Reflection in the Arterial System and the Risk of Coronary Heart Disease

Tomoshige Hayashi, Yasunori Nakayama, Kei Tsumura, Kiyomichi Yoshimaru, and Hiroyasu Ueda

Background: Although it was reported that the augmentation index and inflection time are closely related to reflection in the arterial system and large artery function, it is not known whether these indices of the ascending aortic pressure waveform increase the risk of coronary heart disease (CHD). The purpose of this study was to evaluate whether the aortic reflection of the ascending aortic pressure waveform is related to an increased risk of CHD.

Methods: We enrolled 190 men and women who had chest pain, normal contractions, no local asynergy, and no history of myocardial infarction. We measured the ascending aortic pressure using a fluid-filled system. The inflection time was defined as the time interval from initiation of a systolic pressure waveform to the inflection point. We investigated the association between the inflection time and augmentation index of the ascending aorta and the risk of CHD.

Results: Both the inflection time and augmentation index were associated with an increased risk of CHD. The crude prevalence rates of CHD were 66.0% for the shortest quartile and 10.6% for the longest quartile of the inflection time, and 17.0% for the lowest quartile and 40.4% for the highest quartile of the augmentation index. The multiple-adjusted odds ratio of CHD was 30.8 (95% confidence interval [CI] 7.43–128.05) for the shortest quartile of the inflection time compared with the longest quartile and was 3.82 (95% CI 1.26–11.59) for the highest quartile of the augmentation index compared with the lowest quartile.

Conclusions: The augmentation index and inflection time were associated with an increased risk of CHD.

Key Words: Risk factors, inflection time, coronary disease, stenosis, aorta.

Although previous clinical studies on risk factors have greatly contributed to the understanding and prevention of coronary heart disease (CHD), some risk factors remain a challenge. The major risks studied extensively include smoking, hypertension, high serum cholesterol, low levels of high-density lipoprotein cholesterol, type 2 diabetes, and aging. Although high systolic hypertension, high diastolic hypertension, and high pulse pressure are potent risk factors, the effects of the reflection of the ascending aortic pressure waveform on the occurrence of CHD have not been reported. The fact that the analysis of reflection waveform is detected by high fidelity measurements of arterial pressure waveform makes it impractical in clinical settings. Therefore, we measured inflection point using a fluid-filled recording system and examined whether the inflection time is correctly defined. To quantify the artery reflection, we used the augmentation index and inflection time. The augmentation index and inflection time using a fluid-filled recording system were reliable and unchanged by repeated measurements.

Previous investigators demonstrated that the ascending aortic pressure waveform was divided by the augmentation index and that both inflection time and augmentation index were related to the impedance spectral pattern. Thus, the impedance spectra represent larger reflections as the augmentation index becomes larger. In contrast, the impedance spectra reveal smaller and more diffuse reflections as the augmentation index gets smaller. Both the inflection time and augmentation index are closely related to reflection in the arterial system and large artery function. These indices are promising tools for understanding the arterial system using a fluid-filled recording system. We hypothesized that the inflection time and large artery
function would be associated with coronary artery conditions. Therefore, we investigated the effects of large artery function, using the inflection time and augmentation index, in relation to the risk of CHD.

Methods
Study Subjects
The study group consisted of 190 consecutive patients who were admitted to Ishikiriseiki Hospital, Osaka, Japan, because of a CHD diagnosis using cardiac catheterization. They were eligible for entry into the study if they had normal contractions, no local asynergy shown by left ventriculography, and no history of myocardial infarction to approximately fix cardiac function. We enrolled 1021 men ranging in age from 35 to 78 years between January 1990 and March 1999 in whom cardiac catheterizations were done for the first time. Of these, 831 were excluded from this study because of acute myocardial infarction, the presence of local asynergy shown by left ventriculography, chronic renal failure, severe valvular disease, post cardiac surgery, cardiomyopathy, arterial fibrillation, pacemaker implantation, sick sinus syndrome, or aortic dissection. The protocol was in accordance with the Institutional Guidelines for Human Research, and each individual provided a written statement of informed consent to the diagnostic and therapeutic procedures required for examination, which stated that the results of the examination could be used for the study.

Measurement of Hemodynamic Variables
Hemodynamic measurements were made with the patient in the supine position. Aortic pressure was measured using a fluid-filled system (5F pigtail catheter) at the ascending aorta. A hard copy was made of the pressure tracing using a chart recorder (Nihon Koden, Surgical Monitoring System, Tokyo, Japan) at a paper speed of 100 mm/sec. We compared tracings of systolic, diastolic, mean, and pulse pressures in patients with and without CHD. Ascending aortic pressure at the inflection point dividing into an early and late systolic phase was used as inflection pressure. 8–11
We used the inflection time as the time interval between onset of a systolic pressure waveform and the inflection point. 8–11
To examine whether inflection time measured by a fluid-filled recording system is correctly defined and truly reliable, we compared the values of inflection time measured by interobserver with those by intraobserver. There was a closely linear correlation between the inter- and intraobserver in this study population (Yinter = 0.96 Xintra + 1.4, R = 0.93). The inflection time defined by a fluid-filled recording system was reliable and unchanged by repeated measurements.

Measurement of Angiographic Variables
Cardiac catheterization was performed according to a standard technique. Optimal views of the target lesions from all technically suitable angiograms were analyzed, and measurements were made of the maximal narrowing of the target lesion, as well as a noninvolved segment. Angiographic measurements were calibrated using a guiding catheter as the reference dimension. The absolute values for the minimal lumen diameter (MLD) and the reference lumen diameter were measured at end-diastole. Coronary heart disease was defined as MLD stenosis >50% on the angiogram, and non-CHD was defined as MLD stenosis ≤50% on the angiogram.

Statistical Analysis
Values were expressed as mean ± one standard deviation. Categoric variables were compared using the χ² test. Differences in the mean values between the two groups were compared using an unpaired t test. A P value of <.05 was considered significant. Multiple logistic regression analysis was used to evaluate the simultaneous effects of the augmentation index or inflection time, age, body mass index, smoking habits (current smokers or nonsmokers), hypertension (yes or no), type 2 diabetes (yes or no), hypercholesterolemia (yes or no), calcium channel blockers (yes or no), β-blockers (yes or no), angiotensin converting enzyme (ACE) inhibitors (yes or no), nitrates (yes or no), parental history of CHD, and sex. The linear trends in the risks were evaluated by entering indicators for each categoric level of exposure using the median value for each category. We calculated the 95% confidence interval (CI) for each odds ratio (OR) and all P values were two tailed. Statistical analyses were performed using the SPSS 10.0 software package (SPSS Inc., Chicago, IL).

Results
Baseline Clinical Characteristics
The baseline clinical characteristics of the study group are summarized in Table 1. Although the mean level of body mass index; the distribution of sex; the presence of parental history of CHD, hypertension, type 2 diabetes, or hypercholesterolemia; and the smoking status were similar in the two groups, the mean age was higher in patients with CHD than those without CHD. There were no significant differences in heart rate or ejection fraction between the two groups. Although systolic, diastolic, and mean pressures in the ascending aorta were not different between the two groups, the pulse pressure was higher in patients with CHD than those without CHD (66.5 ± 21.3 and 73.6 ± 19.7 mm Hg, respectively; P = .029). The augmentation index was significantly higher in patients with CHD than in those without CHD (0.22 ± 0.16 and 0.30 ± 0.14, respectively; P = .001), and the inflection time was significantly longer in patients with CHD than in those without CHD (110.3 ± 21.1 and 90.5 ± 22.5, respectively; P < .001).
Illustrated in Fig. 1 are the waveforms of ascending aortic pressure in the cases of patient without CHD (left panel) and patient with CHD (right panel). Although heart
rates are similar in the two cases, the inflection point is much earlier in patients with CHD than in patients without CHD. As a result, inflection time is shorter in patients with CHD than in patients without CHD.

The Augmentation Index and the Risk of CHD

To examine the association between the augmentation index and the risk of CHD, all patients were classified into quartiles of the augmentation index level. The augmentation index was associated with an increase in the risk of CHD (Table 2). The crude prevalence rates of CHD were 17.0% for quartile 1, 25.0% for quartile 2, 47.9% for quartile 3, and 40.4% for quartile 4 of augmentation index levels. After adjustment for age, body mass index, smoking habits, hypertension, hypercholesterolemia, type 2 diabetes, calcium channel blockers, \( \beta \)-blockers, ACE inhibitors, nitrates, parental history of CHD, and sex, the OR of CHD was 1.00 (reference) for quartile 1, 1.85 (95% CI 0.63–5.45) for quartile 2, 4.63 (95% CI 1.57–13.7) for quartile 3, and 5.45 (95% CI 1.85–15.2) for quartile 4.

![FIG. 1. Left] Without coronary heart disease; (right) with coronary heart disease. Schematic representation of augmentation index and inflection time of ascending aortic artery in a representative case. Augmentation index is the ratio of inflection pressure to pulse pressure. The inflection time was defined as the time interval between onset of a systolic pressure waveform and the inflection point.
Table 2. Odds ratio of coronary heart disease according to the augmentation index and inflection time

<table>
<thead>
<tr>
<th>Augmentation index</th>
<th>n</th>
<th>Cases (%)</th>
<th>Crude OR (95% CI)</th>
<th>Multiple-Adjusted* OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quartile 1 (-0.14–0.14)</td>
<td>47</td>
<td>8</td>
<td>17.0</td>
<td>1.00</td>
</tr>
<tr>
<td>Quartile 2 (0.15–0.26)</td>
<td>48</td>
<td>12</td>
<td>25.0</td>
<td>1.63 (0.60–4.43)</td>
</tr>
<tr>
<td>Quartile 3 (0.27–0.36)</td>
<td>48</td>
<td>23</td>
<td>47.9</td>
<td>4.48 (1.74–11.58)</td>
</tr>
<tr>
<td>Quartile 4 (0.37–0.74)</td>
<td>47</td>
<td>19</td>
<td>40.4</td>
<td>3.31 (1.27–8.62)</td>
</tr>
<tr>
<td>Wald, $\chi^2$</td>
<td></td>
<td></td>
<td></td>
<td>12.2</td>
</tr>
<tr>
<td>$P$ for trend</td>
<td></td>
<td></td>
<td></td>
<td>.002</td>
</tr>
<tr>
<td>Continuous, per 0.1</td>
<td></td>
<td></td>
<td></td>
<td>1.40 (1.13–1.72)</td>
</tr>
<tr>
<td>Wald, $\chi^2$</td>
<td></td>
<td></td>
<td></td>
<td>9.4</td>
</tr>
<tr>
<td>Inflection time (mm sec)</td>
<td></td>
<td></td>
<td></td>
<td>6.6</td>
</tr>
<tr>
<td>Quartile 1 (56–85)</td>
<td>47</td>
<td>31</td>
<td>66.0</td>
<td>16.2 (5.38–49.20)</td>
</tr>
<tr>
<td>Quartile 2 (86–102)</td>
<td>47</td>
<td>20</td>
<td>42.6</td>
<td>6.22 (2.08–18.56)</td>
</tr>
<tr>
<td>Quartile 3 (103–123)</td>
<td>49</td>
<td>6</td>
<td>12.2</td>
<td>1.17 (0.33–4.14)</td>
</tr>
<tr>
<td>Quartile 4 (124–208)</td>
<td>47</td>
<td>5</td>
<td>10.6</td>
<td>1.00</td>
</tr>
<tr>
<td>Wald, $\chi^2$</td>
<td></td>
<td></td>
<td></td>
<td>37.9</td>
</tr>
<tr>
<td>$P$ for trend</td>
<td></td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Continuous, per 10 mm sec decreased</td>
<td></td>
<td></td>
<td></td>
<td>1.59 (1.33–1.90)</td>
</tr>
<tr>
<td>Wald, $\chi^2$</td>
<td></td>
<td></td>
<td></td>
<td>26.5</td>
</tr>
</tbody>
</table>

OR = odds ratio; CI = confidence interval.
* Adjusted for age, body mass index, smoking habits, hypertension, type 2 diabetes, hypercholesterolemia, parental history of coronary heart disease, calcium channel blockers (yes or no), $\beta$-blockers (yes or no), angiotensin converting enzyme inhibitors (yes or no), nitrates (yes or no), and sex.

The Inflection Time and the Risk of CHD

To examine the association between the inflection time and the risk of CHD, all patients were classified into quartiles of inflection time. The analysis of inflection time in ascending aorta is summarized in Table 2. The inflection time as it decreased was associated with an increase in the risk of CHD. The crude prevalence rates of CHD were 16.6% for quartile 1, 42.6% for quartile 2, 12.2% for quartile 3, and 10.6% for quartile 4 of inflection time. The multiple-adjusted OR of CHD was increased by 38% when the augmentation index was increased by 0.1 (OR 1.38; 95% CI 1.08–1.76, Wald $\chi^2 = 6.6$).

Index to Quantify Large Artery Function

Because arteriosclerosis decreases the compliance of the aortic artery and increases the characteristic impedance, it causes the aortic arterial input impedance to be relatively high. Although ascending aortic input impedance most clearly demonstrates manifest arteriosclerosis, the fact that the estimation of impedance necessitates high fidelity measurements of instantaneous ascending aortic flow and pressure makes it impractical in clinical settings. Instead of measuring ascending aortic input impedance, we focused on more simple variables pertaining to the dynamic mechanical properties of the arterial system. The augmentation index and inflection time are closely related to reflection in the arterial system and large artery function. These indices are simple to measure and make attractive tools to understand the arterial system. We hypothesized that reflection in the arterial system and large artery function would be related to coronary artery conditions. Therefore, we investigated the effects of reflection in the arterial system and large artery function in relation to the risk of CHD. Our results revealed that these indices were associated with an increased risk of CHD.

Discussion

The inflection time and augmentation index were associated with an increased risk of CHD. Even after adjustment for age, body mass index, smoking habits, hypertension, type 2 diabetes, hypercholesterolemia, calcium channel blockers, $\beta$-blockers, ACE inhibitors, nitrates, parental history of CHD, and sex, the association was significant. The inflection time had a stronger association with the risk of CHD than the augmentation index.
Clinical Implications Regarding the Augmentation Index and Inflection Time

Although major risks include smoking, hypertension, high serum cholesterol, low levels of high-density lipoprotein cholesterol, diabetes mellitus, and aging,1–5 other risk factors for CHD remain a challenge in clinical settings. The augmentation index and inflection time of the ascending aortic pressure waveform can reveal the large artery function. Because large artery function is composed of compliance, characteristic impedance, and resistance, the inflection time and augmentation index of the ascending aortic pressure waveform would enable us to choose the best drugs for patients with hypertension and angina pectoris. This study contributes not only to the understanding and prevention of CHD, but also to the understanding of the arterial system.

References