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Review Article

Stroke and Cardio-Ankle Vascular Stiffness Index: A Clinical Use

Ryuji Sakakibara[1]*, Jun Suzuki[2], Yohei Tsuyusaki[1], Fuyuki Tateno[1], Masahiko Kishi[1] and Takanobu Tomaru[2]

[1]*Department of Neurology and Internal Medicine, Sakura Medical Center, Toho University, Japan*
[2]*Clinical Physiology Unit, Sakura Medical Center, Toho University, Japan*

Abstract

Stroke is the most common cause of neurological disability and impairs quality of life, resulting in early institutionalization. Atherosclerosis is a major contributor to stroke, which can be prevented by early recognition and management. Cardio-ankle vascular stiffness index (CAVI) was introduced clinically as a novel, simple and non-invasive measure in the assessment of atherosclerosis. CAVI is easy to perform, and has adequate reproducibility for clinical use. As compared with healthy control subjects, CAVI is statistically greater in patients with ischemic cerebrovascular diseases, particularly with white matter lesions (WML), large-artery atherosclerosis, and small-vessel occlusion, but not in patients with transient ischemic attack (TIA). CAVI showed clear relationship with carotid ultrasound plaque score. CAVI is useful as a routine test for the early suspicion of ischemic cerebrovascular disease, particularly in clinical practice. It appears that CAVI.

Special Issue on
Ischemic Stroke: A Cerebrovascular Accident

***Corresponding author**
Ryuji Sakakibara, Associate Professor, Neurology, Internal Medicine, Sakura Medical Center, Toho University, 564-1 Shimoshizu, Sakura, 285-8741, Japan, Tel: +81-43-462-8811 ext. 2323; Fax: +81-43-487-4246, E-mail: sakakibara@sakura.med.toho-u.ac.jp

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INTRODUCTION

Cardio-ankle vascular stiffness index (CAVI) was introduced clinically by Shirai [1] and Yambe [2] as a novel, simple and non-invasive measure in the assessment of atherosclerosis. CAVI is easy to perform, and has adequate reproducibility for clinical use [1]. Many brain stroke is thought to be a sequel of advanced systemic arteriosclerosis, particularly in the carotid, vertebral, and intra-cranial arteries. Recently, a relation between abnormal CAVI and stroke has been established [3,4,5]. Here we discuss the clinical use of CAVI in the management of stroke.

Atherosclerosis and arterial stiffness

Arteriosclerosis is a major contributor to stroke, accounting for a high percentage of mortality and morbidity. The degree of atherosclerosis relevant to the cerebral arteries is measured visually (carotid/ vertebral artery sonography, cerebral angiography, and magnetic resonance angiography, etc.) [6,7] and functionally (arterial stiffness) [8,9,10]. Arterial stiffness is the principal physiological change in atherosclerotic vessels, which is known to contribute to systemic hypertension, endothelial dysfunction, and stroke [11,12]. Arterial stiffness has been measured by pulse wave velocity (PWV) [13], stiffness parameter β, etc. , based on the idea that cylindrical walls respond to pulsatile waves. PWV was developed as early as the 1920s by Bramwell and Hill, etc [14,15]. However, the problem with PWV is that it depends on blood pressure, which makes clinical interpretation difficult. The stiffness parameter β was developed in the 1980s by Hayashi et al. , as a marker that is independent of blood pressure [16,17,18]. However, one problem of the stiffness parameter β is that it needs an inner arterial diameter at systole and diastole by ultrasound echography, which lessens its clinical availability.

Cardio-ankle vascular stiffness index (CAVI)

What is CAVI?: CAVI was introduced clinically in the 2000s as a novel, simple and non-invasive measure in the assessment of atherosclerosis [1,2]. CAVI is easy to perform (only monitoring blood pressure and pulse wave at the brachial and tibial arteries, and does not require ultrasound sonography), and has adequate reproducibility for clinical use [5]. CAVI is independent of blood pressure. This is because CAVI is integrated in Bramwell-Hill's formula (volume elastic modulus and PWV) and the stiffness parameter β [1]. In addition, CAVI does not need an ultrasound echography. This is because in the CAVI formula, arterial diameter and its difference between diastole and systole is theoretically approximated by the PWV and its difference [1]. Thereafter, several reports have shown the usefulness of CAVI for the detection of atherosclerosis in patients with atherosclerotic risk factors, e.g. , smoking [10], diabetes [19] and in patients with coronary heart diseases [9]and stroke [3,4,5].

How to measure CAVI?: CAVI is measured with a VaSera CAVI instrument (Fukuda Denshi Inc, Tokyo, Japan) (Figure 1) [1]. CAVI was calculated by the following formula: CAVI = a{ (2ρ/ ΔP) × ln (Ps/Pd) PWV [2]} + b, where Ps is systolic blood pressure, Pd is diastolic blood pressure, PWV is pulse wave velocity, ΔP is Ps– Pd, ρ is blood density, and a and b are constants. Cuffs were applied to bilateral upper arms and ankles, with the subject lying supine and the head held in midline position. After resting for 10 min, the measurement was started. To detect the brachial and ankle pulse waves with cuffs, a low cuff pressure from 30 to 50 mmHg was used to ensure minimal effect of cuff pressure on hemodynamics. Blood pressure was obtained by a cuff at the upper arm. PWV was obtained by dividing the vascular length by the time it takes the pulse wave to propagate from the aortic valve to the ankle. This was measured by the cuffs on both the upper arms and ankles. To be compatible with the aortic PWV method established by Hasegawa and coworkers, [13] scale conversion constants (a, b) were determined so as to match CAVI with the aortic PWV method. By scale conversion constants, data of PWV could be converted to CAVI. All these measurements and calculations were performed automatically in the VaSera. The average coefficient of variation of CAVI is less than 5%, which is small enough for clinical usage and indicates that CAVI has good reproducibility [1].

Application of CAVI to stroke

We recently applied CAVI to brain stroke patients in order to investigate the relationship between them [4]. During a three-year period, we enrolled 854 healthy control subjects. They visited the Clinical Physiology Unit and underwent CAVI as a screening for atherosclerosis. They included 487 men and 367 women, mean age 65.1±9.4 years. During the same period, we enrolled 85 subjects diagnosed with ischemic cerebrovascular disease. They were 63 men and 22 women, with age 70.0±10.8 years. The patients included 17 with large-artery atherosclerosis (embolus/ thrombosis) (13 men, 4 women, mean age 71.4±9.6, none of the patients had cardiogenic emboli by the echocardiography), 30 with small-vessel occlusion (lacune, 25 men, 5 women, mean age 66.1±10.7), and 12 with transient ischemic attack (TIA) (8 men, 4 women, mean age 63.2±10.8 years; none of the patients had abnormalities in diffusion-weighted images of magnetic resonance imaging (MRI) scan) [20]. We added a group of 26 patients with white matter ischemic lesions (WML) (grade 2 or higher by MRI scan; 17 men, 9 women, mean age 76.7±7.6; all patients showed one of the following clinical features; e. g. , cerebrovascular parkinsonism, cerebrovascular dementia, and cerebrovascular urinary frequency/ urgency).

CAVI was measured in the above 854 healthy control subjects and 85 subjects with ischemic cerebrovascular disease. CAVI was performed at least 10 days after the onset of stroke. It is known that CAVI in healthy control depends on age, with a larger value in elderly age [1]. It is also known that CAVI in healthy controls depends on sex, with larger values in males [1]. Therefore, CAVI of control groups and each cerebrovascular disease group were stratified 1) by 10-year layers into 5 subgroups (40-49, 50-59, 60-69, 70-79, 80-89 years), and 2) by gender into 2 subgroups (male, female). We also performed carotid ultrasound sonography was performed in 75 of the 85 patients with ischemic cerebrovascular disease with the linear-array 7.5-MHz transducers (EUB-525, Hitachi, Inc, Tokyo, Japan; SSA-260A, Toshiba, Inc, Tokyo, Japan), and intima-media thickness (IMT) was measured.

In the healthy control group, CAVI in males was 7.70±0.76 (40-49 years), 8.21±0.80 (50-59 years), 9.05±0.82 (60-69 years), 9.67±0.92 (70-79 years), and 10.02±0.87 (80-89 years), respectively. CAVI in females was 7.34±0.89 (40-49 years), 8.27±0.82 (50-59 years), 8.64±0.87 (60-69 years), 9.41±0.92 (70-79 years), and 10.00±0.97 (80-89 years), respectively (Table 1) . The grand average of CAVI in ischemic cerebrovascular diseases was as follows: TIA, 9.3±1.5; WML, 10.3±1.3; large-artery atherosclerosis, 10.2±1.2; and small-vessel occlusion, 10.0±1.6, respectively. Therefore, the differences in CAVI between the ischemic cerebrovascular disease and control groups were as follows: TIA, 0.492 (no statistical significance) ; WML, 0.733 ($p<0.001$ by Fisher's PLSD, Bonferroni-Dunn test, and $p=0.002$ by Scheffe test) ; large-artery atherosclerosis, 0.838 ($p<0.001$ by Fisher's PLSD, Bonferroni-Dunn test, and $p=0.005$ by Scheffe test) ; and small-vessel occlusion, 1.034 ($p<0.001$ by Fisher's PLSD, Bonferroni-Dunn test, and Scheffe test), respectively (Figure 2). Linear regression analysis of CAVI and IMT showed no statistical significant relationship. Linear regression analysis of CAVI and plaque-score showed that there was a weak but statistical

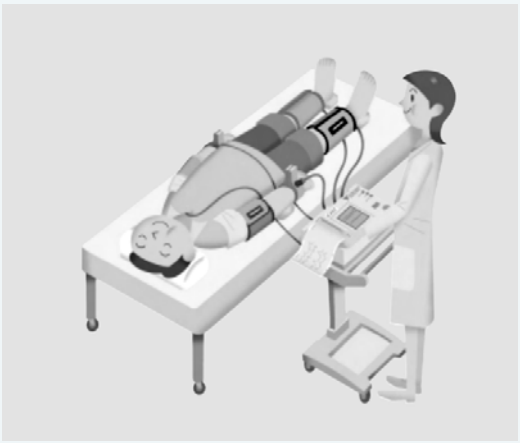

Figure 1 Measurement of CAVI in a lying position.

Table 1: CAVI in healthy control subjects.

Sex	Age (years)	No. of subjects	Mean age (years)	CAVI mean	CAVI SD
Male	40-49	81	45.1 ± 2.6	7.70	0.76
	50-59	81	55.1 ± 3.1	8.21	0.80
	60-69	204	64.4 ±2.8	9.05	0.82
	70-79	140	73.5 ±2.6	9.67	0.82
	80-89	25	82.5 ±2.3	10.02	0.87
Fimale	40-49	23	44.5 ± 2.9	7.34	0.89
	50-59	60	55.8 ± 3.4	8.27	0.82
	60-69	159	64.5 ±2.7	8.64	0.87
	70-79	110	74.5 ±2.8	9.41	0.92
	80-89	15	82.3 ±2.8	10.02	0.97

N=854. CAVI: cardio-ankle vascular stiffness index, SD: standard deviation Cited from ref. 4.

significant relationship between CAVI and plaque score in ischemic cerebrovascular disease patients (p=0.0445) (Figure 3) . There was no statistical significant relationship between CAVI and plaque score in each of large-artery atherosclerosis, small-vessel occlusion, TIA and WML.

Compared with healthy control subjects, CAVI is statistically larger in patients with ischemic cerebrovascular diseases, particularly in those with WML, large-artery atherosclerosis, and small-vessel occlusion (p<0.001). The results were obtained after stratifying CAVI of control groups and each ischemic cerebrovascular disease group by 10-year layers. Therefore, it is not contradictory to the finding that the difference in CAVI between WML and controls increased with age, which is only mild but statistically significant as described below. In contrast, there was no difference in CAVI between patients with TIA and control subjects. The results are in accordance with the fact that TIA is the mildest form among the 4 subgroups of ischemic cerebrovascular diseases. The results indicated that CAVI is useful as a routine test for the early suspicion of ischemic cerebrovascular disease, particularly in clinical practice.

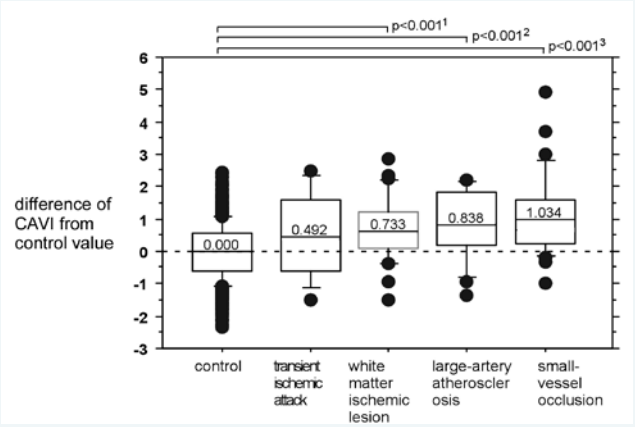

Figure 2 Difference in CAVI between cerebrovascular disease and control groups. Note that horizontal bars and values in the box plot indicate grand average (not median, in order to visualize the objects of statistics). CAVI: cardio-ankle vascular stiffness index. P values 1, 2, and 3 are driven by three different statistical methods: Fisher's protected least significant difference (all p<0.001), Bonferroni-Dunn test (all p<0.001), and Scheffe test (WML, p=0.002, infarction (except for lacuna), p=0.005, lacunar infarction, p<0.001). The TIA group was not significantly different from controls by any method.

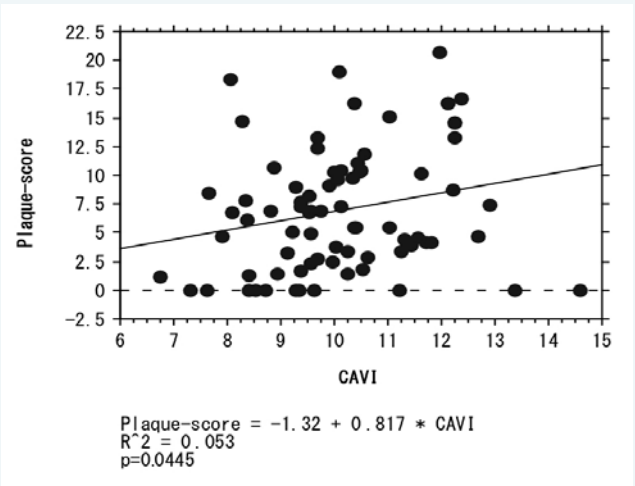

Figure 3 Linear regression analysis of CAVI and plaque-score. There was a weak but statistical significant relationship between CAVI and plaque score in ischemic cerebrovascular disease patients (p=0.0445).

CONCLUSION

Stroke is the most common cause of neurological disability and impairs quality of life, resulting in early institutionalization. Atherosclerosis is a major contributor to stroke, which can be prevented by early recognition and management [21]. CAVI is useful as a routine test for the early suspicion of ischemic cerebrovascular disease, particularly in clinical practice. It appears that CAVI is a simple and non-invasive test for indicating atherosclerosis in patients with stroke.

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