Viscoelastic Deterioration of the Carotid Artery Vascular Wall is a Possible Predictor of Coronary Artery Disease

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Aim: The viscoelastic properties of the artery are known to be altered in patients with vascular diseases. However, few studies have evaluated the viscoelasticity of the vascular wall in humans. We sought to investigate the degree of viscoelastic deterioration of the carotid artery and assess its clinical implications.

Methods: Between January 2011 and June 2013, patients in whom the toe-brachial index was measured at the vascular laboratory were included in this single-institute retrospective observational study. \( I^* \), a parameter of viscoelastic deterioration, was computed using a non-invasive ultrasonic Doppler effect sensor on the carotid artery. \( I^* \) is a non-dimensional value, and \( I^* > 0 \) is considered abnormal. Other patient characteristics were identified and tested for correlations with \( I^* \).

Results: The study included 383 patients. The mean \( I^* \) value was 0.13 ± 0.22 with a normal distribution. Factors that increased the \( I^* \) value were a female sex (0.18 ± 0.23 vs. 0.10 ± 0.21, \( P < 0.001 \)), age ≥ 60 (0.14 ± 0.22 vs. 0.06 ± 0.23, \( P < 0.05 \)) and systolic blood pressure of > 140 (0.15 ± 0.22 vs. 0.10 ± 0.22, \( P < 0.05 \)). \( I^* \) abnormality was a significant risk factor for coronary artery disease (OR 2.20, 95% CI 1.00-4.80, \( P < 0.05 \)) in a univariate analysis. In the multivariate analysis, \( I^* \) abnormality was also found to be an independent risk factor for coronary artery disease (OR 4.56, 95% CI 1.21-30.1, \( P < 0.05 \)).

Conclusions: \( I^* \) may reflect the degree of atherosclerotic changes in the arterial wall and could possibly be used to predict coronary artery disease.

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Key words: Viscoelasticity, Atherosclerosis, Coronary artery disease

Introduction

Because atherosclerosis-related disease is the leading cause of death in developed countries, the application of adequate prophylaxis and treatment based on an accurate evaluation of the degree of arteriosclerosis is essential. Physiological indicators of atherosclerosis, such as the flow mediated dilation (FMD)¹⁻³, pulse wave velocity (PWV)⁴⁻⁶ and ankle brachial index (ABI)⁷, ⁸, are widely used and have been proven, to some extent, to be predictors of vascular disease.

When assessing vascular remodeling from a material mechanics standpoint, it is important to presuppose the artery to be viscoelastic, rather than simply an elastic material. It is known that smooth muscles have a viscous effect, while elastin fibers exert an elastic effect⁹. The importance of evaluating both of these qualities has been previously demonstrated¹⁰. Although various studies assessing the viscoelasticity of the vascular wall non-invasively have been carried
Patient Population

Between January 2011 and June 2013, patients who underwent toe-brachial index (TBI) measurement at the vascular laboratory of The University of Tokyo Hospital (Tokyo, Japan) simultaneously received vascular viscoelasticity measurement and were included in this study. The measurements of the TBI were primarily used for screening or follow-up of peripheral arterial disease (PAD). All measurements were obtained by cardiovascular technologists.

Arterial Viscoelasticity

The viscoelasticity of the arterial wall was measured as previously described (Fig. 1A). Briefly, an ultrasonic Doppler effect sensor was set perpendicular to the blood vessel to measure the deformation velocity. The $I^*$ parameter was then automatically obtained from the ratio of deceleration ($P_2$) to acceleration ($P_1$) of the vascular wall during its expansion and the time of the maximum deformation velocity ($t_m / T$), as shown in Fig. 1A and 1B. This is a non-dimensional value ranging from $-1.0$ to $1.25$. An $I^*$ value of $>0$ is considered to indicate abnormal viscoelastic degeneration. The proposed calculation was originally derived from observational studies of a sufficient number of patients. Moreover, most studies referring to the viscoelastic properties of the artery have focused only on elastic properties, such as stiffness or the elastic modulus.

Aim

In this single-institute retrospective study, we examined the degree of viscoelastic deterioration of the arterial wall by measuring the $I^*$ value in the carotid artery. This method, which is non-invasive and based on the use of Doppler ultrasound to calculate values in real time, has been shown in previous studies to reflect atherosclerotic changes. The aim of the present study was to determine how these data were related to the clinical characteristics, comorbidities and physiological parameters in patients with or at high risk of atherosclerosis and evaluate the clinical usefulness of the above method.

Methods

This study was approved by the ethics committee of the Graduate School of Medicine, The University of Tokyo.
clinical data obtained from subjects with and without atherosclerosis, and its adequacy was confirmed using in vitro pulsatile pressure testing machines. In addition, measuring the I* value in vitro employing different types of rubber with various elastic and viscoelastic properties has been shown to have high reproducibility.

A small Doppler effect sensor of TRY-1 (21600BZX00440000, Taiyo Denshi Co. Ltd., Miyagi, Japan), which is the diagnostic equipment for the method described above, was placed on the cervical region in each patient in the supine position, and the deformation velocity of the common carotid artery was measured based on the pulsatile Doppler wave sound. This procedure normally takes no more than 15 seconds for a non-obese patient. The contralateral common carotid artery was then evaluated. The higher value was adopted for the analysis.

### Other Physiological Measurements

Prior to the arterial viscoelasticity assessment, all patients underwent measurement of the blood pressure (BP) in the bilateral brachial and ankle arteries, ABI, TBI and cardio-ankle vascular index (CAVI) using the VaSera VS-1500ATN device (Fukuda Denshi Co. Ltd., Tokyo, Japan) in the supine position. Height and weight were also recorded. If the patient had undergone measurement of the maximum intima-media thickness (IMT) of the common carotid artery on ultrasonography within a year of the examinations described above, that value was used for the analysis.

Regarding the observed right and left data, the higher values for BP, CAVI and maximum IMT and the lower values for ABI and TBI were adopted for the analysis. In patients with an ABI of ≤ 0.90, the CAVI was marked as a missing value considering the possibility of underestimation.

### Clinical Characteristics

A patient was assumed to have diabetes mellitus, hypertension or dyslipidemia if they were on corresponding medications. Cerebrovascular disease (CVD) was diagnosed based on a medical history of ischemic stroke or transient ischemic attack. Coronary artery disease (CAD) was diagnosed based on a medical history of percutaneous coronary intervention, coronary artery bypass graft surgery or previous myocardial infarction. PAD was diagnosed according to an ABI of ≤ 0.90, critical limb ischemia (CLI) or history of related surgical or endovascular intervention. CLI was defined as the occurrence of chronic ischemic rest pain, ulcer formation or the onset of gangrene attributable to objectively proven arterial occlusive disease.

Polyvascular disease (PVD) was defined as the presence of more than one of the following: CVD, CAD and/or PAD.

### Statistical Analysis

All statistical evaluations were performed using standard software programs (JMP Pro 10.0.2, SAS Institute, Cary, NC, USA). The Shapiro-Wilk test was used to analyze the normality of the distribution of each sample. Student’s t-test was used for comparisons between groups of patients. Correlation analyses were performed using the Pearson’s correlation test. For the univariate analysis, descriptive statistics were used to compare characteristics between the patients with and without vascular diseases. Associations with vascular diseases were assessed using the chi-square test for categorical variables. Variables with n ≤ 5 were evaluated using a two-tailed Fisher’s exact probability test instead. In addition, variables associated with vascular diseases with a P value of <0.10 in the univariate analysis were included in a multivariate logistic regression model. The multivariate analysis was carried out for P values of I* abnormality of <0.10. A P value of <0.05 was regarded as being statistically significant. The values are reported as the mean± standard deviation (SD), unless otherwise specified.

### Results

#### Study Population

There were a total of 462 consecutive examinations in 393 patients. The first calculated value was included in the analysis of patients who underwent measurements on multiple occasions. One patient < 20 years of age and 9 patients whose vascular viscoelasticity could not be measured due to mechanical problems were excluded, leaving 383 patients. The baseline characteristics of the study population are presented in Table 1.

#### Viscoelasticity of the Arterial Wall

The I* values ranged from −0.73 to 1.09 and had a normal distribution (P<0.001, Fig.2). The I* values in women (0.18±0.23) were significantly higher than those observed in men (0.10±0.21, P<0.001, Table 2). Patients with an age of ≥ 60 years had significantly greater values (0.14±0.22) than those <60 years of age (0.06±0.23, P=0.007), while the subjects with a systolic BP of >140 mmHg had significantly higher values (0.15±0.22) than those with a systolic BP of ≤ 140 mmHg (0.10±0.22, P=0.037). There were no significant differences between the patients with and without other comor-
Correlations of I* with the other Parameters

There was a tendency for the I* value to increase with age, although the correlation was not significant ($R=0.08$, Fig. 3). However, a weak positive correlation between I* and CAVI was observed ($R=0.16$, Fig. 4). When the patients were subdivided according to age and the renal function, this correlation diminished as age increased and the renal function worsened (Fig. 5A and 5B). The I* values displayed no significant correlations with the body mass index ($R=-0.11$), systolic or diastolic BP ($R=0.06$ and 0.01, respectively), ABI ($R=-0.002$), TBI ($R=0.02$), maximum IMT of the common carotid artery ($R=0.03$) or estimated glomerular filtration rate (eGFR, $R=0.06$).

I* and Vascular Disease

I* abnormality was a significant risk factor for CAD (OR 2.20; 95% CI 1.00-4.80; $P=0.045$), but not PAD (OR 0.82; 95% CI 0.49-1.38; $P=0.449$) or PAD, a significant risk factor for CAD (OR 2.20; 95% CI 1.00-4.80; $P=0.045$), but not PAD (OR 0.82; 95% CI 0.49-1.38; $P=0.449$).

Table 1. Patient demographics

| Characteristics                      | All patients ($n=383$) |
|--------------------------------------|------------------------|
| Age, y                               | 69.4 ± 11.1            |
| Male sex, $n$ (%)                    | 244 (63.8)             |
| Body mass index, kg/m²               | 23.4 ± 3.7             |
| I*                                  | 0.13 ± 0.22            |
| Systolic blood pressure, mmHg        | 141 ± 20               |
| Ankle-brachial index                 | 0.92 ± 0.24            |
| Toe-brachial index                   | 0.66 ± 0.22            |
| Cardio-ankle vascular index, m/sec   | 9.1 ± 1.6              |
| Comorbidity                          |                        |
| Diabetes mellitus, $n$ (%)           | 221 (57.7)             |
| Hypertension, $n$ (%)                | 265 (69.2)             |
| Dyslipidemia, $n$ (%)                | 194 (50.8)             |
| Cerebrovascular disease, $n$ (%)     | 39 (10.2)              |
| Coronary artery disease, $n$ (%)     | 71 (18.5)              |
| Peripheral arterial disease, $n$ (%) | 132 (34.5)             |
| Abdominal aortic aneurysm, $n$ (%)   | 43 (11.2)              |
| Chronic kidney disease, $n$ (%)      | 180 (49.3)             |
| Current or ex-smoking, $n$ (%)       | 192 (50.1)             |

Table 2. I* values according to risk factors for atherosclerosis

| Variable                      | Yes ($n$) | No ($n$) | $P$ value |
|-------------------------------|-----------|----------|-----------|
| Male sex                      | 0.10 ± 0.21 (244) | 0.18 ± 0.23 (139) | <0.001**   |
| Age ≥ 60                      | 0.14 ± 0.22 (320) | 0.06 ± 0.23 (63) | 0.007**    |
| sBP >140                      | 0.15 ± 0.22 (180) | 0.10 ± 0.22 (202) | 0.037*     |
| ABI ≤ 0.90                    | 0.12 ± 0.23 (124) | 0.13 ± 0.22 (258) | 0.798      |
| TBI ≤ 0.70                    | 0.13 ± 0.23 (188) | 0.12 ± 0.20 (164) | 0.661      |
| CAVI ≥ 9                      | 0.15 ± 0.22 (148) | 0.10 ± 0.23 (143) | 0.064      |
| eGFR < 60                     | 0.15 ± 0.22 (145) | 0.12 ± 0.22 (185) | 0.189      |
| Dialysis dependent            | 0.09 ± 0.19 (35)  | 0.13 ± 0.22 (337) | 0.229      |
| DM                            | 0.12 ± 0.22 (221) | 0.14 ± 0.22 (162) | 0.480      |
| HT                            | 0.12 ± 0.22 (265) | 0.14 ± 0.23 (118) | 0.411      |
| DL                            | 0.14 ± 0.23 (194) | 0.12 ± 0.21 (188) | 0.323      |
| Current or ex-smoking         | 0.11 ± 0.23 (192) | 0.14 ± 0.22 (191) | 0.276      |

sBP: systolic blood pressure; ABI: ankle-brachial index; TBI: toe-brachial index; CAVI: cardio-ankle vascular index; eGFR: estimated glomerular filtration rate; DM: diabetes mellitus; HT: hypertension; DL: dyslipidemia
*: $P<0.05$, **: $P<0.01$
Fig. 3. Relationship between age and I*  
The I* values tended to increase with age, although not with statistical significance ($R=0.08$).

Fig. 4. Relationship between CAVI and I*  
There was a weak positive correlation between the CAVI values, which represent the stiffness of the artery, and the I* values, which represent the viscoelasticity of the artery ($R=0.16$).

Fig. 5A. Relationship between CAVI and I* according to the subgroup of age  
There was a strong to moderate positive correlation between the CAVI and I* values in the younger age group; however, this correlation was diminished in the elderly group.
of arterial stiffness, in the elderly or those with an impaired renal function warns clinicians that when risk factors for atherosclerosis increase, the stiffness as well as viscoelasticity must receive attention since the two factors do not have a linear relationship. Unlike ABI and IMT, which measure the decrease in BP in the lower extremities and degree of stenosis in the arteries, \( I^* \) is more of an integrated parameter that quantifies the extent of viscoelastic deterioration of the artery.

In this study, we chose the carotid artery as a representative vessel of the systemic vasculature. Comparing the IMT and degree of stiffness of the carotid artery and thoracic aorta, Pearson et al.\(^{17}\) pointed out that alterations in the carotid artery may generally be regarded as being representative of changes in large vessels throughout the body. A sufficient correlation between \( I^* \) of the carotid artery and that of the femoral artery in PAD patients has also been demonstrated.\(^{13} \) Another advantage of using the carotid artery is its accessibility, which is a crucial factor for routine medical checkups. The Doppler sensor of arterial stiffness, in the elderly or those with an impaired renal function warns clinicians that when risk factors for atherosclerosis increase, the stiffness as well as viscoelasticity must receive attention since the two factors do not have a linear relationship. Unlike ABI and IMT, which measure the decrease in BP in the lower extremities and degree of stenosis in the arteries, \( I^* \) is more of an integrated parameter that quantifies the extent of viscoelastic deterioration of the artery.

**Discussion**

In the present study, we found that \( I^* \), a parameter indicative of the deterioration of arterial wall viscoelasticity, showed unique features compared to traditional physiological indicators of atherosclerosis. Another finding was the strong relationship between \( I^* \) abnormality and comorbid CAD, which no other studies conducted to date have demonstrated. There was also a close relationship between \( I^* \) abnormality and CVD, although it was statistically insignificant.

The decorrelation of \( I^* \) with CAVI, a parameter of arterial stiffness, in the elderly or those with an impaired renal function warns clinicians that when risk factors for atherosclerosis increase, the stiffness as well as viscoelasticity must receive attention since the two factors do not have a linear relationship. Unlike ABI and IMT, which measure the decrease in BP in the lower extremities and degree of stenosis in the arteries, respectively, \( I^* \) is more of an integrated parameter that quantifies the extent of viscoelastic deterioration of the artery.

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TRY-1 is only 2.4 cm in diameter, and the I* value can be measured by simply exposing the patient’s cervical region.

Quantification of the viscoelasticity of the artery has been previously attempted using different techniques. Armentano et al.\textsuperscript{10} used ultrasonographic tracking devices to measure the elasticity and viscosity behaviors separately in the carotid and femoral arteries. The authors were able to show differences between normotensive and hypertensive patients, although individuals with echogenic plaque were excluded from the study. Balocco et al.\textsuperscript{11} proposed an ultrasonography-based method for estimating viscoelastic parameters in a three-element Maxwell vascular wall model using an experimental setup, but not in vivo. In addition, Bukač et al.\textsuperscript{18} used a computational viscoelastic model of the carotid artery to assess the role of longitudinal displacement in the pathophysiology of arte-

Table 3. Factors associated with and without CAD

| Variable          | Univariate                          | Multivariate                        |
|-------------------|-------------------------------------|-------------------------------------|
|                   | Odds ratio  | 95% CI | P value | Odds ratio  | 95% CI | P value |
| Male sex         | 1.45        | 0.83-2.53 | 0.192 | 4.56        | 1.21-30.1 | 0.022* |
| Age ≥ 60         | 1.44        | 0.68-3.08 | 0.342 | 1.95        | 0.67-5.40 | 0.216 |
| I* > 0           | 2.20        | 1.00-4.80 | 0.045* | 1.93        | 0.87-4.48 | 0.104 |
| sBP > 140        | 1.42        | 0.84-2.39 | 0.184 | 2.56        | 1.17-5.80 | 0.018* |
| ABI ≤ 0.90       | 3.12        | 1.83-5.31 | <0.001** | 1.93        | 0.87-4.48 | 0.104 |
| TBI ≤ 0.70       | 2.20        | 1.22-3.95 | 0.008** | 1.22        | 0.66-2.34 | 0.387 |
| CAVI > 9         | 2.33        | 1.16-4.71 | 0.016* | 2.35        | 1.05-5.43 | 0.037** |
| eGFR < 60        | 2.91        | 1.55-5.48 | <0.001** | 2.35        | 1.05-5.43 | 0.037** |
| Dialysis dependent| 4.62        | 2.23-9.56 | <0.001** | 1.71        | 0.66-4.98 | 0.276 |
| DM               | 1.34        | 0.79-2.28 | 0.283 | 1.71        | 0.66-4.98 | 0.276 |
| HT               | 2.04        | 1.08-3.82 | 0.025* | 1.71        | 0.66-4.98 | 0.276 |
| DL               | 1.75        | 1.03-2.97 | 0.037* | 1.42        | 0.64-3.24 | 0.387 |
| Current or ex-smoking | 2.43  | 1.41-4.20 | 0.001** | 2.35        | 1.05-5.43 | 0.037** |

CAD: coronary artery disease; sBP: systolic blood pressure; ABI: ankle-brachial index; TBI: toe-brachial index; CAVI: cardio-ankle vascular index; eGFR: estimated glomerular filtration rate; DM: diabetes mellitus; HT: hypertension; DL: dyslipidemia; CI: confidence interval

*: P<0.05, **: P<0.01

Table 4. Factors associated with and without CVD

| Variable          | Univariate                          | Multivariate                        |
|-------------------|-------------------------------------|-------------------------------------|
|                   | Odds ratio  | 95% CI | P value | Odds ratio  | 95% CI | P value |
| Male sex         | 2.85        | 1.22-6.63 | 0.012** | 2.31        | 0.79-8.51 | 0.133 |
| Age ≥ 60         | 1.09        | 0.44-2.73 | 0.850 | 3.86        | 0.73-71.3 | 0.126 |
| I* > 0           | 3.23        | 0.97-10.8 | 0.055 | 0.73        | 0.11-2.95 | 0.692 |
| sBP > 140        | 0.76        | 0.39-1.48 | 0.421 | 2.89        | 1.32-6.34 | 0.006** |
| ABI ≤ 0.90       | 2.15        | 1.10-4.20 | 0.022* | 3.35        | 1.15-12.2 | 0.026* |
| TBI ≤ 0.70       | 2.89        | 1.32-6.34 | 0.006** | 3.35        | 1.15-12.2 | 0.026* |
| CAVI > 9         | 5.12        | 1.70-15.4 | 0.002** | 3.35        | 1.15-12.2 | 0.026* |
| eGFR < 60        | 3.96        | 1.71-9.18 | <0.001** | 3.35        | 1.15-12.2 | 0.026* |
| Dialysis dependent| 2.47        | 1.00-6.11 | 0.045* | 2.54        | 0.96-7.18 | 0.060 |
| DM               | 1.19        | 0.61-2.36 | 0.609 | 1.19        | 0.61-2.36 | 0.609 |
| HT               | 0.88        | 0.43-1.78 | 0.719 | 0.88        | 0.43-1.78 | 0.719 |
| DL               | 0.91        | 0.47-1.77 | 0.785 | 0.91        | 0.47-1.77 | 0.785 |
| Current or ex-smoking | 1.49  | 0.76-2.92 | 0.244 | 1.49        | 0.76-2.92 | 0.244 |

CVD: cerebrovascular disease; sBP: systolic blood pressure; ABI: ankle-brachial index; TBI: toe-brachial index; CAVI: cardio-ankle vascular index; eGFR: estimated glomerular filtration rate; DM: diabetes mellitus; HT: hypertension; DL: dyslipidemia; CI: confidence interval

*: P<0.05, **: P<0.01
rial wall mechanics; however, their method requires the use of complicated simulations and equations. $I^*$, the parameter evaluated in the present study, is a non-dimensional, easy-to-comprehend value, features that are of great usefulness in daily clinical practice.

In the current study, the $I^*$ values were significantly higher in women than in men. It is known that, after menopause, the decrease in estrogen predisposes the subject to atherosclerosis because this hormone not only inhibits low-density lipoprotein, but also has direct effects on nitric oxide synthesis and smooth muscle proliferation, providing vascular protection. Taking into account the fact that nearly all the women included in this study were >50 years of age, the hormonal environment may have contributed to the marked viscoelastic deterioration of the arteries noted in women compared with men in the present study.

Another factor found to be associated with a higher $I^*$ value was high BP, which is consistent with the report of Armentano et al. demonstrating altered elasticity and viscosity of the carotid artery in patients with high BP levels. Theoretically, the effects of BP and pulse rate on $I^*$ can be ignored because the pulse is converted into a non-dimensional value, that is, normalized according to the maximum amplitude and its period (Fig. 1). Therefore, this result reflects the adverse viscoelastic effects of continuous stress caused by a high BP on the artery and indicates the importance of achieving BP control.

The strong correlation between $I^*$ abnormality and CAD observed in this study may be due to an increase in myocardial oxygen consumption as a result of viscoelastic deterioration in peripheral vessels. It is known that larger vessels, such as the thoracic aorta, are more compliant and exhibit both elastic and viscoelastic distention, while smaller vessels are more rigid; thus, viscoelastic deformation dominates the response in these vessels. Such viscoelastic alterations may affect cardiovascular homeostatic control, thereby modulating various parameters, including arterial impedance, cardiac afterload and myocardial oxygen consumption.

The reasons for the close but statistically insignificant relationship between $I^*$ abnormality and comorbid CVD remain unclear. The presumably smaller impact of peripheral arterial viscoelastic deterioration on cerebral oxygen demand compared with that exerted on cardiac oxygen consumption is one potential factor. Another may be the small portion of patients with CVD included in the present study. However, there were no evident relationships between $I^*$ abnormality and comorbid PAD. This result is reasonable because the definition of PAD used in the present study was based on the ABI measurements and our findings demonstrated the lack of any significant correlations between $I^*$ and ABI.

The limitations of this study include the retrospective design and selection bias in the patient population. Most of the participants were patients from the Division of Vascular Surgery or Department of Diabetes and Metabolic Diseases. Further studies investigating the $I^*$ values in a broader population, including subjects with low to no risk of atherosclerosis, are therefore needed to delineate the clinical characteristics and usefulness of $I^*$.

Another issue is the possibility of intra-individual and inter-individual error. As for the former, since $I^*$ measurement is not based on image assessments, the values may be influenced by the presence of heterogeneous viscoelastic regions along the blood vessel. As for the latter, although the reproducibility of $I^*$ measurements has been previously shown in vitro, the reproducibility in patients must be examined in future studies.

Conclusions

Our method of measuring $I^*$, an index of viscoelastic deterioration of the vascular wall, is simple, non-invasive and feasible in the clinical setting and may effectively be used to predict coronary artery disease.

Acknowledgements

None.

Conflicts of Interest

None.

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