Correlation of Ultrasound-Measured Common Carotid Artery Stiffness With Pathological Findings

Takashi Wada, Kuniyasu Kodaira, Kentaro Fujishiro, Ken-ichi Maie, Eiji Tsukiyama, Tsutomu Fukumoto, Tomoko Uchida, Sayaka Yamazaki

Abstract To quantitatively and noninvasively evaluate common carotid atherosclerosis in a series of patients, we measured the stiffness parameter \( \beta \), which represents the mechanical properties of the vessel. \( \beta \) was calculated from the relationship between blood pressure and the diameter of the artery as measured by an ultrasonic, phase-locked, echo-tracking system. Increases in the severity grade of atherosclerosis as subsequently determined at autopsy were correlated with increased \( \beta \) values in 60 common carotid arteries \((r=.88)\).

Common carotid atherosclerosis has been reported to precede cerebral atherosclerosis.\(^{1,2}\) Therefore, evaluating the severity of sclerosis in the common carotid artery may prove to be a useful prognosticator for the development of cerebrovascular sclerosis in asymptomatic individuals. Early detection of this condition can help to reduce the risk of cerebrovascular accident. Atherosclerosis causes structural changes in artery walls that alter their physical properties. The stiffness parameter \( \beta \) proposed by Hayashi et al\(^3\) is one quantitative index of the elastic properties of large arteries. \( \beta \) can be calculated from the measurements of blood pressure and arterial diameter. Although advances in ultrasound technique have made it possible to visualize common carotid arteries, their quantitative measurement has only recently been developed. Nakayama and Sato\(^4\) have designed an ultrasonic measuring method of arterial wall movement that uses a phase-tracking system. Moreover, Yoshimura et al\(^5\) have developed an ultrasonic Doppler flow meter with this system that allows transcutaneous measurement of the arterial diameter and its pulsatile change. We calculated \( \beta \) from the measurements of blood pressure, arterial diameter, and its pulsatile change. A few clinical studies have included measurements of \( \beta \),\(^4,5\) but no previous study has compared clinical studies with pathological findings.

The aim of this study was to define the relationship between \( \beta \) of the common carotid artery and the severity grade of atherosclerosis on the basis of postmortem pathological analysis. These findings may serve as reference data for noninvasively diagnosing atherosclerosis.

Patients with \( \beta \) values greater than 13 had a pathological diagnosis of atherosclerosis in the common carotid artery. The sensitivity of this discrimination ratio was 80%, and the specificity was 80% as well. Thus, \( \beta \) shows promise as a useful diagnostic indicator for detecting asymptomatic common carotid atherosclerosis. (Arterioscler Thromb. 1994;14:479-482.)

Key Words • carotid arteries • pathological findings • ultrasound • arterial stiffness • atherosclerosis

Methods

Hayashi et al\(^3\) analyzed the behavior of arterial walls by assessing changes in vessel inner radii resulting from distending pressure. A stress-strain relation was then determined from this pressure-diameter data by using finite deformation theory. Kawasaki et al\(^6\) then extrapolated this concept to the clinical setting by modifying the equation as follows:

\[
\beta = \left[ \frac{\log Ps/Pd}{Ds-Dd} \right] \times \frac{Dd}{(Ds-Dd)}
\]

where \( Ps \) is systolic pressure, \( Pd \) is diastolic pressure, \( Ds \) is the inner diameter at systole, and \( Dd \) is the inner diameter at diastole. \( \beta \) is a coefficient when the constitutive stress-strain relation is expressed as an exponential function. The parameter \( \beta \) then represents the stiffness of the vascular walls.

We measured the common carotid artery inner diameter and its pulsatile change with an ultrasonic instrument (QFM-2000, Hayashi-Denki Co, Ltd). This measurement system has been described in detail elsewhere.\(^4,5\) Briefly, this technique is based on a method in which ultrasonic (7.5 MHz) pulse echoes from anterior and posterior walls are continuously tracked with a phase-locked loop. The vascular internal diameter and its pulsatile change are measured from the inner-surface wall echoes. The errors in measuring vessel diameter are 0.2 mm or less. Using this method, we calculated \( \beta \) values of the common carotid artery from blood pressure, arterial diameter, and its pulsatile change.

A group of patients with a variety of diagnoses were admitted to Jikei University Hospital, and appropriate measurements \((N=465)\) were made by all authors except one (Dr Wada). Patients with arteritis, valvular heart disease, or arrhythmias were excluded from the study. Arterial diameter measurements were made with subjects in a supine position, and mean values for diameter were calculated from 20 heartbeats on the left and right common carotid arteries. Brachial arterial pressure was then measured by the conventional cuff method.

Postmortem morphological comparisons were made over the next 60 to 370 days \((\text{mean} = \pm \text{SD}, 90.4 \pm 94.6 \text{ days})\). This examination was carried out in a blinded fashion by Dr Wada, who was unaware of the premortem \( \beta \) values. The postmortem study group consisted of 19 men and 11 women ranging in age from 35 to 86 years \((\text{mean} = \pm \text{SD}, 68.2 \pm 13.5 \text{ years})\). The 60 left
and right common carotid artery specimens were obtained within 3 hours of death and were fixed in 10% formalin. The tissue sections were cut transversely 8 cm from the origin, the site at which premortem \( \beta \) values had been measured. The sections were processed routinely, embedded in paraffin, and stained with elstica-van Gieson’s and Masson’s trichrome stains. Each specimen was examined by light microscopy and assigned to one of seven grades (0 through 6) representing the severity of pathological atherosclerosis. The seven grades were determined according to the following nine categories, which documented changes in the media, internal elastic lamina, and intima* (Fig 1): (A) Medial thickness was (1) even, (2) partially even, or (3) uneven. (B) Destruction of the intimal elastic membrane (4) has occurred or (5) has not occurred. (C) Intimal thickness was (6) nil, (7) slight, (8) moderate, or (9) advanced.

The following microscopic findings conformed to the pathological grade of atherosclerosis: (1) Grades 0, 1, and 2 showed no disarrangement of elastic fibers in the media and no destruction of the intimal elastic membrane, but intimal thickening was increased. (2) Grade 3 showed degeneration and scattering of elastic fibers in the media and a disconnected intimal elastic membrane in areas of intimal thickening. (3) Grade 4 showed straight elastic fibers in the media and a rough, partially destroyed intimal elastic membrane. (4) Grade 5 showed straight elastic fibers in the media, destruction of the elastic fiber network, and a moderately increased intimal thickness. (5) Grade 6 showed remarkable intimal atheroma.

Then the specimens were magnified with a projector. The circumference of the residual lumen and the outer circumference were traced. We used a microcomputer to determine the area of each circumference and to calculate the vessel wall area, mean wall thickness, and wall thickness ratio (mean wall thickness divided by outer radius) of each specimen.

We then correlated \( \beta \) values with atherosclerosis grade. We summed the cumulative curves of the graded groups to determine a low (0 to 3) and a high (4 to 6) atherosclerosis grade group. The value of \( \beta \) at the point of intersection of the curves defines the boundary between early and advanced atherosclerosis. We also investigated the correlation between \( \beta \) and vessel wall area, mean wall thickness, and wall thickness ratio. All values were averaged and expressed as mean±SD. Correlation coefficients were calculated by standard statistical methods.

**Results**

The 60 \( \beta \) values measured while the patients were alive ranged from 3.91 to 27.6 (mean, 12.0±5.21). The correlation between \( \beta \) and postmortem pathological atherosclerosis grade was significant \((r=.68, P<.0001)\), as shown in Fig 2. Fig 3 represents the minimum-maximum cumulative discrimination graph for \( \beta \). The respective curves for low and high atherosclerosis grade groups intersected at 13, the discrimination threshold for both groups, with a discrimination rate of 74%. When cases with \( \beta \) values greater than 13 were diagnosed with advanced atherosclerosis, the sensitivity was 80% (12/15), as was specificity (80%, or 36/45).

There was a close correlation between \( \beta \) and vessel wall area \((r=.61, P<.0001)\) (Fig 4) and between \( \beta \) and mean wall thickness \((r=.53, P<.0001)\) (Fig 5), but that with \( \beta \) and wall thickness ratio was nil \((r=.18)\).

Atherosclerosis grade correlated well with mean wall thickness \((r=.63, P<.0001)\) and vessel wall area \((r=.64, P<.0001)\). These correlation coefficients were lower than that between atherosclerosis grade and \( \beta \). However, there was no statistically significant difference among the correlation coefficients of atherosclerotic grade with wall thickness, vessel wall area, and \( \beta \).

**Discussion**

Carotid atherosclerosis is one of the principal etiologic factors in ischemic cerebrovascular disorders. Therefore, quantitative assessment of early changes in the carotid artery may lead to improved preventive measures early in the asymptomatic phase of the condition.

Two characteristics of atherosclerosis are stenosis due to atheroma and wall stiffness due to tissue degeneration. At present, most of the effort for improving noninvasive and quantitative measurement of atherosclerosis is focused on ultrasound. In the present study, we observed and quantitatively documented arterial distensibility of the common carotid artery with an ultrasonic, phase-locked, echo-tracking system. \( \beta \) is the slope of the exponential function between relative arterial pressure and the arterial distension ratio for an arterial diameter at a given pressure. This parameter \( \beta \) characterizes the entire deformation behavior of the vascular wall.

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**Table**

<table>
<thead>
<tr>
<th>Grade</th>
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<th>destruction of intimal elastic memb.</th>
<th>intimal thickness</th>
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<tbody>
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<td>partially uneven</td>
<td>-</td>
<td>-~+</td>
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<tr>
<td>4</td>
<td>uneven</td>
<td>+</td>
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<td>5</td>
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**Fig 1.** Graphic showing grading criteria for histological classification of common carotid artery atherosclerosis. See text for details.

**Fig 2** Bar graph showing correlation between \( \beta \) and pathological atherosclerosis grade of the common carotid artery.
vascular wall and is independent of the intraluminal pressure within the physiological range.\textsuperscript{3}

Common carotid arterial diameter and changes in diameter under dilated and pulsatile conditions decrease with aging.\textsuperscript{9,10} These findings support the evidence that $\beta$ increases with age. Kawasaki et al\textsuperscript{6} have shown that $\beta$ is 4.3 for ages 0 to 19 years, 5.9 for 20 to 39 years, 7.8 for 40 to 59 years, and 11.3 for subjects over 60 years, and Hirai et al\textsuperscript{7} have deduced the following equation: $\beta=0.11 \times \text{age}+2.8 \ (r=.84, \ P<.05)$.

We substituted brachial arterial pressure for common carotid artery pressure in calculating values for $\beta$. The pulse pressure of the brachial artery is usually about 10\% to 15\% higher than that of the common carotid artery.\textsuperscript{8} Although brachial pressure may be overestimated when measured by cuff sphygmomanometry in patients with very stiff arteries, there are few such patients in general screening protocols. Moreover, these differences in pressures are almost within the total tolerance of noninvasive measurement methods.
Collagen and elastin are the principal factors that affect the elastic behavior of the arterial wall. Hayashi et al have shown that the common carotid arterial stiffness parameter \( \beta \) in dogs correlated positively with arterial collagen content \( (r = .74) \) but negatively with elastin content \( (r = -.87) \). Hasegawa et al have reported that the media of the common carotid artery changes with age as well as with atherosclerosis in humans. The amount of elastin decreases after 20 years, and elastic fiber arrangement becomes disordered. The amount of collagen increases in the arteriosclerotic specimens. Thus, \( \beta \) is thought to represent vessel wall structural changes that occur in response to aging or atherosclerosis.

Mikawa has determined the original pathological grading of the common carotid artery, which shows arteriosclerotic changes in both intima and media because the common carotid artery is elastic. In the original study, the seven grades reflected micropathological changes as well as gross pathological changes, namely decreases in elastin. Many cases in grades 5 and 6 showed the presence of acid mucopolysaccharide and calcium. No cases in grades 0 through 4 showed the presence of calcium. In the comparative study with clinical data, the grade levels increased with aging. In the autopsy studies, 73.8% of cerebral infarction cases and 80.6% of myocardial infarction cases had grades of 4 or greater, which represent severe pathological changes. On the other hand, 25.8% of nonvascular disease cases also had grades of 4 or greater. The aforementioned pathological and clinical findings confirmed that assessment on the basis of these grades was superior to assessment that was based solely on intimal change in detecting atherosclerosis in the common carotid artery.

Moreover, the correlation between grade and vessel wall area was significant, and 77% of cases with a wall area of 0.125 cm\(^2\) or greater showed a grade of 4 or higher. Aizawa has reported a correlation between age and these measurements in a pathological analysis of the common carotid artery. The mean vessel wall thickness and outer radius increased with age, but the ratio of wall thickness to outer radius was constant for all ages.

Atherosclerosis grade correlated well with wall thickness \( (r = .63, P < .0001) \) and vessel wall area \( (r = .64, P < .0001) \) in this study. B-mode ultrasound has made it possible to measure the thickness of the intimal-medial complex in the far wall. Because it is difficult to precisely measure arterial wall thickness (intima, media, and adventitia) noninvasively, measurement of \( \beta \) is useful in clinically detecting atherosclerosis.

Our data show that \( \beta \) is closely correlated with pathological atherosclerosis grades \( (r = .68) \) and that the correlation of \( \beta \) with vessel area and mean wall thickness is significant \( (r = .61 \text{ and } r = .53, \text{ respectively}) \). Thus, our findings are consistent with prior reports. Our pathological study confirms that \( \beta \) represents not only elastic properties of the artery but also atherosclerotic damage that affects vessel wall thickness and area.

In conclusion, \( \beta \) is closely correlated with the pathologically confirmed degree of atherosclerosis. Common carotid atherosclerosis was advanced in subjects with \( \beta \) values greater than 13, and the histopathological findings in our study confirmed a quantitative standard for measuring the severity of common carotid atherosclerosis. Thus, examination of arterial stiffness with the ultrasonic, phase-locked, echo-tracking system may be useful in screening patients at risk for atherosclerosis. This method is inexpensive and noninvasive, and the study is quickly and easily performed. This method should allow the detection of atherosclerosis in asymptomatic individuals.

References
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