Influence of Age and Hypertension on the Association Between Small Artery Compliance and Coronary Artery Disease

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Small artery elasticity index (SAEI) as determined by a new non-invasive pulse-wave contour analysis has been used to identify abnormalities of the arterial wall associated with aging, hypertension (HT), endothelial dysfunction, and coronary artery disease (CAD). The present study examined the influence and interaction of CAD risk factors on the association between SAEI in risk-associated patients with CAD (case subjects, \( n = 178 \)) and without CAD (control subjects, \( n = 202 \)). Case subjects had a lower SAEI than control subjects, and age was consistently and negatively correlated with SAEI. The HT was related to reduced SAEI in female subjects overall and in male case subjects. In male patients with hypertension, the association between SAEI and CAD was significant \(( P < .05)\) after considering conventional risk factors of CAD. In conclusion, age and HT should be considered when using SAEI in the early diagnosis of CAD, and lower SAEI could be of greatest diagnostic value in male patients with HT. Am J Hypertens 2004;17:1188–1191 © 2004 American Journal of Hypertension, Ltd.

**Key Words:** Small artery elasticity index (SAEI), non-invasive pulse wave contour analysis, coronary artery disease (CAD), CAD risk factors, hypertension (HT).

Endothelial dysfunction, which is characterized by decreased activity or bioavailability of nitric oxide (NO) derived from the endothelium, is a critical event in the early stage of atherosclerosis or arteriosclerosis. Recently, a new non-invasive technique that can measure the elasticity (compliance) of small arteries, or arterioles, using a small artery elasticity index (SAEI) estimated by combining a pulse-wave contour analysis recorded by tonometry from the radial artery and a computer analysis of diastolic decay based on a modified Windkessel model of the vasculature has been developed and validated. As the endothelial release of NO affects the elasticity of thinner-walled branch vessels and arterioles, SAEI has been shown to be able to identify the presence of endothelial dysfunction in the microvascular circulation because it decreases in response to the inhibition of NO synthesis by \( \text{N}^\text{G}\text{-nitro-L-arginine methyl ester} \) and is restored by the infusion of L-arginine in humans. It has been noted that SAEI is lower in postmenopausal women with symptomatic coronary artery disease (CAD) than in those without CAD. Small artery compliance as measured by SAEI also reflects subtle vascular alterations due to aging and HT, and type 1 diabetes, and is gender-dependent: female subjects have been observed to have lower SAEI than male subjects. In subjects with high-normal blood pressure (BP), SAEI is inversely related to intima-media thickness (IMT) of the common carotid artery. A very recent study by Syeda et al indicated that lower SAEI was associated with diffuse-CAD, although the validity of SAEI measurements in hypertensive patients has been called into question in another recently published article. Therefore, SAEI appears to be a useful tool for the clinical screening of individuals who are predisposed to CAD, especially considering that the measurement of SAEI by this new technique is simple to perform, operator independent, and time saving.

However, because SAEI is associated with both risk factors for CAD including age, gender, HT, diabetes,
and CAD itself, it is not yet clear whether the association between SAEI and CAD is independent of or may interact with these risk factors for CAD. Therefore, in the present study we examined the association among SAEI, CAD risk factors, and CAD in a group of risk-associated subjects to clarify whether or how conventional risk factors of CAD may affect the association between SAEI and CAD.

**Methods**

This study included 380 inpatients and outpatients (214 men and 166 women, 40 to 80 years of age) at Fukuoka University Hospital from 2000 to 2002. All patients were risk associated (ie, all had one or more risk factors for CAD). This study was approved by the Ethics Committee of Fukuoka University Hospital and informed consent was obtained from each patient. Patients who had typical chest pain that lasted 5 to 15 min and was accompanied by ischemic changes on electrocardiography, who had previously experienced myocardial infarction, or who had ≥75% stenosis in one or more coronary arteries according to coronary angiography for suspected angina pectoris were defined as those with evident CAD (case subjects, n = 178; 42 female and 136 male), whereas the others were considered to be without evident CAD (control subjects, n = 202; 124 female and 78 male). Patients with spastic angina pectoris were excluded from the study. Patients with arteriosclerosis obliterans, valvular heart disease, arrhythmia, or heart failure were also excluded because of inaccuracy in pulse-wave recording and analysis. Patients who were taking antihypertensive therapy daily for >6 months comprised 43% of the total subjects; the drugs included β-blockers, Ca antagonists, angiotensin converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARB). Patients who were receiving lipid-lowering therapy daily for >6 months comprised 30.5% of the total subjects; the drugs included statins and fibrates.

Small artery compliance was estimated by the new non-invasive pulse-wave contour analysis developed and validated by the research group of Cohn et al. The computer-based Research CardioVascular Profiling system (CR-2000, Hypertension Diagnostics Inc., Eagan, NM) was used to perform the analysis. The SAEI was estimated from the diastolic decay portion of the cardiac cycle using an electrical analog model (ie, a modified Windkessel model) that considers the vasculature to consist of an oscillatory or reflective compliance element. Pulse waves were recorded in all of the patients by the same investigator.

Statistical analysis was performed using the Statistical Analysis System (SAS) version 6.12 software package (SAS Institute Inc., Cary, NC) at Fukuoka University. Categorical variables (such as gender) were compared between case subjects and control subjects by a χ² analysis. Differences in variables between patients with and without evident CAD were examined by analysis of variance, and variables were adjusted for age and gender by analysis of covariance. The correlations between SAEI and other variables were examined by Pearson analysis or simple regression analysis. The multiple logistic model was used to evaluate the consistency of the association between SAEI and CAD with and without adjusting for risk factors for CAD. For all odds ratios, we calculated 95% confidence intervals (CI). All P values are two tailed. The significance level was considered to be 5% unless indicated otherwise.

**Table 1.** Characteristics of patients with (case subjects) and without evident coronary artery disease (control subjects)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control Subjects</th>
<th>Case Subjects</th>
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<tbody>
<tr>
<td></td>
<td>All (n = 202)</td>
<td>Male (n = 78)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>59.6 ± 9.4</td>
<td>61.3 ± 9.9</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>23.8 ± 3.4</td>
<td>24.1 ± 3.1</td>
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<tr>
<td>Hypertension (%)</td>
<td>126 (62.4%)</td>
<td>60 (76.9%)</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>32 (15.8%)</td>
<td>17 (21.8%)</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>38 (18.8%)</td>
<td>26 (33.3%)</td>
</tr>
<tr>
<td>Lipid-lowering drugs (%)</td>
<td>49 (24.4%)</td>
<td>14 (18.0%)</td>
</tr>
<tr>
<td>Anti-hypertensive drugs (%)</td>
<td>74 (36.7%)</td>
<td>38 (48.7%)</td>
</tr>
</tbody>
</table>

* P < .05, case v control subjects, assessed by analysis of variance.

Among all subjects, patients with CAD were older, included more men (male/female ratio: 136/42 v 78/124, P < .05) and smokers, had a higher prevalence of HT and DM, and included a higher percentage of patients on lipid-lowering drugs or anti-hypertensive drugs than those without CAD (Table 1). Both male and female patients with CAD were older and had higher prevalence of DM...
than male and female patients without CAD, respectively. Male patients with CAD included more smokers and patients on lipid-lowering drugs than did male patients without CAD (Table 1).

We found that SAEI was significantly lower in patients with CAD than in patients without CAD (3.1 ± 1.6 vs 3.6 ± 2.1 mL/mm Hg × 100, P < .05), whereas the large artery elasticity index (LAEI) was similar in patients with and without CAD (11.1 ± 4.2 and 11.3 ± 3.9 mL/mm Hg × 10, respectively). In male and female patients with CAD, SAEI values were also lower than in male and female patients without CAD, respectively.

The SAEI was negatively correlated with age in male and female patients with and those without CAD (r_p = −0.38, −0.46, −0.34, and −0.44, respectively), which reflects the natural decrease in arterial compliance with age. The SAEI was negatively correlated (P < .05) with hypertension in male patients with CAD (r_p = −0.19) or female patients without CAD (r_p = −0.29), but not in male patients without CAD and female patients with CAD.

Because age, gender, and hypertension were related to CAD (Table 1), the association between SAEI and CAD was examined after stratification by gender and hypertension and after adjusting for age. Among male patients with HT, SAEI in case subjects was significantly lower than that in control subjects over the entire range of age (Fig. 1A). The difference in SAEI between case subjects and control subjects was significant after adjusting for age in male hypertensive patients (type II sum of squares: 13.5, F value = 4.8, P < .05), indicating that SAEI was associated with CAD independent of age, gender, and hypertension.

The consistency of the relation between SAEI and CAD in male patients with hypertension was tested by a multiple logistic regression analysis (Fig. 1B). In male hypertensive patients, a low SAEI was associated with a 3.2-fold higher (95% CI: 1.5 to 7.3, P < .01) odds ratio for CAD associated with a low SAEI (model 1). After controlling for the effects of age (model 2), the odds ratio for CAD associated with a low SAEI was 2.9 (95% CI: 1.3 to 6.9, P < .01) in male hypertensive patients. When DM and smoking were progressively added to the model (models 3 and 4), only a slight variation in the initially estimated values for the odds ratios (3.1 [95% CI: 1.4 to 7.3] and 2.8 [95% CI: 1.2 to 6.8], respectively) was observed in hypertensive patients, indicating that the association between SAEI and CAD in male hypertensive patients were independent of conventional risk factors for CAD. When lipid-lowering drugs were added to the model (model 5), there was a slight decrease in the odds ratios (2.4 [95% CI: 1.0 to 6.1], P < .1), which indicates that lipid-lowering drugs affect the association between SAEI and CAD.

### Discussion

This study examined the influence and interaction of CAD risk factors on the association between SAEI, as estimated by the new non-invasive pulse-wave contour technique developed by Cohn et al. and CAD. We found that a low SAEI in patients with hypertension indicates an increased risk of CAD despite antihypertensive therapy. Our results in a group of risk-associated patients confirmed the known facts that age, male gender, HT, DM, and smoking are risk factors for CAD.

Our finding that SAEI in patients with CAD was lower than that in patients without CAD (although LAEI was similar between these groups, with and without stratification by gender) confirms findings of Cohn et al in post-
menopausal women \(^2\) and results of Syeda et al.\(^10\) Our finding that SAEI was strongly and inversely correlated with age in both male and female patients, either with or without CAD, is consistent with those of other investigators.\(^6,10\) This result is reasonable, as aging is known to have a profound effect on arterial compliance because of the increased collagen content of the elastic arteries and reduced endothelial function throughout the entire vascular tree.\(^6\) Thus, because the effects of age and a diseased state on SAEI cannot be separated, age should be controlled for when using SAEI to discriminate between subjects with and without disease, as done by Syeda et al.\(^10\)

A negative relationship between SAEI and HT in male patients with CAD and female patients without CAD confirmed the finding of Cohn et al that patients with essential hypertension had lower SAEI values than normotensive subjects.\(^2\) Our finding that SAEI was related to CAD in male hypertensive patients with and without controlling for age, DM, smoking, and lipid-lowering drug treatment, is supported by that of Duprez et al,\(^9\) who found that SAEI is inversely correlated with IMT of the common carotid artery in male subjects with high-normal BP. In addition, the observation by Syeda et al that SAEI is useful to identify patients with diffuse atherosclerotic process of the coronary arteries was made in a group of patients that apparently contained more hypertensive \((n = 105)\) than normotensive patients \((n = 46)\) and more male \((n = 110)\) than female subjects \((n = 41)\),\(^10\) although the validity of SAEI in hypertensive subjects has been called into question in a recently published article.\(^11\) However, because this study had a case-control design, we cannot draw a conclusion as to whether SAEI can be used to predict future coronary events.

Since we included risk-associated patients in our study partly because of our intention to use this new non-invasive pulse-wave technique as a clinical screening tool, we did not control the effects of lipid-lowering drugs or anti-hypertensive drugs, which may have caused a bias in our results. In the present study, control subjects were not matched with case subjects in regard to age and gender. Also, although gender was stratified and age was adjusted in the data analysis, biases associated with the selection of control subjects and the small sample size, especially regarding female case subjects, may have limited the power of this study.

In conclusion, the effects of risk factors for CAD, including age and hypertension, should be considered when non-invasive pulse-wave analysis of small artery elasticity is used as a tool for the early diagnosis of CAD. This new technique could be of greatest value in male patients with hypertension. Further clinical investigations are needed to evaluate the ability of SAEI to predict CAD.

References