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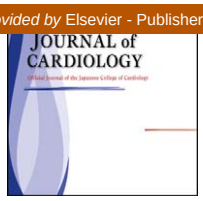

Original article

Aortic stiffness is strikingly increased with age ≥50 years in clinically normal individuals and preclinical patients with cardiovascular risk factors: Assessment by the new technique of 2D strain echocardiography

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KEYWORDS
Aortic stiffness;
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Summary
Background: Various measures of aortic stiffness have been proposed as cardiovascular risk markers, but interest has now shifted to more direct and easier evaluation of aortic function. The present study was conducted to determine the feasibility of measuring aortic stiffness (β) with two-dimensional (2D) strain echocardiography and the impact of age and gender on preclinical atherosclerosis.
Methods and results: The peak circumferential strain of the abdominal aorta was measured using 2D strain echocardiography, and β was determined in 54 clinically normal individuals and 104 patients with cardiovascular risk factors and no evidence of cardiovascular disease. The β correlated significantly with age in all 158 patients. However, the relationship was nonlinear, and β was markedly greater in patients ≥50 years. In 54 clinically normal individuals, the relationship was comparatively linear. The systolic blood pressure and pulse pressure were significantly greater in patients ≥50 years. There were no significant differences in β and blood pressure parameters between genders.
Conclusions: The β increased dramatically with advanced age (≥50 years), regardless of gender, in clinically healthy and community-based patients with cardiovascular risk factors. The aortic circumferential strain was measured with 2D strain echocardiography which is a new tool that can be used to directly and easily evaluate aortic stiffness.

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Introduction

It is well recognized that physiologic aging [1—3] and cardiovascular risk factors [3,4] lead to structural and functional alterations in large arteries, and that also aortic stiffness is the best predictor of cardiovascular morbidity and mortality [5,6]. Therefore, there is increasing interest in the detection of preclinical vascular involvement [7,8]. Because invasive measurements of arterial stiffness are not feasible in routine clinical use, several noninvasive techniques, such as M-mode ultrasonography [9] and pulse wave velocity [10,11], have been proposed for the purpose. However, these techniques produce fairly imprecise approximation, are dependent on age or blood pressure, and have low reproducibility. Two-dimensional (2D) strain echocardiography has been developed to allow rapid, accurate, and simple determination of regional myocardial deformation [12]. Furthermore, it has been clarified that this novel approach is applicable to the evaluation of aortic stiffness [13]. The present study sought to investigate the feasibility and usefulness of the vascular strain analysis related to changes in aging in clinically normal individuals and patients with cardiovascular risk factors and no known heart disease by using 2D strain echocardiography as a new echocardiographic measure of aortic stiffness.

Methods

Study population

The study group consisted of 205 consecutive patients undergoing routine health check up at our hospital between 2008 and 2009. They had never been treated before. A total of 47 patients were excluded because the following exclusion criteria were fulfilled: left ventricular (LV) ejection fraction $\leq$60%, clinically significant valvular heart disease, known coronary artery disease, previous stroke, chronic obstructive pulmonary disease, renal disease, and aortic disease. The residual 158 patients (59 men, 99 women, mean age: 63 $\pm$ 19 years, range: 12—88 years) who had adequate acoustic windows, were divided into 2 groups; clinically normal individuals with no cardiovascular risk factors (n = 54) and patients with cardiovascular risk factors (n = 104). The latter group included current smokers (n = 19), body mass index $\geq$25 kg/m^2 (n = 42), hypertension with systolic (SBP) or diastolic blood pressure (DBP) >140 mm Hg or 90 mm Hg, respectively (n = 85), hyperlipidemia with total cholesterol >220 mg/dl or triglycerides >150 mg/dl (n = 52), and/or hyperglycemia with fasting glucose concentration $\geq$110 mg/dl with no retinopathy, nephropathy, or neuropathy (n = 27). In 104 patients with cardiovascular risk factors, one risk factor was observed in 50 patients, 2 risk factors in 33 patients, 3 risk factors in 17 patients, and 4 risk factors in 4 patients. These patients' flow is shown in Fig. 1.

The protocol used for the present study was approved by the ethics committee of the institution involved. An informed consent was given by all patients.

Aortic ultrasonography

A short-axis view of the abdominal aorta at a level of subcostal region was obtained at end-expiration breath holding with the use of a commercially available ultrasound system (Vivid 7, General Electric Medical Systems, Milwaukee, WI, USA) equipped with a harmonic 4.0-MHz variable-frequency phased-array transducer [13]. Two-dimensional image acquisition was performed at a frame rate of 70—90 frames per second, and 3 cardiac cycles were stored in cineloop format for subsequent analysis. Adequate tracking was verified in real time and corrected, if needed. The global strain was calculated with the use of entire circumferential length of the aortic wall. Using a dedicated software package (EchoPac, General Electric Healthcare, Waukesha, WI, USA), peak circumferential strain (Ao-S) was measured (Fig. 2).

The stiffness of the abdominal aorta was evaluated at the same position as 2D strain measurements by M-mode ultrasonography (Fig. 3), and determined by the stiffness parameter as validated by Hirai et al. [9]: stiffness $\beta_1 = \ln(\mathrm{SBP}/\mathrm{DBP})/[(D_{max} - D_{min})/D_{min}]$, where D_{max} and D_{min} are maximal and minimal aortic diameters, respectively. Also, stiffness of the abdominal aorta was evaluated by 2D strain echocardiography: stiffness $\beta_2 = \ln(\mathrm{SBP}/\mathrm{DBP})/\mathrm{Ao\text{-}S}$, where Ao-S is peak strain determined by aortic circumferential strain curve.

All 2D strain and M-mode ultrasonographic measurements were averaged for at least 3 consecutive beats.

Statistical analysis

Values are expressed as the mean $\pm$ standard deviation (SD). The differences in the mean values among the groups were compared using the one-way analysis of variance (ANOVA). The relationships between age and aortic stiffness measured by M-mode ultrasonography and 2D strain echocardiography were tested using linear and non-linear correlations, and the best fit was retained. A p-value less than 0.05 was considered statistically significant.

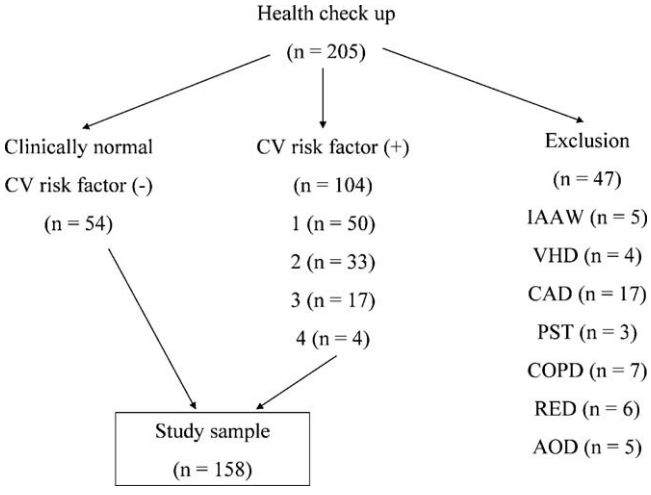

Figure 1 Patient flow of the study sample. CV, cardiovascular; IAAW, inadequate acoustic window; VHD, valvular heart disease; CAD, coronary artery disease; PST, previous stroke; COPD, chronic obstructive pulmonary disease; RED, renal disease; AOD, aortic disease.

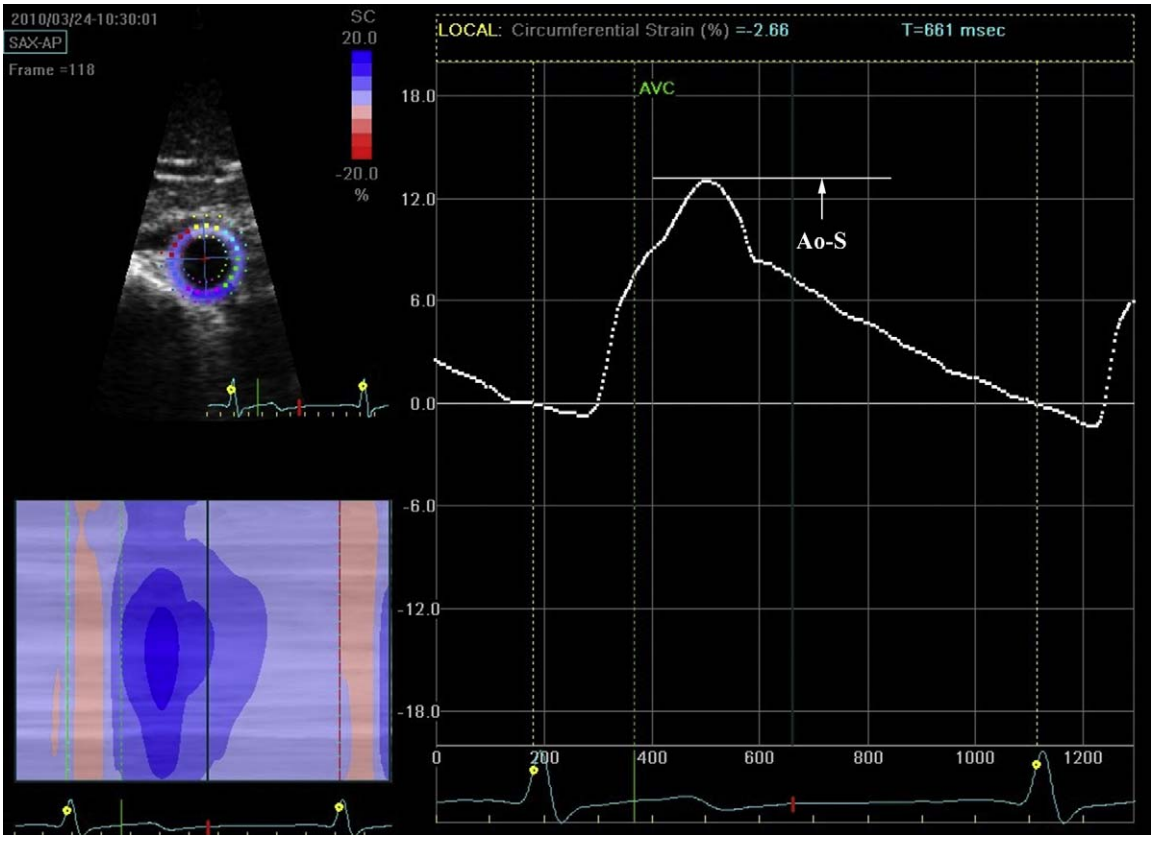

Figure 2 Measurement method of aortic circumferential strain by 2D strain echocardiography. Ao-S, peak strain determined by aortic circumferential strain curve.

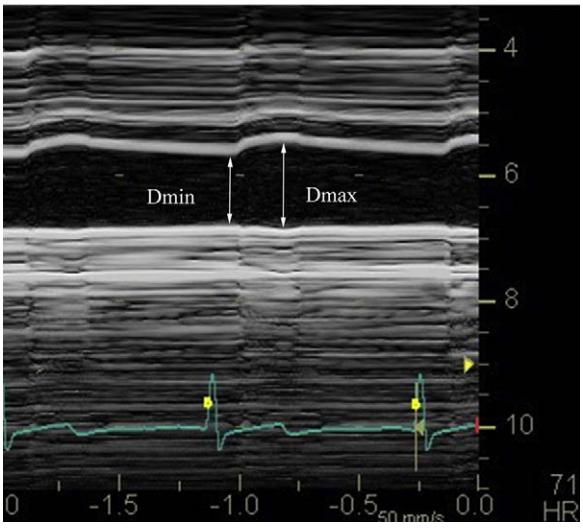

Figure 3 Measurement method of aortic stiffness parameter β_1 by M-mode ultrasonography. D_{max}, maximal aortic diameter; D_{min}, minimal aortic diameter.

Results

The aortic stiffness β_1 determined by M-mode ultrasonography and aortic stiffness β_2 determined by 2D strain echocardiography correlated significantly with age ($r = 0.44$, $p < 0.0001$ and $r = 0.54$, $p < 0.0001$, respectively) in all 158 patients, particularly the latter parameter β_2 correlated well (Fig. 4). The stiffness β_1 and β_2 in patients $\geq$50 years were significantly greater than those <50 years (Table 1). In addition, the relation between aortic stiffness β_2 and age was linear regression in 54 clinically normal individuals ($r = 0.71$, $p < 0.0001$) (Fig. 5).

The SBP and pulse pressure (PP) were significantly greater in patients $\geq$50 years than in patients <50 years, whereas there was no significant difference in DBP between the 2 groups.

There were no significant differences in aortic stiffness β_1 and β_2, SBP, DBP, and PP between men and women in all 158 patients (Table 2) and patients $\geq$50 years (Table 3).

Reproducibility of measurements

The reproducibility of the measurements of 2D strain echocardiographic parameter β_2 was assessed by 2 experienced investigators in 15 randomly selected patients. The mean $\pm$ SD intraobserver reproducibility was $4.3 \pm 0.9\%$, and mean $\pm$ SD interobserver reproducibility was $5.2 \pm 1.2\%$.

Discussion

To the best of our knowledge, this is the first study to demonstrate the abrupt increase in aortic stiffness progression in clinically normal individuals and preclinical patients with

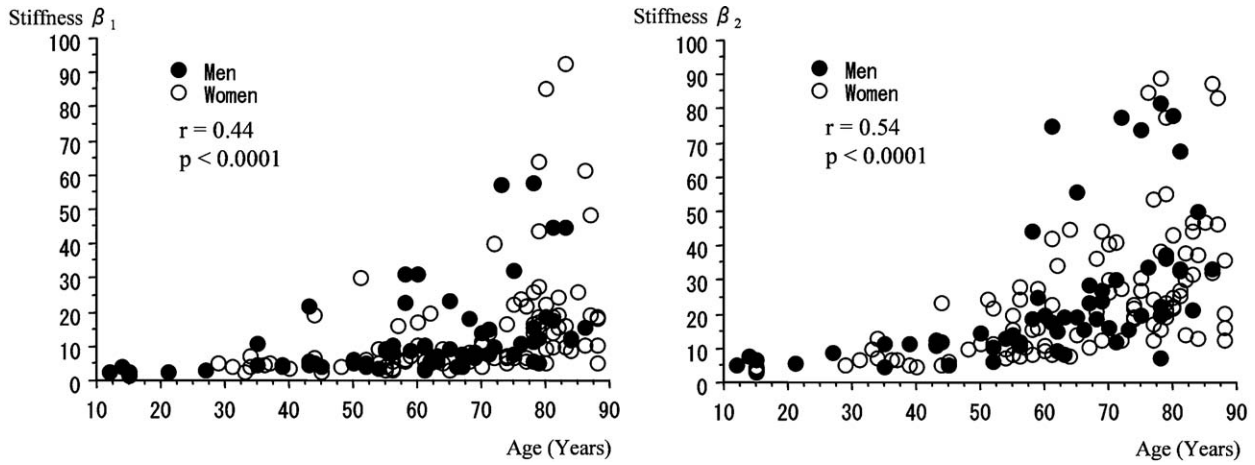

Figure 4 Correlations between the aortic stiffness β_1 determined by M-mode ultrasonography (left) and β_2 determined by 2D strain echocardiography (right) and age in all 158 patients.

Table 1 Comparisons of aortic stiffness and blood pressure parameters between patients <50 years and ≥50 years.

	<50 years (n = 30)	≥50 years (n = 128)	p-Value
Stiffness β_1	5 ± 5	16 ± 16	<0.001
Stiffness β_2	8 ± 4	29 ± 20	<0.0001
SBP (mm Hg)	118 ± 20	137 ± 20	<0.0001
DBP (mm Hg)	67 ± 11	71 ± 10	NS
PP (mm Hg)	51 ± 12	66 ± 18	<0.0001

β_1, aortic stiffness determined by M-mode ultrasonography; β_2, aortic stiffness determined by 2D strain echocardiography; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; NS, not significant.

Table 2 Comparisons of stiffness and blood pressure parameters between genders in all 158 patients.

	Men (n = 59)	Women (n = 99)	p-Value
Stiffness β_1	13 ± 13	15 ± 17	NS
Stiffness β_2	25 ± 21	25 ± 19	NS
SBP (mm Hg)	137 ± 20	132 ± 22	NS
DBP (mm Hg)	72 ± 12	70 ± 11	NS
PP (mm Hg)	64 ± 18	62 ± 18	NS

β_1, aortic stiffness determined by M-mode ultrasonography; β_2, aortic stiffness determined by 2D strain echocardiography; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; NS, not significant.

cardiovascular risk factors of greater than 50 years using 2D strain echocardiography.

Aortic stiffness has been highlighted as an independent prognosticator of cardiovascular events in some populations [5,6]. Increased aortic stiffness is an important pathophysiologic feature that leads to augmented SBP and attenuated DBP, resulting in elevated PP [14]. Higher SBP may be responsible for pressure overload and LV hypertrophy, and have decrimental impacts on diastolic relaxation [15,16]. Also, lower DBP induces a reduction of coronary perfusion. Therefore, simple and accurate measurements of aortic stiffness may contribute to the diagnosis of heart failure with preserved LV ejection fraction by documenting abnormal ventriculo-arterial coupling at an earlier stage [17,18].

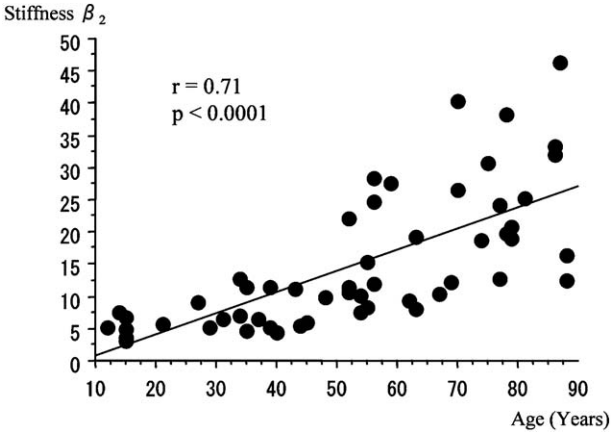

Figure 5 Correlation between aortic stiffness β_2 determined by 2D strain echocardiography and age in 54 clinically normal individuals.

Table 3 Comparisons of stiffness and blood pressure parameters between genders in patients ≥50 years.

	Men (n = 46)	Women (n = 82)	p-Value
Stiffness β_1	15 ± 14	17 ± 17	NS
Stiffness β_2	29 ± 21	28 ± 19	NS
SBP (mm Hg)	140 ± 19	136 ± 21	NS
DBP (mm Hg)	73 ± 12	70 ± 10	NS
PP (mm Hg)	66 ± 19	66 ± 17	NS

β_1, aortic stiffness determined by M-mode ultrasonography; β_2, aortic stiffness determined by 2D strain echocardiography; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; NS, not significant.

A wide variety of indexes on aortic stiffness can now be noninvasively assessed using M-mode ultrasonography [9], pulse wave velocity [10,11], stroke volume and SBP [4], and cardio-ankle vascular index [19,20]. It is very important to easily and accurately evaluate arterial stiffness in clinical practice. A recent study [13] has proposed that aortic circumferential strain measured by 2D strain echocardiography allows simple, accurate, and direct determination of the aortic stiffness.

In the present study, our data using 2D strain echocardiography suggest that the relationship between age and aortic stiffness is non-linear rather than simple linear regression, and changes in aortic stiffness are more marked in older individuals ($\geq$50 years) in clinically normal individuals and patients with cardiovascular risk factors and no evidence of cardiovascular disease. In addition, we confirmed that 2D strain echocardiography is a sensitive tool for assessing arterial aging as well as M-mode ultrasonography.

There is increasing evidence to suggest that abnormalities in aortic stiffness correlate with physiologic aging [1—3] and pathologic states with cardiovascular risk factors [3,4]. O'Rourke and Hashimoto [21] reported that arterial aging is the story of what happens beyond age 30 years. Therefore, it is important to know both the prevalence and age distribution of abnormal aortic properties in the preclinical patient population.

Previous studies using arterial stiffness parameters, such as pulse wave velocity, cardio-ankle vascular index, and stroke volume and SBP, indicated that arterial compliance is associated with age in normal individuals and/or patients with cardiovascular risk factors. However, their results showed a linear relationship between both parameters [3,4,20,21]. On the other hand, some studies demonstrated that age-related changes in aortic stiffness are more marked in older patients, indicating a non-linear distribution [2,22,23]. The latter reports are in line with our present results, although the relationship in clinically normal individuals showed a comparatively linear distribution.

Multiple mechanisms have been proposed to explain age-dependent vascular stiffening, including alterations in endothelial function, structural protein composition, collagen crosslinking, geometric changes, and neurohumoral signaling [24]. Large artery stiffness increases with age even in the absence of vascular disease or risk factors [1,2]. However, previous epidemiological data indicated that PP increases significantly only after the fifth decade, suggesting that aortic stiffening occurs predominantly in later life [25]. Likewise, in the present study, SBP and PP were markedly greater in patients $\geq$50 years.

It has been established that preclinical atherosclerosis is not an irreversible but rather a dynamic process. Therefore, earlier medical treatment, such as with statins [26] and angiotensin II receptor blockers [27], on cardiovascular risk factors have been shown to slow or even regress the progression of atherosclerosis.

In the present study, no direct relation between aortic stiffness and gender is inconsistent with the results of previous studies in which large-artery stiffness is higher in women [28,29]. Although the mechanism of the association remains controversial, Waddell et al. [29] suggested that age-related stiffening of large arteries is more pronounced in women, which is consistent with changes in female hormonal status.

Study limitations

The main limitation is that subgroup analysis for each cardiovascular risk factor was not performed as the sample size was thought to be too small for significant comparisons in the present study. Future study including large numbers of patients will likely improve this problem.

Conclusions

Increase in aortic stiffness β_2 measured by 2D strain echocardiography was evident in clinically normal individuals and preclinical patients with cardiovascular risk factors aged $\geq$50 years and thus β_2 can be used as a new echocardiographic parameter of aortic stiffness.

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