$). The AVI was also significantly associated with biomarkers of renal condition such as the estimated glomerular filtration rate ($r = -0.22$, $P < 0.001$) and urinary albumin excretion ($r = 0.42$, $P < 0.001$). Multiple regression analysis revealed that hs-cTnT and urinary albumin excretion were independent variables that were correlated with the AVI when it was used as a subordinate factor.

Conclusion The results of this study indicate that the AVI is significantly associated with hs-cTnT and urinary albumin excretion in patients with type 2 diabetes mellitus.

Keywords Arterial velocity pulse index · High-sensitivity troponin T · Urinary albumin · Skin autofluorescence · Oxidative stress · Type 2 diabetes mellitus

Introduction

The importance of pulse wave analysis, such as the pulse wave velocity (PWV) and the cardio-ankle vascular index (CAVI), has been reported in recent years. Numerous studies have indicated the clinical usefulness of these artery wall stiffness parameters as markers of atherosclerosis or predictors of cardiovascular events [1, 2]. To measure the arterial velocity pulse index (AVI), a novel marker of atherosclerosis, oscillometric cuffs are employed to monitor pulse waveforms [3]. The AVI can be automatically measured using an oscillometric cuff on one side of the upper arm while the patient is in the sitting position (the same position as used in conventional blood pressure measurement). On the contrary, evaluating the PWV or the CAVI requires some degree of technical expertise to measure the pulse waves, or occlusion/sensing cuffs adapted to both arms and both ankles must be used in the supine position. Thus, measurement of the AVI is very simple compared with the measurement of artery wall stiffness parameters such as the PWV or the CAVI. Increases in the AVI are thought to be due to enhanced arterial reflected waves resulting from increases in artery wall stiffness or other parameters. However, little is known about the clinical significance of the AVI because it has only recently been explored and used in clinical settings [3–5].

It is well known that diabetes mellitus effects systemic organ damage through high glucose levels and/or other factors. In particular, the heart and kidneys are important

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target organs because damage to these organs is closely associated with the incidence of cardiovascular events. Studies have indicated that these organs are impaired at the subclinical stage in patients with diabetes mellitus as compared to those without the disease [6, 7]. Some biomarkers have been shown to be clinical indicators of cardiac or renal condition in recent years. Blood levels of brain natriuretic peptide (BNP) and high-sensitivity cardiac troponin T (hs-cTnT) are used to evaluate cardiac condition, whereas the estimated glomerular filtration rate (eGFR) and urinary albumin concentration are used to evaluate renal condition. Furthermore, these biomarkers of cardiac or renal condition are reported to be clinically useful for predicting the incidence of cardiovascular events [8–11].

To the best of our knowledge, there are no reports regarding the clinical significance of the AVI in the pathogenesis of cardiac or renal conditions in patients with type 2 diabetes mellitus. Therefore, the purpose of this study was to clarify the relationships between the AVI and biomarkers of cardiac or renal condition in patients with type 2 diabetes mellitus.

Subjects and methods

Study population

Patients were enrolled in this study between January 2015 and December 2016. The study population comprised 301 outpatients [116 (38.5%) males and 185 (61.5%) females; mean age $\pm$ standard deviation: 63 ± 12 years] undergoing treatment for diabetes. None of the patients had a history of cardiovascular events, such as ischemic heart disease, stroke, perivascular disease, persistent atrial fibrillation, or heart failure. All participants provided informed consent, and the study protocol was approved by the Local Ethics Committee of the Hitsumoto Medical Clinic (date of approval: January 8, 2015; approval number: 2015-01).

Measurement of the AVI

The AVI was measured using a commercially available instrument (PASSESA AVI-1500; Shisei Datum, Tokyo, Japan) in the sitting position as previously described [3]. Measurements were performed when participants were in a quiet room, with the temperature maintained at 20–25 °C. Treatment with antihypertensive drugs was discontinued at least 24 h prior to performing measurements. The theory behind AVI measurement is shown in Fig. 1. The AVI has the characteristics of a pulse wave pattern at higher cuff pressures than the systolic blood pressure. Two variables

Fig. 1 The theory behind AVI measurement. **a** Normal pulse wave pattern. **b** Abnormal pulse wave pattern caused by enhanced arterial reflected waves. The AVI has the characteristics of a pulse wave pattern at higher cuff pressures than the systolic blood pressure. Two variables are automatically measured: V_f (the first peak of the differential of the waveform with respect to time) and V_r (the absolute value of the bottom of the valley of the differential of the waveform with respect to time), and the AVI is automatically calculated as $20 \times (V_r/V_f)$. The systolic waveform rapidly increases and decreases in response to reflected arterial waves, but the initial waveform is not influenced by reflected waves. V_f is indicative of the initial waveform while V_r is indicative of the subsequent waveform influenced by reflected arterial waves; as the wave reflections increase in strength, the AVI increases in parallel with an increase in V_r . AVI arterial velocity pulse index

are automatically measured: V_f (the first peak of the differential of the waveform with respect to time) and V_r (the absolute value of the bottom of the valley of the differential of the waveform with respect to time), and the AVI is automatically calculated as $20 \times (V_r/V_f)$. The systolic waveform rapidly increases and decreases in response to reflected arterial waves, but the initial waveform is not influenced by the reflected arterial waves. V_f is indicative of the initial waveform while V_r is indicative of the subsequent (weaker) waveform influenced by reflected arterial waves. As the wave reflections become stronger, the AVI increases in parallel with an increase in V_r . Previous reports have confirmed the validity and reliability of the AVI measured using this method [4, 5].

Estimation of cardiovascular risk factors

Various clinical parameters such as classic cardiovascular risk factors, insulin resistance, skin autofluorescence (AF), left ventricular hypertrophy (LVH), biomarkers of cardiac condition (hs-cTnT, BNP), biomarkers of renal condition (eGFR, urinary albumin), inflammation, and oxidative stress were evaluated. The degree of obesity was estimated from the body mass index, which was calculated as the weight in kilograms divided by the square of the height in meters. Obesity was defined as a body mass index of ≥ 25 kg/m². Current smoking was defined as smoking at least one cigarette

per day during the previous 28 days. Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or the use of an antihypertensive medication. The right brachial blood pressure was measured twice using a mercury sphygmomanometer while each participant was in the sitting position. The average of two readings was used to determine the systolic and diastolic blood pressures. Skin AF, which reflects the accumulation of advanced glycation end-products (AGEs), was measured on the volar side of the forearm using a commercial instrument (AGE ReaderTM; DiagnOptics, Groningen, Netherlands), as previously described [12]. Dyslipidemia was defined as low-density lipoprotein cholesterol level ≥ 140 mg/dL, high-density lipoprotein cholesterol level ≤ 40 mg/dL, triglyceride level ≥ 150 mg/dL, or ongoing treatment for dyslipidemia. The number of risk factors was defined as the number of classical cardiovascular risk factors (such as hypertension, dyslipidemia, smoking, or obesity) identified for an individual. The severity of LVH was evaluated using Cornell (R wave in aVL + S wave in V3) electrocardiographic voltage calculations [13].

Blood samples were collected from the antecubital veins of participants the morning after a 12-h fast. Glucose and insulin levels were measured using the glucose oxidase method and an enzyme immunoassay, respectively. To measure insulin resistance, the homeostatic model assessment of insulin resistance (HOMA-IR) was calculated as follows [14]: $\text{HOMA-IR} = \text{fasting glucose concentration (mg/dL)} \times \text{fasting insulin concentration (}\mu\text{g/mL)} / 405$. Glycated hemoglobin (HbA1c) levels were expressed using the National Glycohemoglobin Standardization Program. Total cholesterol and triglyceride levels were measured using standard enzymatic methods. Serum high-density lipoprotein cholesterol levels were measured using selective inhibition. Serum low-density lipoprotein cholesterol levels were calculated using the Friedewald equation [15]. Blood BNP levels were measured using a commercial kit (SHIONOSPOT Reader; Shionogi & Co., Ltd., Osaka, Japan). The hs-cTnT levels were also measured using a commercial kit (Roche Diagnostics, Rotkreuz, Switzerland) [16]. For the hs-cTnT assay, the lower limit of detection was 0.003 ng/mL. The eGFR was calculated using the adjusted Modification of Diet in Renal Disease Study equation, which was proposed by the working group of the Japanese Chronic Kidney Disease Initiative [17], and urinary albumin concentration was measured using a commercial kit (Siemens/Bayer DCA 2000+ analyzer, Siemens Healthineers, Tokyo, Japan). High-sensitivity C-reactive protein (hs-CRP) levels were measured using high-sensitivity latex-enhanced immunonephelometry. The reactive oxygen metabolites

(d-ROMs) test, which reflects blood hydroperoxide concentrations, was performed using a commercial kit (Diacron, Grosseto, Italy) [18].

Statistical analysis

A commercially available statistical software program (Stat View-J 5.0; HULINKS Inc., Tokyo, Japan) was used for all statistical analyses. Data were expressed as mean $\pm$ standard deviation. Between-group comparisons were performed using Student's *t* test, and the correlation coefficient was estimated using Spearman's rank-order correlation analysis. To clarify which independent factors helped to increase the AVI, a multiple regression analysis was performed using the AVI as a subordinate factor. *P* values < 0.05 were considered to indicate statistical significance.

Results

Patient characteristics are shown in Table 1. The AVI was distributed from 11 to 49; the mean value was 27.6 ± 6.7 , and the distribution was near-normal. Hs-cTnT was detected in 269 (89.3%) patients. The relationships between the AVI and biomarkers of cardiac condition are shown in Fig. 2. There was a weak positive correlation between the AVI and BNP level. The AVI was significantly higher for patients with detectable hs-cTnT than in those with undetectable hs-cTnT. Furthermore, there was a significantly positive correlation between the AVI and hs-cTnT for patients with detectable hs-cTnT. The relationships between the AVI and biomarkers of renal condition are shown in Fig. 3. The AVI showed a weak negative correlation with eGFR and a significant positive correlation with urinary albumin concentration. Table 2 shows correlations between the AVI and various clinical parameters. Sex, age, height, current smoking habit, hypertension, systolic blood pressure, pulse rate, HbA1c level, skin AF, number of risk factors, Cornell electrocardiographic voltage, hs-CRP level, and d-ROMs test were all significantly correlated with the AVI.

Multiple regression analysis using the AVI as a subordinate factor was performed with the explanatory variables that were found to be significant during univariate analysis. Age, hs-cTnT, urinary albumin concentration, skin AF, Cornell electrocardiographic voltage, height, pulse rate, d-ROMs test, and number of risk factors were the independent variables that were found to be significantly correlated with the AVI in multiple regression analysis (Table 3).

Table 1 Baseline clinical characteristics

<i>n</i> (male/female)	301 (116/185)
Age (years)	63 ± 12
Obesity, <i>n</i> (%)	90 (30)
Height (<i>m</i>)	1.59 ± 1.0
Body weight (kg)	60.0 ± 10.0
Body mass index	23.7 ± 3.9
Current smoker <i>n</i> (%)	69 (23)
Hypertension <i>n</i> (%)	223 (74)
Systolic blood pressure (mmHg)	139 ± 20
Diastolic blood pressure (mmHg)	85 ± 13
Pulse rate (/s)	67 ± 11
Fasting blood glucose (mg/dL)	133 ± 27
HbA1c (%)	7.1 ± 1.0
Immunoreactive insulin (μg/ml)	7.8 ± 4.8
HOMA-IR	2.6 ± 1.6
Skin autofluorescence (AU)	2.6 ± 0.4
Dyslipidemia <i>n</i> (%)	212 (70)
Total cholesterol (mg/dL)	221 ± 39
LDL cholesterol (mg/dL)	143 ± 37
Triglyceride (mg/dL)	148 ± 62
HDL cholesterol (mg/dL)	47 ± 13
Number of risk factors	2.0 ± 0.9
Cornell voltage (mm)	14.9 ± 4.9
eGFR (ml/min/1.73 m ²)	65 ± 28
Log urinary albumin (mg/g Cr)	1.5 ± 0.5
Log hs-CRP (mg/L)	−1.1 ± 0.5
d-ROMs test (U.Carr)	337 ± 104
Log BNP (pg/ml)	1.7 ± 0.4
Detection of hs-cTnT (%)	269 (89)
Log hs-cTnT (ng/mL)	−2.0 ± 1.6
AVI (range)	27.6 ± 6.7 (11–49)
Medication	
Sulfonylurea <i>n</i> (%)	160 (53)
DPP-4 inhibitor <i>n</i> (%)	135 (45)
Insulin <i>n</i> (%)	24 (8)
RAS inhibitor <i>n</i> (%)	132 (44)
Calcium blocker <i>n</i> (%)	114 (38)
Statin <i>n</i> (%)	144 (48)

Values of continuous parameters are given as mean ± SD. *HbA1c* hemoglobinA1c, *HOMA-IR* homeostasis assessment insulin resistance, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *eGFR* estimated glomerular filtration rate, *hs-CRP* high-sensitivity C reactive protein, *d-ROMs* derivatives of reactive oxygen metabolites, *Risk factor* obesity, current smoker, hypertension, dyslipidemia, *AVI* arterial velocity pulse index, *DPP* dipeptidyl peptidase, *RAS* renin-angiotensin system

Discussion

Okamoto et al. examined the relationship between the AVI and risk factors for cardiovascular disease in 7248 healthy adults. Their results indicated that the mean AVI was 16.6

in subjects with a mean HbA1c level of 5.5% and a mean age of 45.5 years. Furthermore, the AVI values in patients with diabetes mellitus were significantly higher than in those without the disease [5]. On the contrary, the mean AVI in this study was 27.6, with a mean HbA1c level of 7.0% and a mean age of 63 years. This high AVI of patients with diabetes mellitus indicates a high glucose concentration or other factors. Arterial wave reflection is affected by age, sex, height, and pulse rate [19–21]. The results of this study also indicate that these parameters are significantly associated with the AVI, even though the correlation coefficient was found to be weak in the univariate analysis. Furthermore, age, height, and pulse rate were identified as independent variables that are significantly correlated with the AVI. Thus, the AVI is considered to characterize the features of arterial wave reflection. The augmentation index (Aix) is another useful marker of arterial wave reflection and can be noninvasively measured in the radial or carotid artery by tonometry. While the Aix from tonometry is an important marker of arterial wave reflection and cardiovascular risk factors [22], expertise is required to accurately measure the Aix. Conversely, the AVI can be automatically calculated using conventional blood pressure measurements, so AVI measurements have procedural advantages over Aix measurements.

In this study, relatively strong correlations were observed between the AVI and hs-cTnT as a marker of myocardial injury in univariate analysis. Furthermore, hs-cTnT was found to be an independent variable that is correlated with the AVI in multivariate analysis, indicating that the AVI changes with the progression of subclinical myocardial damage in patients with type 2 diabetes mellitus. It is well known that artery wall stiffness is one of the most important factors influencing arterial wave reflection [23]. Okamoto et al. also reported that the AVI is significantly related to the CAVI [5]. Some clinical studies have indicated that artery wall stiffness is significantly related to subclinical myocardial damage (as reflected in the levels of troponin or serum heart-type fatty acid-binding proteins) [24–26]. Several studies have pointed to a significant association between left ventricular dysfunction and myocardial damage [27, 28]. Furthermore, increases in aortic artery wall stiffness cause left ventricular dysfunction [29]. Therefore, the significant relationship between hs-cTnT and the AVI identified in this study can be partly explained by the occurrence of myocardial damage via left ventricular dysfunction resulting from increased artery wall stiffness.

Among the biomarkers of renal condition considered in this work, urinary albumin concentration showed a relatively strong correlation with AVI in univariate analysis. Furthermore, urinary albumin concentration was identified as an independent variable that is correlated with AVI in

Fig. 2 Relationships between the AVI and biomarkers of cardiac condition. There was a weak positive correlation between AVI and BNP level. AVI was significantly higher in patients with detectable hs-cTnT than in those with undetectable hs-cTnT. Furthermore, there was a significant positive correlation between AVI and hs-cTnT in patients with detectable hs-cTnT. Abbreviations used are defined in Table 1

Fig. 3 Relationships between the AVI and biomarkers of renal condition. AVI showed a weak negative correlation with eGFR and a significant positive correlation with urinary albumin concentration. Abbreviations used are defined in Table 1

multivariate analysis. Albuminuria is reported to reflect systemic endothelial dysfunction [30]. Flow-mediated vasodilation in the brachial artery (FMD) is the most widely used noninvasive test for assessing endothelial function [31, 32], but the measurement of FMD requires some degree of technical expertise. The AVI can be used to relatively simply evaluate systemic endothelial function in the clinical setting, although other factors influence the AVI too.

In this study, skin AF, a marker of the accumulation of AGEs in tissue, was found to be the only independent glucose-related variable correlated with the AVI. A number of basic research and clinical studies have reported that AGEs play an important role in the pathogenesis of diabetic complications [33, 34]. Furthermore, some studies have indicated that an increase in skin AF is significantly associated with arterial dysfunction, as evaluated using the

PWV or FMD [35, 36]. The results of the present study indicate that an increase in skin AF levels is indicative of a deterioration in arterial function given the correlation of skin AF with increased arterial wave reflection. Yamagishi et al. reported that the accumulation of AGEs is a marker compatible with the “hyperglycemic memory” theory [34]. Therefore, the results of the present study and previous studies indicate that long-term hyperglycemia affects arterial function, including the AVI, in patients with type 2 diabetes mellitus.

LVH is reported to be independently associated with diabetes mellitus, even in the absence of hypertension [37, 38]. Furthermore, in the present study, LVH was found to be an independent variable that was correlated with AVI in patients with type 2 diabetes mellitus. Some studies have reported a significant relationship between arterial wave

Table 2 Relationships between the AVI and various clinical parameters

Parameter	<i>r</i>	<i>P</i> value
Sex (female = 0, male = 1)	−0.18	<0.01
Age	−0.28	<0.001
Obesity (no = 0, yes = 1)	0.06	0.287
Height	−0.28	<0.001
Body weight	−0.10	0.083
Body mass index	−0.10	0.087
Current smoker (no = 0, yes = 1)	0.12	<0.05
Hypertension (no = 0, yes = 1)	0.23	<0.001
Systolic blood pressure	0.24	<0.001
Diastolic blood pressure	0.11	0.059
Pulse rate	−0.31	<0.001
Fasting blood glucose	0.10	0.076
HbA1c	0.17	<0.01
Immunoreactive insulin	0.06	0.295
HOMA-IR	0.08	0.173
Skin autofluorescence	0.45	<0.001
Dyslipidemia	0.09	0.102
Total cholesterol	0.05	0.345
LDL cholesterol	0.08	0.180
Triglyceride	0.04	0.458
HDL cholesterol	−0.08	0.162
Number of risk factors	0.29	<0.001
Cornell voltage	0.40	<0.001
Log hs-CRP	0.12	<0.05
d-ROMs test	0.42	<0.001
Sulfonylurea (no = 0, yes = 1)	0.04	0.493
DPP-4 inhibitor (no = 0, yes = 1)	−0.05	0.363
Insulin (no = 0, yes = 1)	0.07	0.215
RAS inhibitor (no = 0, yes = 1)	−0.08	0.199
Calcium blocker (no = 0, yes = 1)	−0.02	0.852
Statin (no = 0, yes = 1)	−0.09	0.103

r Correlation coefficient between AVI and the relevant clinical parameter. Abbreviations used are defined in Table 1

reflection and LVH [39]. Thus, the results of the present study and previous studies indicate that arterial wave reflection is an important determinant of LVH in patients with type 2 diabetes mellitus.

Clinical studies have indicated that oxidative stress is associated with arterial function in patients with type 2 diabetes mellitus [40]. In this study, the d-ROMs test—a marker of oxidative stress in vivo—was significantly correlated with the AVI. The suggested underlying mechanism is that oxidative stress causes an increase in arterial wave reflection, such as an increase in the PWV or peripheral vascular resistance [40, 41]. Thus, oxidative stress is considered to be an important factor in increased AVI.

Table 3 Multiple regression analysis for AVI

Explanatory factor	β	<i>t</i> value	<i>P</i> value
hs-cTnT	0.27	6.3	<0.001
Age	0.25	6.0	<0.001
Log urinary albumin	0.23	5.6	<0.001
Skin AF	0.23	5.2	<0.001
Cornell voltage	−0.22	−3.6	<0.001
Height	−0.12	−2.9	<0.01
Pulse rate	−0.11	−2.8	<0.01
d-ROMs test	0.11	2.7	<0.01
Number of risk factors	0.09	2.0	<0.05
BNP	0.09	1.9	0.063
Sex	0.09	1.8	0.132
Systolic BP	0.07	1.5	0.168
Hypertension	0.06	1.4	0.170
Log hs-CRP	0.06	1.4	0.173
eGFR	−0.04	−1.2	0.289
Current smoker	0.03	1.0	0.376
HbA1c	0.03	0.9	0.458

$R^2 = 0.44$, *F* value = 24.9, *P* < 0.001 (*n* = 301)

Abbreviations used are defined in Table 1

This study has several limitations. First, treatment with antihypertensive drugs was discontinued at least 24 h prior to performing the measurements to avoid any influence on the AVI. However, 24 h was not a sufficient period of time to mitigate the effects of long-acting drugs such as amlodipine. Second, ultrasonic echocardiography, coronary angiography, and multidetector computed tomography angiography were not performed. Therefore, cardiovascular diseases such as heart failure or coronary artery disease might have gone undetected. Third, medical treatments may have influenced the study results. Finally, this was a cross-sectional single-unit study, and the sample size was relatively small. Additional prospective studies that include evaluations of interventional therapies are required to clarify the clinical significance of the AVI as a marker of atherosclerosis or cardiovascular risk in patients with type 2 diabetes mellitus.

In conclusion, the results of this study indicate that the AVI—a novel marker of atherosclerosis that is determined using pulse wave analysis—is correlated with biomarkers for cardiac or renal condition, such as increased hs-cTnT and urinary albumin concentration, in patients with type 2 diabetes mellitus.

Compliance with ethical standards

Conflict of interest The author declares that there is no conflict of interest.

Human rights statement All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent or a substitute for it was obtained from all patients before they were included in the study.

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