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Review

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Is Stiffness Parameter β Useful for the Evaluation of Atherosclerosis?

~ Its Clinical Implications, Limitations, and Future Perspectives ~

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Atherosclerosis comprises two components, atherosis and sclerosis, characterized by morphological wall thickening and functional stiffening, respectively, of the arterial wall. In recent years, much interest has been directed to the role of functional changes in large arteries, i.e., increased stiffness or decreased elasticity, on the development of cardiovascular diseases. In fact, the clinical evaluation of arterial stiffness is increasingly performed in patients with cardiovascular risk factors. Local arterial stiffness is measured using an ultrasound technique implemented with an echo-tracking system at the common carotid and femoral arteries. Several indices of local arterial stiffness are obtained by ultrasound, among which stiffness parameter β is unique because it is the least affected by blood pressure at the time of measurement. Evidence from cross-sectional studies indicates that increased stiffness parameter β is associated with a number of cardiovascular risk factors, such as older age, smoking, insufficient physical activity, hypertension, obesity, metabolic syndrome, insulin resistance, type 2 diabetes, chronic kidney disease, and comorbid cardiovascular disease. Results from several prospective observational studies also suggest that carotid stiffness parameter β is a useful surrogate marker of cardiovascular events and/or mortality, although the results differ depending on the characteristics of the study subjects. Furthermore, several interventional studies have shown that carotid stiffness parameter β improved after lifestyle modification or drug treatment. In this review, we summarize the current evidence of stiffness parameter β of the carotid artery and discuss its clinical implications as a marker of vascular health or as a predictor of cardiovascular outcomes.

Key words: **Atherosclerosis, Arterial stiffness, Cardiovascular disease, Ultrasound**

Introduction

Atherosclerosis has two different pathophysiological features: morphological and functional changes in vasculature. The former, atherosis, is characterized by thickening and/or plaque formation of the arterial wall, and the latter, sclerosis, is characterized by increased stiffness or decreased elasticity of the arterial wall[1)]. Atherosis and subsequent stenosis of the artery induce ischemia in various organs, leading to myocardial infarction, stroke, and peripheral artery disease, all of which seriously affect the quality of life and survival of affected individuals. Therefore, many basic and clinical studies have focused on atherosis[2)]. On the other hand, sclerosis, functional changes in the artery, is rather related to local and/or systemic hemodynamics and is less likely to be focused on as a clinical or research issue than atherosis. Therefore, arterial sclerotic change has received less attention than atherotic change in the field of basic and clinical research.

There are several methods to evaluate arterial stiffness or elasticity in humans[3, 4)]. Local arterial stiffness in the common carotid and femoral arteries is measured by ultrasound with an echo-tracking system, while regional stiffness in the aorta is measured by pulse wave velocity (PWV)[4, 5)] and cardio-ankle vascular index[6, 7)]. Several indices of local arterial

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Table 1. Summary of stiffness-related indices of the carotid and femoral arteries measured by ultrasound

Term	Alternative term Abbreviation	Definition	Unit	References in the text
Stiffness parameter β	stiffness index β β index	· log-transformed ratio of systolic/diastolic blood pressure to relative change of arterial diameter during cardiac cycle · stiffness parameter $\beta = \ln (Ps/Pd) / [Ds-Dd/Dd]$ $= \ln (Ps/Pd) / [\Delta D/Dd]$	unitless	3, 24, 104-106, 108-110
Arterial distensibility coefficient	DC AD	· Relative change in lumen area during systole for a given pressure change · $DC = \Delta A/A \cdot \Delta P$ or $\Delta D/D \cdot \Delta P$	kPa^{-1}	3, 4, 105-108, 110
Arterial compliance coefficient	CC AC	· Absolute change in lumen area during systole for a given pressure change · $CC = \Delta A/\Delta P$ or $\Delta D/\Delta P$	m^2kPa^{-1}	3, 4, 105, 106, 108, 110
Peterson elastic modulus	Ep	· Inverse of distensibility coefficient: the pressure change driving an increase in relative lumen area (ie, pressure change for theoretical 100% increase in diameter) · $Ep = A \cdot \Delta P/\Delta A$ or $\Delta P \cdot D/\Delta D$	kPa	3, 4, 104-106, 110
Young's elastic modulus	YEM Incremental elastic modulus (E_{inc})	· Elastic properties of the arterial wall material, considering arterial wall thickness · Wall tension per centimeter wall thickness for 100% diameter increase · $YEM = \Delta P \cdot D/h \cdot \Delta D$ or $(PP \cdot Dd^2)/(\Delta D \cdot 2 \cdot IMT)$ · $E_{inc} = [3(1 + A/WCSA)]/DC$	kPa	3, 4, 104-106, 108, 110

Ps and Pd, systolic and diastolic blood pressure; Ds and Dd, maximum and minimum of arterial diameter during systolic and diastolic period; ΔD, change in arterial dimeter during cardiac cycle; ΔP, local pulse pressure; ΔA, change in lumen area during systole, π $(Ds^2 - Dd^2)/4$ (mm^2); DC, distensibility coefficient; AD, arterial distensibility; CC, compliance coefficient; AC, arterial compliance; Ep, Peterson elastic modulus; YEM, Young's elastic modulus; Einc, Incremental elastic modulus; h, wall thickness; PP, pulse pressure; IMT, intima-media thickness; WCSA, wall cross-sectional area = π $(De^2 - Di^2)/4$ (mm^2) with De, external diameter and Di, internal diameter, measured in diastole.

stiffness are measured by ultrasound (Table 1). Among these indices, stiffness parameter β of the superficial arteries and aorta is a unique index. The parameter was proposed by Hayashi in Japan[8, 9] and has been mainly developed in Japan and Europe. Recently, a high-resolution ultrasound technique implemented with an echo-tracking system has been developed, which allows us to measure arterial stiffness noninvasively and repeatedly with high precision. However, clinical and research data on stiffness parameter β are currently limited. It remains unclear whether stiffness parameter β is useful as an index of atherosclerosis in a clinical setting.

This review aims to summarize the current evidence of stiffness parameter β of the carotid artery and discuss its clinical implications and limitations as a marker of atherosclerosis, in comparison with other stiffness-related indices and carotid intima-media thickness (IMT), a morphological change.

What Is Stiffness Parameter β ? How Is It Measured?

1. Historical View and the Definition of Stiffness Parameter β

In 1974, Hayashi *et al.* proposed stiffness parameter β as an index of arterial stiffness peculiar to the arterial wall independent of blood pressure, which was obtained from the changes in arterial diameter during cardiac cycle and blood pressure of the local artery at the measurement site[8, 9]. They found that human arterial walls of carotid, femoral, and vertebral arteries obtained from autopsy showed nonlinear intraluminal pressure-external radius curve in their ex vivo experimental apparatus[10]. Since the external radius (Ro, mm) of human arteries showed a logarithmic relationship with intraluminal pressure (P, mmHg), the ratio of external radius (Ro/Rs) of artery correlated linearly with natural logarithm of the ratio of blood pressure (P/Ps) at local site of artery as shown in the following formula[8]:

$$\ln (P/Ps) = \beta (R/Rs - 1) \quad \text{.....(1)}$$

ln, natural logarithm; P, arterial inner pressure; Ps, standard pressure of 100 mmHg; R, radius of local artery; Rs, radius of artery at the pressure of Ps

In the above formula, the coefficient, β, is the slope of each linear regression line and proved to be a parameter that represents the stiffness of the arterial wall.

The linear relationship between the two ratios, ln (P/Ps) and R/Rs, was reported to be extremely high in the physiological range of blood pressure from 60 to 160 mmHg[8].

According to this relation (1), when arterial radius and intraluminal pressure were substituted for arterial diameter and blood pressure during cardiac cycle, stiffness parameter β is defined as follows:

$$\text{stiffness parameter } \beta = \ln (Ps/Pd) / [(Ds - Dd)/Dd] \quad \text{.....(2)}$$
$$= \ln (Ps/Pd) / [\Delta D/Dd]$$

Ps, systolic and Pd, diastolic blood pressure; Ds, maximum and Dd, minimum of arterial diameter during systolic and diastolic period; ΔD, change in arterial diameter during cardiac cycle

As expected from this definition (2), stiffness parameter β represents the log-transformed ratio of blood pressure to relative changes in arterial diameter during cardiac cycle. It is expressed as a unitless index and also the reciprocal of distensibility index of the arterial wall. Therefore, the higher the stiffness parameter β, the stiffer the arterial wall. Stiffness parameter β is less affected by mean arterial pressure compared with other indices of arterial distensibility/elasticity such as distensibility coefficient (DC), arterial compliance coefficient (CC), and pressure-strain elastic modulus (Ep) shown in **Table 1**, and its variation due to changes in arterial pressure is the smallest among these indices[11]. In fact, in healthy subjects, stiffness parameter β of the common carotid artery did not change after decrease in blood pressure induced by systemic infusion of phentolamine, α-adrenergic blockade, but increased after nitric oxide synthase inhibition induced by N^G-monomethyl-L-arginine infusion[12]. These findings suggest that stiffness parameter β is the least dependent on blood pressure at measurement and represents the stiffness inherent in the local arterial wall.

2. Measurement of Stiffness Parameter β of Superficial Arteries

Stiffness-related indices including stiffness parameter β of superficial arteries can be determined by ultrasound devices equipped with echo-tracking system. The measurement requires the detection of pulsatile changes in arterial diameter with high precision. In the early years of vascular ultrasonography in Japan, stiffness parameter β was measured by an ultrasound phase-locked echo-tracking system composed of Aloka SSD-610 with 7.5 MHz probe, RF echomonitor, and calculation monitor. Currently, ultrasound devices are widely used in Japan, which is equipped with a phase-locked echo-tracking system with real-time scanner and high-resolution linear array probe (e.g., ProSound II, SSD6500, α7, α10, Hitachi-Aloka Co. Ltd.). Furthermore, the latest device, α10 with 10–13 MHz linear array probe, can allow us not only to measure changes in arterial diameter with higher precision and reproducibility than previous ones but also to simultaneously and automatically calculate other stiffness-related indices than stiffness parameter β, such as Ep, CC, augmentation index, and PWV calculated from stiffness parameter β (PWVβ) at each superficial artery.

The standard technique for measuring stiffness parameter β of the carotid and femoral arteries has not yet been established in detail. In most clinical settings, stiffness parameter β of the carotid or femoral artery is simultaneously measured with IMT. In fact, several major studies on arterial stiffness parameter β have performed simultaneous measurements of IMT in the same subject[13-21]. Therefore, the basic technique for measuring stiffness parameter β is almost similar to that for measuring IMT of the common carotid and femoral arteries as follows[14, 17, 21, 22]: in the supine position with the neck slightly stretched to the right or left, bilateral carotid arteries are scanned at the level of the bifurcation, bulb, ~4 cm of the common carotid artery and 1 cm each of the internal and external carotid arteries. The bilateral femoral arteries are scanned distal to the inguinal ligament at the site of bifurcation into the superficial and deep femoral arteries, including ~4 cm proximal and 1 cm distal to the flow divider. It is an important technique for an examiner to put a probe on the neck surface as softly as possible not to restrict the movement of the arterial wall with the cardiac cycle. Theoretically, stiffness-related indices require local blood pressure measurement in each artery, which can be obtained using applanation tonometry[4]. However, in a clinical setting, blood pressure at the brachial artery measured using sphygmomanometer is usually substituted for local blood pressure when measuring carotid and femoral stiffness parameter β.

With regard to the reproducibility of

measurements, the coefficient of variation (CV) within the same examiner (intra-observer CV) of stiffness parameter β of the common carotid artery was reported to be 19%, while that of IMT and DC were 11.7% and 12.3%, respectively[23]. However, the reproducibility of stiffness parameter β measurement has been much improved by using the latest equipment. Using Aloka SSD-5500 equipped with a 7.5 MHz linear probe and echo-tracking subsystem (Aloka-Hitachi), the intra-observer CV at the same measurement was 9.3%, intra-observer CV at the different measurement was 14.4%, and inter-observer CV at the same measurement was 16.5%[24]. Likewise, the intra-observer CV at different measurement was 3.8% by using the latest ultrasound system (Prosound α10, Aloka-Hitachi)[25].

3. Reference Range of Carotid Stiffness Parameter β

To date, there is no consensus on the reference range or upper limit of stiffness parameter β of the carotid or femoral artery, as its value differs by age, sex, and ethnicity. However, several studies have reported on the reference range of carotid stiffness parameter β[11, 17, 24, 26, 27].

Wada *et al.* reported invaluable findings on the relationship between stiffness parameter β and the severity of atherosclerosis as subsequently determined by autopsy in 60 common carotid arteries[28]. Carotid stiffness parameter β was closely associated with the histopathological severity grade of atherosclerosis ($r=0.68$). Moreover, the study demonstrated that patients with stiffness parameter β greater than 13.0 had a pathological diagnosis of atherosclerosis in the common carotid artery and that the sensitivity of this discrimination ratio was 80% and the specificity was also 80%[28]. The same group also reported that the mean value of carotid stiffness parameter β was 11.2 in Japanese healthy individuals aged 40 to 59 years[27].

In the early years, Hasegawa *et al.* determined the mean and standard deviation (SD) of carotid stiffness parameter β in 1,307 healthy subjects categorized every 10 years of age: 20–29 years, 4.9 ± 1.4; 30–39 years, 6.6 ± 2.1; 40–49 years, 8.3 ± 3.1; 50–59 years, 9.9 ± 3.4; 60–69 years, 11.7 ± 3.7; and 70–79 years, 12.4 ± 3.2 [26].

Afterward, Niki *et al.* reported the mean and SD of carotid stiffness parameter β using SSD-5500 (Aloka, Tokyo) with 7.5 MHz linear probe by sex and by 10-year age group in 135 healthy subjects as follows[24]: in men, under 25 years, 5.8 ± 1.4; 26–35 years, 8.9 ± 3.1; 36–45 years, 9.8 ± 2.6; 46–55 years, 12.1 ± 3.5; 56–66 years, 11.8 ± 2.5; and over 66 years, 16.5 ± 6.8, and in women, under 25 years, 4.7 ± 0.7; 26–35 years, 6.5 ± 1.0; 36–45 years, 8.4 ± 2.0; 46–55 years, 9.9 ± 1.8; 56–66 years, 14.6 ± 4.0; and over 66 years, 15.4 ± 5.4. In 439 non-diabetic participants in the health-check program (146 men and 293 women, mean age 56 ± 14 years)[17], the mean and SD of carotid stiffness parameter β was 11.6 ± 5.4, which was almost equivalent to that in other reports[24, 26, 27].

Factors Affecting Stiffness Parameter β

1. Healthy Individuals

In healthy subjects, stiffness parameter β of the common carotid artery has been reported to be associated with various factors, such as age[18, 20, 24, 29-33], physical activity[34, 35], smoking[31], obesity, hypertension, cardiac function[36], hyperuricemia[37], low-grade inflammation[38], coagulation-fibrinolysis factor[39], and vascular calcification factor[32]. The Amsterdam Growth and Health Longitudinal Study investigated the impact of habitual physical activity between the ages of 13 and 36 years on carotid stiffness parameter β assessed at age 36 years in 373 young healthy subjects[34]. The study found that subjects in the highest tertile of stiffness parameter β had spent less time in vigorous habitual physical activity throughout the observation period than those in the lowest tertile[34]. The result suggested the beneficial effects of vigorous intensity habitual activity on carotid arterial stiffness in young adults[34]. Another study in 103 postmenopausal women showed that carotid stiffness parameter β was inversely associated with the duration of moderate to high habitual activity after adjusting for age, height, body mass index (BMI), and mean blood pressure[35]. Kozakova *et al.* also showed that an average daily physical activity measured by accelerometer was correlated inversely with carotid stiffness parameter β and positively with longitudinal systolic myocardial function, independently of age and established cardiovascular risk factors in 45 healthy subjects[40]. Moreover, the carotid stiffness parameter β was shown to increase with the number of sources and daily hours of environmental tobacco smoke in healthy adult nonsmokers with higher BMI and greater carotid IMT[31].

Cardiac function also affects carotid stiffness parameter β in healthy individuals. In 92 healthy subjects, carotid stiffness parameter β, but not carotid IMT, was inversely associated with index of left ventricular diastolic function evaluated by transthoracic echocardiographic Doppler independent of age, sex, pulse pressure, and BMI[36].

With regard to biomarkers of low-grade inflammation, carotid stiffness parameter β was shown to be associated with serum high-sensitivity C-reactive protein (hsCRP), but not with biomarkers

of endothelial dysfunction in the Hoorn study, a population-based cohort study including 572 elderly individuals with a high prevalence of cardiovascular disease (CVD) and its risk factors[38]. Serum level of fetuin-A, an inhibitory factor of vascular calcification, was reported to be correlated with carotid stiffness parameter β independent of traditional risk factors for atherosclerosis in 141 healthy subjects[32].

2. Hypertension, Dyslipidemia, and Sex Hormones

In general, patients with hypertension have higher stiffness parameter β of the carotid artery, femoral artery, and aorta than those without. The parameter was shown to be associated with age, blood pressure, and left ventricular cardiac function[33, 41-46]. Saba *et al.* reported that carotid stiffness parameter β was correlated with age, blood pressure, and BMI in 202 hypertensive adults[44]. Moreover, the same group demonstrated no significant difference in carotid stiffness parameter β between hypertensive patients with and without hypercholesterolemia, suggesting that hypercholesterolemia does not substantially affect carotid stiffness[45]. Other groups also demonstrated in hypertensive adults that stiffness parameter β was positively correlated with age and smoking and negatively correlated with relative wall thickness of the left ventricle[33, 46]. Other studies also showed that stiffness parameter β was associated with age, diastolic function[41, 42], and wall thickness[43] of the left ventricle in patients with hypertension[41, 43] or with cardiovascular risk factors[42]. Carotid stiffness parameter β was also shown to be associated with hsCRP[47], brain natriuretic peptide[47], and cardio-ankle vascular index[48] in patients with hypertension.

Sex hormones may affect age-related stiffening of the large arteries. In the elderly subjects with hypertension (n=670), women showed higher aortic arch stiffness parameter β than men[49]. Interestingly, carotid stiffness parameter β was lower in postmenopausal women (n=172) treated with estrogen replacement therapy than those without, after adjustment for blood pressure and other risk factors in the Baltimore Longitudinal Study of Aging[50]. These reports suggest that the decline in female hormones contributes to age-related arterial stiffening.

3. Obesity, Metabolic Syndrome, and Diabetes

(a) Metabolic Syndrome and Type 2 Diabetes

The Atherosclerotic Risk in Communities (ARIC) study, an observational cohort study including 4,701 adults aged 45 to 64 years, assessed several indices of carotid arterial stiffness using noninvasive ultrasound methods[51]. The study clearly demonstrated that carotid stiffness parameter β was higher in patients with impaired glucose tolerance or type 2 diabetes than that in control subjects and was correlated with fasting plasma glucose and insulin levels[51]. The association between carotid stiffness parameter β and fasting insulin levels observed in this study was first suggestive of the impact of insulin resistance on carotid arterial stiffness. Afterward, Emoto *et al.* demonstrated in 60 type 2 diabetes patients that carotid and femoral stiffness parameter β were closely and inversely associated with insulin resistance evaluated by euglycemic hyperinsulinemic clamp using artificial pancreas, a gold standard for assessing insulin resistance in humans[22]. The other indices of arterial stiffness, DC and CC, were also found to be associated with insulin sensitivity assessed by euglycemic hyperinsulinemic clamp in healthy women[52].

Insulin resistance underlies the metabolic syndrome, which consists of visceral obesity, hypertension, hyperglycemia, and dyslipidemia[53, 54]. Therefore, there is an emerging interest in the relationship between arterial stiffness and visceral obesity and/or metabolic syndrome[53]. In the Baltimore Longitudinal Study on Aging including 471 participants, the mean carotid stiffness parameter β and IMT were higher by 32% and 16%, respectively, in patients with metabolic syndrome than in control subjects[20]. Notably, the metabolic syndrome was also independently associated with carotid stiffness parameter β and IMT even after adjusting for the individual components of metabolic syndrome[20]. Teramura *et al.* investigated the impact of the modified NCEP-ATPIII criteria for metabolic syndrome on carotid stiffness parameter β and IMT in 615 Japanese adults including 307 type 2 diabetes patients[21]. Both carotid stiffness parameter β and IMT were higher in subjects with metabolic syndrome than those without and increased according to the numbers of components of the criteria for metabolic syndrome[21]. Another study also examined carotid DC and stiffness parameter β in 89 Japanese subjects with either high-normal blood pressure, impaired glucose regulation, or both[13]. Carotid DC was significantly lower in subjects with metabolic syndrome (n=45) than those without (n=44), while stiffness parameter β was not significantly different between the groups[13]. In the Northern Manhattan Study including 1,133 stroke-free individuals, the metabolic syndrome was significantly associated with increased carotid stiffness parameter β after adjusting for age, sex, race-ethnicity, current smoking, education, carotid plaque, and IMT[55]. Among the individual components of metabolic syndrome, waist circumference and blood

pressure were independently associated with stiffness parameter β[55].

Although one study in a small number of subjects failed to show a difference[13], previous reports generally suggest that individuals with metabolic syndrome have higher carotid stiffness parameter β than those without.

(b) Adolescents with Obesity

The impact of obesity on carotid stiffness parameter β and other stiffness-related indices has also been investigated in children and adolescents. In young subjects including 182 lean, 136 obese, and 128 type 2 diabetes aged 10 to 24 years, Urbina *et al.* demonstrated higher stiffness parameter β in obese and type 2 diabetes subjects than in lean subjects and that age, blood pressure, and BMI independently contributed to stiffness parameter β[56]. In Indian children, carotid stiffness parameter β and Ep were higher in overweight/obese children than in normal-weight children and were associated with the percentage of body fat, serum triglyceride levels, and the score of metabolic syndrome[57-59].

(c) Possible Underlying Mechanisms

The mechanisms underlying the relationship between insulin resistance/visceral obesity and arterial stiffness has not yet been fully identified. Several studies have indicated the independent association between visceral fat accumulation and carotid stiffness parameter β in Japanese patients with type 2 diabetes[30, 60]. These studies suggest a possible role of adipocytokines in the link between obesity/insulin resistance and arterial stiffness. Araki *et al.* demonstrated a weak but significant correlation between serum adiponectin levels with carotid stiffness parameter β in 116 non-diabetic controls, but not in 98 patients with type 2 diabetes[29]. The same group further reported that the increase in serum adiponectin levels after treatment with pioglitazone was closely associated with the decrease in carotid stiffness parameter β[61]. Konishi *et al.* also demonstrated that carotid stiffness parameter β was correlated with visceral fat area measured by computed tomography and the ratio of serum tumor necrosis factor-α/adiponectin level in 151 type 2 diabetes patients and 83 non-diabetic controls[30]. Plasma levels of leptin, an anti-obesity adipocytokine, was shown to be positively correlated with carotid arterial stiffness, as estimated by Ep and CC, independently of age, sex, BMI, and other risk factors, in 155 overweight patients, but not in 163 lean patients, with type 2 diabetes[62].

In addition to adipocytokines, several atherosclerosis-related factors were indicated to be associated with carotid stiffness parameter β in patients with type 2 diabetes[16, 63, 64]. Glomerular filtration rate precisely measured by ^{99m}Tc was independently and inversely correlated with both carotid stiffness parameter β and IMT in 61 patients with type 2 diabetes[63]. The ACE gene polymorphism was found to be an independent determinant of carotid stiffness parameter β independent of age and blood pressure in 137 patients with type 2 diabetes, but not in 260 healthy controls[64]. The platelet expression of P-selectin, which plays an important role in the progression of atherosclerotic lesion, was associated with carotid IMT, but not stiffness parameter β, in 517 Japanese patients with cardiovascular risk factors, among which 187 had type 2 diabetes[16].

(d) Type 1 Diabetes

Studies on stiffness parameter β are much limited in patients with type 1 diabetes than in those with obesity or type 2 diabetes, especially in the 1980s and 1990s. In the 1980s, Christensen *et al.* demonstrated that stiffness parameter β of the femoral artery was higher in patients with type 1 diabetes than in controls[65, 66] and that it correlated with femoral IMT in 19 young type 1 diabetes patients[67]. Ryden Ahlgren *et al.* demonstrated that carotid stiffness parameter β was higher only in women (n=30), but not in men (n=26), with type 1 diabetes than controls[68]. In the Stockholm Diabetes Intervention Study, carotid stiffness and IMT were assessed in type 1 diabetes patients who had been randomized to intensive insulin treatment (n=29) or standard insulin treatment (n=25) for more than 12 years[15, 69]. In the study, patients with higher stiffness parameter β showed lower heart rate variability assessed from power spectral analysis of 24-h Holter recordings, an index of autonomic neuropathy, suggesting the implication of autonomic neuropathy on macroangiopathy[69]. The study further showed that carotid stiffness parameter β was associated with high systolic blood pressure, high HbA1c, high fibrinogen, and high high-density lipoprotein (HDL) cholesterol level, while carotid IMT was associated with high HbA1c, high cholesterol levels, and low HDL-cholesterol level[15].

4. Cardiovascular Disease

In the early era of the studies on stiffness parameter β, Hirai *et al.* first demonstrated that stiffness parameter β of the abdominal aorta and the carotid artery was significantly higher in patients with myocardial infarction than in healthy subjects and

were higher in patients with higher number of diseased coronary vessels[70].

Later in the 2000s, several studies investigated the association between stiffness parameter β and CVD in a cross-sectional design[17, 19, 71]. Sugioka *et al.* examined the association of stiffness parameter β, plaque score, and percent area stenosis of the carotid artery with the severity of coronary artery disease (CAD) in 104 patients with preserved left ventricular function[71]. Plaque score and percent area stenosis, but not stiffness parameter β, of the carotid artery were found to be correlated with the extent of CAD[71]. Moreover, plaque score and percent area stenosis, but not stiffness parameter β, were independently associated with multivessel CAD in multivariate analysis adjusting for conventional coronary risk factors[71]. The study suggests that morphological rather than functional changes in the carotid artery are a predictor of the extent of CAD and multivessel CAD.

On the other hand, in type 2 diabetes patients, a positive association has been observed between stiffness parameter β and CVD[17, 19]. Lee *et al.* demonstrated the impact of carotid stiffness parameter β and IMT on CAD in 1,528 Japanese type 2 diabetes patients and 439 non-diabetic controls[17]. Higher carotid stiffness parameter β, as well as higher IMT, was observed in the order of type 2 diabetes patients with CAD, those without CAD, and non-diabetic controls, in each 10-year group of age. The study also found that each of high stiffness parameter β (≥ 20.0) and high IMT (≥ 1.30 mm) significantly predicted the coexistence of CAD with multivariate odds ratios of 1.548 and 2.205, respectively[17]. Moreover, patients with both high stiffness parameter β and high IMT had higher odds ratio of 3.115 than those with high stiffness or high IMT alone, suggesting that the combination of arterial stiffness and IMT by noninvasive ultrasound is useful for evaluation of atherosclerosis in type 2 diabetes[17]. Makita *et al.* demonstrated in 481 patients with peripheral artery disease that carotid stiffness parameter β was higher in those with diabetes than those without, after adjusting for cardiovascular risk factors, such as gender, hypertension, dyslipidemia, obesity, and smoking[19]. On the other hand, no significant difference in carotid IMT was found between diabetic and non-diabetic patients, suggesting that diabetic status differentially affects carotid stiffness and IMT in patients with peripheral artery disease[19].

In addition, several studies showed that increased stiffness parameter β of the carotid artery was associated with concentric left ventricular geometry[43] and impaired left ventricular diastolic function[41, 42] in patients with hypertension[41, 43] or cardiovascular risk factors[41-43]. These studies suggest a close link between left ventricular diastolic dysfunction and arterial stiffness in patients with risk factors for CVD.

There are several reports available on the cross-sectional relationship between stiffness parameter β and cerebrovascular disease[72, 73]. The aortic stiffness parameter β assessed by transesophageal echocardiography was greater in elderly patients aged over 55 years with ischemic stroke than in those without stroke and was independently associated with ischemic stroke after adjustment for aortic plaque score and other stroke risk factors[73]. Carotid stiffness parameter β was also shown to be higher in patients with silent cerebral infarction estimated by magnetic resonance imaging than in those without, while no significant difference was found in carotid IMT and plaque score between the groups[72].

Collectively, results from many, but not all, cross-sectional studies have demonstrated a significant association between increased carotid stiffness parameter β and concurrent CAD, peripheral artery disease, and stroke, although the results may differ depending on the research subjects.

5. Chronic Kidney Disease

Patients with chronic kidney disease (CKD) and/or those on dialysis therapy have multiple risk factors for CVD[74, 75]; thus, it is critical to predict and prevent CVD by making use of surrogate markers[76, 77]. There are several reports regarding stiffness parameter β in patients with CKD and/or those undergoing hemodialysis.

Kawada *et al.* demonstrated that carotid stiffness parameter β was higher in 35 hemodialysis patients with hypertension than in non-hemodialysis patients with (n=71) or without (n=30) and that hemodialysis was independently and positively associated with stiffness parameter β on multiple regression analysis[78]. Ogawa *et al.* showed in 64 hemodialysis patients that age and pulse pressure were independent determinants of carotid stiffness parameter β[72]. Interestingly, hemodialysis patients with silent cerebral infarction showed higher stiffness parameter β than those without, despite of no significant differences in mean IMT and plaque score between the groups[72].

Uremia is well known to cause insulin resistance by different mechanism than that found in diabetes[79-81]. Homeostasis model assessment (HOMA-R) is a simple and useful index of insulin resistance not only in diabetes and obesity[82-86] but also in CKD[87]. Zhou *et al.* demonstrated that HOMA-R index was independently correlated with

carotid stiffness parameter β in 80 non-diabetic hemodialysis patients[88]. Visceral fat area measured by computed tomography was also shown to be correlated with carotid stiffness parameter β, but not with IMT, in 77 non-diabetic hemodialysis patients[89]. These findings suggest that insulin resistance or hyperinsulinemia per se affects carotid stiffness parameter β in CKD regardless of diabetes status.

Makita *et al.* investigated stiffness parameter β and IMT of the carotid artery in 3,406 participants of the health-check-up program[18]. Stiffness parameter β in the participants with CKD (mean estimated glomerular filtration rate, 56.6 mL/min/1.73m^2) was significantly higher than that in those without, even after adjustment for conventional risk factors such as hypertension, diabetes, dyslipidemia, smoking, and obesity. On the other hand, neither IMT nor plaque score of the carotid artery showed significant differences between CKD and non-CKD participants[18]. This study suggests a preferential effect of CKD on carotid stiffness over wall thickness.

6. Other Diseases

Reports on carotid stiffness parameter β in diseases other than the abovementioned metabolic or cardiovascular diseases, including hyperthyroidism[90], hypothyroidism[91-93], and polycystic ovary syndrome (PCOS)[94], are limited. In 70 patients with Graves' disease, carotid stiffness parameter β was correlated with systolic blood pressure and pulse pressure and was significantly reduced by antithyroid drugs[90]. The same group also demonstrated that carotid stiffness parameter β was higher in patients with hypothyroidism than in normal controls and was decreased by normalization of thyroid function for 1 year by levothyroxine replacement therapy[91, 92]. Another group also demonstrated that carotid stiffness parameter β was higher in 93 patients with subclinical hypothyroidism than in 90 age-matched normal controls and was positively correlated with thyroid-stimulating hormone levels[93]. These reports suggest that dysregulation of thyroid hormone influences carotid stiffness parameter β.

Women with PCOS usually manifest dysregulation of sex hormones and insulin resistance. Soares *et al.* reported that carotid stiffness parameter β was higher in 40 patients with PCOS than in age- and BMI-matched controls, while neither carotid IMT nor flow-mediated dilatation of the brachial artery differed between the groups[94]. Since no difference was found in BMI or insulin resistance index between the groups, the researchers assumed that the increased carotid stiffness was attributed to hyperandrogenism inherent in PCOS. The increased carotid stiffness parameter β has been shown in other diseases, albeit with a limited number of reports, such as Takayasu's disease[95], Kawasaki disease[96], systemic lupus erythematosus[97], tetralogy of Fallot[98, 99], HIV infection[100], and β-thalassemia[101, 102] as compared with each control group.

Major factors or pathological conditions associated with increased stiffness parameter β mainly shown in cross-sectional studies are summarized in **Table 2**.

Is Stiffness Parameter β Useful for Risk Stratification of CVD?

Longitudinal observational studies on the relationship between stiffness parameter β and CVD risk are much limited than other surrogate markers for atherosclerosis, such as IMT[2, 103] and PWV[5]. However, several reports are interesting and valuable in terms of the predictive value of stiffness parameter β for CVD outcomes (**Table 3**).

The population-based ARIC study prospectively examined the relationship between various noninvasive measures of arterial elasticity, such as stiffness parameter β, arterial diameter change, Ep, and Young's elastic modulus (YEM), and the development of hypertension in 6,922 normotensive adults aged 45 to 64 years over 6 years[104]. The mean values of all these measures at baseline were higher in participants who developed hypertension during the observational period than in those who did not[104]. The multivariable-adjusted cumulative incident rate of hypertension from the highest to the lowest quartiles of stiffness parameter β was 9.6%[104]. Furthermore, 1-SD increase in stiffness parameter β was associated with 15% greater risk of hypertension, independent of established risk factors for hypertension and baseline blood pressure[104].

To date, several cohort studies have investigated the implications of stiffness parameter β of the carotid artery on future CVD events using a prospective design (**Table 3**). Several studies indicated the usefulness of stiffness parameter β as a predictor of future CVD outcomes[105], at least in part[106, 107], while the others did not[108]. Stork *et al.* investigated the associations of carotid plaque number and carotid stiffness-related indices, including stiffness parameter β with all-cause and cardiovascular mortality during 48-month follow-up in 367 elderly men (mean age, 78 years)[105]. In age-adjusted Cox model, the number of plaques, YEM, and stiffness parameter β were independent predictors of cardiovascular mortality (hazard ratio [95% confidence interval (CI)], 1.18 [1.05–1.34], 1.59 [1.19–2.14] and 1.05 [1.01–1.08],

Table 2. Factors or pathological conditions associated with increased stiffness parameter β shown in cross-sectional studies

Factors/pathological conditions	References in the text
Older age	13, 18, 20-22, 24, 29-33, 45, 56, 72
Sex	24, 44, 45, 49
Smoking	31, 33
Insufficient physical activity/lack of exercise	34, 35, 40, 58, 113
Hypertension/higher systolic or mean blood pressure	15, 18, 21, 44, 55, 56, 78
LV diastolic dysfunction	36, 41, 42
LV ventricular hypertrophy	33, 43
Low-grade inflammation: hsCRP	38, 47
Decreased female hormones	49, 50
Higher fasting glucose/HbA1c	15, 16, 20, 31, 51
Insulin resistance	22, 51, 52, 88
Obesity/higher BMI	16, 18, 31, 56-58
Metabolic syndrome	20, 21, 55, 59
Visceral fat accumulation/waist circumferences	30, 55, 58, 60, 89
Dyslipidemia: higher TG, lower HDL-cholesterol	57, 59
Adipocytokines: low adiponectin, high TNF-α	29, 30, 61
Type 1 diabetes	65-67
Type 2 diabetes	18, 22, 29, 30, 56
Coronary artery disease	17, 70
Ischemic stroke	72, 73
Chronic kidney disease	18, 63, 78

Abbreviations: LV, left ventricular; hsCRP, high-sensitivity C-reactive protein; BMI, body mass index; TG, triglycerides; HDL, high-density lipoprotein; TNF, tumor necrosis factor.

respectively)[105]. However, in the multivariate Cox model, stiffness parameter β no longer predicted cardiovascular mortality, while the number of plaque and YEM did (hazard ratio [95% CI], 1.18 [1.04–1.33] and 1.68 [1.26–2.26], respectively)[105].

The Second Manifestations of ARTerial disease (SMART) study examined whether carotid arterial stiffness-related indices, including DC, AC, stiffness parameter β, Ep, and YEM, are related to the occurrence of CVD events and death in a large cohort of 2,183 patients with manifest arterial disease[106]. In unadjusted models, decreased DC and CC and increased stiffness parameter β, EP, and YEM were significantly associated with increased risk of all vascular events and vascular death[106]. In the multivariate model with adjustment for blood pressure, sex, age, smoking, and use of antihypertensive drugs, none of the stiffness-related indices were significantly related to the occurrence of vascular event or death[106]. However, in the tertile with the lowest systolic blood pressure at baseline (79–131 mmHg), increased stiffness parameter β and Ep were associated with the risk for CVD events (hazard ratio per 1-SD [95% CI], 1.06 [1.01–1.10] and 1.05 [1.09–2.08], respectively)[106].

The Rotterdam study evaluated whether arterial stiffness, aortic PWV, and carotid DC predict CAD and stroke in a population-based study including 2,835 apparently healthy subjects[107]. The hazard ratios [95% CI] of CAD and stroke for subjects in the second and third tertiles of aortic PWV were 1.72 [0.91–3.24] and 2.45 [1.29–4.66] for CAD and 1.22 [0.55–2.70] and 2.28 [1.05–4.96] for stroke, respectively, after adjustment for age, gender, mean arterial pressure, and heart rate. The data indicated that the risk of CAD and stroke increased according to an increase in aortic PWV. On the other hand, carotid DC failed to show any significant hazard ratio for CAD or stroke in multivariable-adjusted models, although only that in the lowest tertile of carotid DC for CAD and stroke combined was significant, 2.12 [1.27–3.55], in the age- and gender-adjusted model[107].

In the Three-City study, a population-based cohort study in France, the association of indices of carotid arterial stiffness, including stiffness parameter β, distension (%), DC, CC, and YEM, with incident CAD were examined in 3,337 participants aged greater than 65 years with 9.0% diabetes and 12.2% CVD history[108]. During a median follow-up of 43.4 months, 128 CAD events occurred. Among the indices of carotid stiffness, only carotid distension (%) was associated with CAD risk with a hazard ratio of

Table 3. Summary of findings from cohort studies on the association between carotid stiffness-related indices and incident cardiovascular events and/or mortality

Author Study Year Reference	Design Region	·No. of subjects ·% of male ·Subjects ·mean age	Mean follow-up period	Stiffness-related index of carotid artery	HR [95% confidence interval] of each index for CVD events or mortality
Stork S, *et al.* 2004 [105]	Single center Netherlands	·367 ·100% ·elderly men ·78 years	48 months	·β index ·YEM ·No. of plaques	All-cause mortality: HR per 1-unit ·β index 1.01 [0.99–1.04] [a] ·YEM 1.26 [0.95–1.66] [a] ·No. of plaques 1.35 [1.12–1.64] [b] CVD mortality: HR per 1-unit ·β index 1.05 [1.01–1.08] [a] ·YEM 1.68 [1.26–2.26] [b] ·No. of plaques 1.18 [1.04–1.33] [b]
Dijk J, *et al.* The SMART study 2005 [106]	Single center Netherlands	·2,183 ·75% ·Subjects with manifest arterial diseases or CVD risks ·59.7 years	2.8 years (range, 0.1-6.5 years)	·β index ·DC ·CC ·Ep ·YEM	CVD events ·β index 1.03 [1.02–1.05], 1.01 [0.99–1.03] [c] ·DC 0.94 [0.91–0.97], 0.97 [0.93–1.01] [c] ·CC 0.55 [0.31–0.95], 0.84 [0.43–1.64] [c] ·Ep 1.24 [1.13–1.38], 1.07 [0.91–1.25] [c] ·YEM 1.49 [1.21–1.83], 1.15 [0.84–1.57] [c] CVD death ·β index 1.04 [1.03–1.06], 1.01 [0.98–1.04] [c] ·DC 0.88 [0.84–0.92], 0.94 [0.88–1.00] [c] ·CC 0.29 [0.13–0.66], 1.00 [0.39–2.57] [c] ·Ep 1.37 [1.22–1.53], 1.07 [0.87–1.30] [c] ·YEM 1.79 [1.44–2.23], 1.29 [0.90–1.86] [c]
Mattace-Raso F, *et al.* The Rotterdam study 2006 [107]	Population-based study Netherlands	·2,835 ·39.2% ·Healthy subjects ·71.7 years	4.1 years for CAD 3.2 years for stroke	·DC	CVD: HR of 1st or 2nd vs 3rd tertile as reference (1.00) ·1st tertile 2.12 [1.27–3.55] [d], 1.37 [0.752–2.47] [e] ·2nd tertile 1.52 [0.91–2.53] [d], 1.23 [0.72–2.09] [e] CAD: HR of 1st or 2nd vs 3rd tertile as reference (1.00) ·1st tertile 1.81 [0.94–3.49] [d], 1.32 [0.68–2.54] [e] ·2nd tertile 1.67 [0.89–3.13] [d], 1.12 [0.52–2.39] [e] Stroke: HR of 1st or 2nd vs 3rd tertile as reference (1.00) ·1st tertile 2.13 [0.96–4.76] [d], 1.39 [0.55–3.52] [e] ·2nd tertile 1.03 [0.44–2.42] [d], 0.86 [0.35–2.09] [e]
Leone N *et al.* The Three-City Study 2008 [108]	Population-based study France	·3,337 ·39.4% ·The elderly (> 65 years) ·73.2 years	43.4 months*	·β index ·Distension (%) ·DC ·CC ·YEM	CAD: HR of 2nd or 3rd tertile vs 1st tertile as reference (1.00) β index ·2nd tertile 1.03 [0.67–1.58], 0.95 [0.61–1.47] [f] ·3rd tertiel 1.12 [0.73–1.71], 0.93 [0.59–1.45] [f] ·Per 1-SD 1.15 [0.98–1.34], 1.06 [0.90–1.25] [f] HRs for any other indices were statistically non-significant.
Shoji T, *et al.* 2010 [109]	Single center Japan	·423 ·61% ·Subjects on hemodialysis ·59.6 years	70 months	·β index ·IMT	CVD mortality: HR per 1-SD ·β index 1.99 [1.65–2.42], 1.36 [1.08–1.71] [g] ·IMT 2.00 [1.73–2.33], 1.37 [1.16–1.62] [g]
Yang E, *et al.* The ARIC study 2012 [110]	Population-based study United States	·10,407 ·63.6% ·Middle-aged individuals (45 to 64 years) ·56.8 years	13.8 years	·β index ·CC ·DC ·Ep ·YEM	CAD: HR per 1-SD** ·β index 1.12 [1.06–1.18] [h], 0.97 [0.91–1.03] [i] ·CC 1.12 [1.05–1.19] [h], 0.96 [0.90–1.02] [i] ·DC 1.28 [1.20–1.37] [h], 1.01 [0.94–1.09] [i] ·Ep 1.20 [1.14–1.26] [h], 0.96 [0.90–1.02] [i] ·YEM 1.05 [0.997–1.11] [h], 0.96 [0.90–1.03] [i] Stroke: HR per 1-SD** ·β index 1.29 [1.19–1.40] [h], 1.14 [1.04–1.25] [i] ·CC 1.23 [1.09–1.40] [h], 1.02 [0.89–1.16] [i] ·DC 1.58 [1.38–1.81] [h], 1.19 [1.02–1.39] [i] ·Ep 1.38 [1.28–1.48] [h], 1.16 [1.06–1.28] [i] ·YEM 1.25 [1.16–1.35] [h], 1.16 [1.05–1.28] [i]

*, median of follow-up period; **, 1-SD decrease for CC and DC, 1-SD increase for β index, Ep, and YEM.
[a], adjusted for age; [b], adjusted for age and multiple covariates; [c], adjusted for age, mean blood pressure, sex, smoking, and the use of antihypertensive drugs; [d], adjusted for age and gender, [e], adjusted for 11 additional known risk factors including IMT, ankle-arm index, and pulse pressure; [f], adjusted for16 covariates including IMT, and carotid plaque; [g], adjusted for 13 covariates; [h], adjusted for age, gender, study site, and race; [i], adjusted for multiple covariates including 12 risk factors and IMT.
Abbreviations: No., number; HR, hazard ratio; CVD, cardiovascular disease; YEM, Young's elastic modulus; β index, stiffness parameter β; DC, distensibility coefficient; CC, compliance coefficient; Ep, Peterson's elastic modulus or pressure-strain modulus; CAD, coronary artery disease; IMT, intima-medial thickness; SD, standard deviation.

2.01 (95% CI, 1.27–3.17; tertile 3 versus tertile 1) in a multivariate model[108]. The other indices of carotid stiffness including stiffness parameter β failed to show a significant hazard ratio of CAD risk in multivariable-adjusted models (0.93; 95% CI, 0.59–1.45; tertile 3 versus tertile 1)[108].

In addition to the abovementioned studies of the general population, a longitudinal study investigated the impact of carotid stiffness on CVD mortality in hemodialysis patients at high risk of CVD. Shoji *et al.* investigated whether carotid stiffness parameter β or IMT was a predictor of CVD death in 423 hemodialysis patients in an observational cohort study[109]. During the follow-up period from 1996 to 2005, 216 all-cause deaths occurred including 124 deaths from CVD. The subjects were divided into four subgroups based on the median values of stiffness β and IMT. The subgroup with higher IMT and higher stiffness β showed the highest risk of CVD death among the subgroups with the hazard ratio of 5.87 (95% CI, 3.43–10.05), which was extremely higher than that of the subgroup with lower IMT and lower stiffness[109]. In multivariate Cox models, both stiffness parameter β and IMT independently predicted CVD mortality with hazard ratios [95% CI] of 1.38 [1.23–1.55] and 1.39 [1.23–1.55] per 1-SD in log unit, respectively[109]. This study suggests the distinct roles of arterial stiffness and thickness in the pathogenesis of CVD and the clinical utility of the combination of carotid stiffness parameter β and IMT in the prediction of CVD in a high-risk population.

The ARIC study with long-term follow-up (n=10,407) has provided important findings regarding the relationship between carotid stiffness-related indices and CVD events[110]. During a mean follow-up of 13.8 years, 1,267 incident CAD and 383 ischemic stroke events occurred. All carotid stiffness-related indices were significantly associated with incident stroke, but not with CAD, after full adjustment for risk factors and carotid IMT: hazard ratio [95% CI] of stroke for 1-SD difference toward adverse arterial stiffness, DC, 1.19 [1.02–1.39]; stiffness parameter β, 1.14 [1.04–1.25]; Ep, 1.16 [1.06–1.28]; and YEM, 1.16 (1.05–1.28) and hazard ratio [95% CI] of CAD for 1-SD difference toward adverse arterial stiffness, DC, 1.01 [0.94–1.09]; stiffness parameter β, 0.97 [0.91–1.03]; Ep, 0.96 [0.90–1.02]; and YEM, 0.96 [0.90–1.03], respectively[110]. Among the stiffness-related indices, only CC failed to show significant association with incident CAD and stroke[110]. The ARIC study is characterized by a middle-aged population with a large number of subjects, long follow-up period, and enough event numbers as compared to the other abovementioned cohort studies[105-109]. Taken together, it remains controversial whether or not carotid stiffness parameter β is useful as a predictor of CVD events and/or survival. It may depend on the characteristics of the patient, such as age, comorbidities, ethnicity, and the type of CVD.

Does Stiffness Parameter β Serve as a Surrogate Endpoint for Intervention?

1. Effect of Physical Activity or Exercise on Stiffness Parameter β

As mentioned earlier, cross-sectional studies have demonstrated higher carotid stiffness parameter β in individuals with CVD risk factors such as insulin resistance, obesity, hypertension, metabolic syndrome, and diabetes than in those without. It is evident that moderate physical activity and/or exercise is effective in managing those risk factors[111]. Therefore, it is reasonable to assume that exercise has a beneficial effect on arterial stiffness, and in fact, several studies have examined the hypothesis[35, 112-115]. Currently, it remains controversial whether exercise has a beneficial effect on carotid arterial stiffness or not, because research subjects and types, intensity, and duration of exercise greatly vary between studies.

(a) Resistance Exercise

Miyachi *et al.* examined the effect of resistance training on carotid arterial stiffness in 28 healthy men aged 20 to 38 years, in a randomized control study[116]. The intervention group (n=14) underwent three supervised resistance training sessions per week for 4 months and subsequent detraining period for 4 months, while control subjects were instructed not to alter their normal activity levels throughout the study period. In the intervention group, carotid arterial CC decreased by 19%, and stiffness parameter β increased by 21% after resistance training, which returned completely to the baseline levels after cessation of the training[116]. In addition, changes in carotid stiffness-related indices were inversely correlated with changes in left ventricular mass index and hypertrophy index[116]. The same group also examined in a cross-sectional study the carotid arterial vasoreactivity to cold pressor test in men participating in regular resistance exercise training for more than 10 years (n=12; mean age, 38.7 years)[117]. Carotid stiffness parameter β and systolic and mean blood pressure were higher in the resistance training group than in age-matched controls; however, no difference was found in vasoreactivity to cold pressor test between groups, suggesting an intact endothelial function, despite of increased arterial stiffness, in the resistance

training group[117].

On the other hand, Rakobowchuk *et al.* demonstrated that whole-body resistance training five times a week for 12 weeks reduced brachial and carotid pulse pressure but did not change carotid CC, stiffness parameter β, or cardiac dimensions in 28 young healthy men[118]. Conversely, Cook *et al.* reported that carotid stiffness parameter β was lower in habitual rowers (mean age, 50 years) who perform a combination of endurance and strength training during their training regimen than in sedentary controls, although it was a cross-sectional study[113]. The study suggested that simultaneously performed endurance training negated the stiffening effects of strength or resistance training on the arterial wall[113].

(b) Aerobic Exercise

In contrast to the inconsistent findings of the effect of resistance training on carotid arterial stiffness, studies on aerobic training have generally indicated beneficial effects on carotid stiffness parameter β.

Sugawara *et al.* showed that carotid stiffness parameter β significantly decreased after moderate or vigorous intensity cycling exercise training (900 kcal/week, 3 to 5 sessions per week, for 12 weeks) in sedentary postmenopausal women ($n=17$)[35].

In overweight and obese men ($n=21$; mean age, 50 years; mean BMI, 30 kg/m^2), Miyaki *et al.* demonstrated that 12-week aerobic exercise training significantly increased carotid DC and decreased stiffness parameter β, along with a significant decrease in body weight[114]. Similarly, Dengo *et al.* examined the effect of weight loss via a hypocaloric diet ($n=25$; mean age, 61.2 years; mean BMI, 30.0 kg/m^2) versus a control diet ($n=11$; mean age, 66.1 years; mean BMI, 31.8 kg/m^2) on carotid stiffness parameter β and carotid-femoral PWV in overweight and obese middle-aged and older adults[119]. After the 12-week intervention, both carotid stiffness parameter β (-1.24 ± 0.22 versus 0.52 ± 0.37) and carotid-femoral PWV (-187 ± 29 versus 15 ± 42 cm/s) significantly decreased in the weight loss group (weight change, -7.1 ± 0.7 kg), but not in the control group (-0.7 ± 1.1 kg)[114]. Since changes in total body or abdominal adiposity were not correlated with changes in stiffness parameter β, mechanisms responsible for the improved carotid arterial stiffness after weight loss intervention remain unclear.

In patients with type 2 diabetes, Yokoyama *et al.* reported a beneficial effect of short-term aerobic exercise on arterial stiffness[115]. An aerobic exercise protocol including ergometer and walking with mild to moderate intensity was performed for 3 weeks under supervision in 23 participants with type 2 diabetes. Stiffness parameter β of both common carotid and femoral arteries significantly decreased after the exercise protocol[115]. Furthermore, the decrease in both carotid and femoral stiffness parameter β was found to be greater in patients with greater improvement in insulin sensitivity measured by euglycemic hyperinsulinemic clamp after the exercise protocol[115]. The findings in the interventional study are consistent with those in cross-sectional[22, 29] and drug intervention[61] studies by the same group showing a close relationship between carotid stiffness parameter β and insulin resistance in patients with type 2 diabetes[22, 29, 61]. Aizawa *et al.* also demonstrated a beneficial effect of a 24-week lifestyle intervention including aerobic exercise and Mediterranean-style diet on carotid DC and stiffness parameter β in 63 subjects with pre-hypertension and/or pre-diabetes[112]. The results showed a reduction in arterial stiffness and an improvement in several components of metabolic syndrome in subjects with metabolic syndrome, suggesting a favorable effect of lifestyle intervention on carotid stiffness and on metabolic risk factors[112].

2. Effect of Pharmacotherapy on Carotid Arterial Stiffness

(a) Antihypertensive Drugs

It is evident that carotid stiffness parameter β is associated with hypertension as shown in many cross-sectional studies[15, 18, 44, 55, 56], although stiffness parameter β is not affected by arterial pressure at measurement. Patients with hypertension also have higher stiffness parameter β than healthy controls[44, 78]. Therefore, it is clinically important to study the effect of antihypertensive drugs on carotid arterial stiffness. Among various antihypertensive drugs, renin-angiotensin system inhibitors are the most interesting, because the renin-angiotensin system is well known to be involved in structural and functional changes in the vasculature[120]. Okura *et al.* investigated the effect of 24-month treatment with valsartan (80–160 mg/day), an angiotensin II receptor antagonist, on carotid DC, stiffness parameter β, and IMT in 24 patients with hypertension[121]. Treatment with valsartan significantly improved DC and stiffness parameter β, but not IMT, along with decrease in systolic and diastolic blood pressure[121]. Mizuguchi *et al.* examined the effects of telmisartan (20–40 mg/day), another angiotensin II receptor antagonist, on carotid stiffness parameter β, and IMT after medication had been continued for 1–2 months with normal blood pressure (phase I) and for 12 months (phase II), in 35 patients with untreated hypertension[122]. Both stiffness parameter β and IMT were significantly lower in phase II than in phase I[122]. Moreover, the study revealed that age,

blood pressure, and left ventricular diastolic variables were strong determinants of carotid stiffness β and IMT. The findings are also interesting in terms of the relationship between arterial stiffness and insulin resistance, because telmisartan partially activates peroxisome proliferator-activated receptor-γ, increases circulating adiponectin levels, and subsequently improves insulin sensitivity[123].

(b) Antidiabetic Drugs

There are two types of oral antidiabetic drugs (biguanides and thiazolidinediones) currently available in a clinical setting, which directly improve insulin resistance. The most widely used drugs are metformin and pioglitazone, respectively. Araki *et al.* compared the effects of 6-month treatment with those 2 drugs on carotid stiffness parameter β in 20 type 2 diabetes patients[61]. In patients treated with pioglitazone, stiffness parameter β significantly decreased along with significant increase in plasma adiponectin levels, whereas neither stiffness parameter β nor adiponectin levels significantly changed in patients treated with metformin[61]. Notably, the changes in stiffness parameter β were significantly and inversely correlated with those in plasma adiponectin levels after treatment[61]. Since both drugs equally improved insulin resistance in those patients, the results suggested that pioglitazone improves arterial stiffness through a mechanism independent of improving insulin resistance, such as increased adiponectin levels.

Newer antidiabetic drugs, sodium-glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP1-RA), are recently suggested to improve CVD outcomes, especially in patients with type 2 diabetes at high risk for CVD[124, 125]. Reducing arterial stiffness and endothelial dysfunction have been suggested to be the mechanisms by which those drugs improve the CVD outcomes in patients with type 2 diabetes[126-128]. While several studies have shown beneficial effects of SGLT2 inhibitors[128] and GLP1-RAs[126] on arterial stiffness assessed by PWV, only one report is currently available on the effect of SGLT2 inhibitors on carotid arterial stiffness in patients with diabetes[129]. Lunder *et al.* demonstrated that a SGLT2 inhibitor empagliflozin and metformin added to insulin therapy improved carotid stiffness parameter β greater than did metformin alone in patients with type 1 diabetes (n=40)[129].

Conclusions and Future Perspectives

Stiffness parameter β is a unique index to represent stiffness specific to local arterial wall at the carotid and femoral artery and aorta. The parameter was originally proposed in Japan and has been mainly developed/investigated in Japan and Europe. The index of the carotid/femoral artery can be obtained with high precision noninvasively and simultaneously with IMT by ultrasound equipped with echo-tracking system. Not only in theory but in practice, stiffness parameter β is less affected by blood pressure at the time of measurement than other arterial stiffness-related indices. Various diseases and risk factors for atherosclerosis affect stiffness parameter β of the carotid artery, such as aging, insufficient physical activity, hypertension, obesity, insulin resistance, hyperglycemia, and chronic kidney disease. The contribution factors do not necessarily match between carotid arterial stiffness and IMT in the same individual. Therefore, it is suggested that stiffness parameter β has a unique potential as a surrogate marker for CVD, which is distinct from IMT.

Results from several longitudinal studies suggested the possibility of stiffness parameter β as a useful surrogate marker for future CVD events independent of traditional risk factors, especially in studies of high-risk populations or in studies with long follow-up periods[105, 106, 109, 110], although some studies failed to identify stiffness parameter β as a significant predictor of CVD[108]. In addition, there are only a few studies available on stiffness parameter β with a large number of subjects or with long observational period than studies on other surrogate markers for CVD. Therefore, the value of stiffness parameter β for predicting future CVD events or stratifying the risk of CVD remains to be determined.

On the other hand, results from several interventional studies suggest that lifestyle or drug intervention improves stiffness parameter β of the carotid artery even for a relatively short period[35, 61, 112-115, 121, 122, 129]. These findings suggest the unique values of stiffness parameter β as a surrogate for changes in vascular health status induced by lifestyle or drug intervention. The reversibility of stiffness parameter β may be useful for motivating individuals with CVD risk factors receiving lifestyle and/or drug interventions to prevent CVD.

Further studies are warranted to investigate the following issues to verify the clinical utility of stiffness parameter β: (1) its association with stroke, cognitive function, dementia, or heart failure in a cross-sectional design, (2) its predictive value for CVD in an observational design with a large number of subjects and a long-term follow-up period, (3) its usefulness in monitoring the effect of lifestyle and/or drug interventions on vascular health, and (4) comparison of clinical utility between stiffness parameter β and other surrogate markers and the usefulness of

combining those indices in predicting CVDs or in monitoring treatment effects.

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