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Validity of CAVI measurements for diagnosing hypertension in middle-aged and elderly patients and correlations of these measurements with relevant factors

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Abstract.
BACKGROUND: The high risk of hypertension in middle-aged and elderly people has led to the development of the cardio-ankle vascular index (CAVI), a novel predictor of cardiovascular events.
OBJECTIVE: This paper aimed to determine how reliably hypertension can be diagnosed in middle-aged and elderly people by measuring CAVI.
METHODS: One hundred and ninety-five subjects (69 males/126 females; mean age of 56.06 ± 2.08 years) were enrolled. CAVI were measured using a blood pressure and pulse monitor device.
RESULTS: The CAVI was positively correlated with age, SBP, PP and PPI in the hypertension group ($r = 0.656$, 0.388, 0.445, 0.376; all $P < 0.05$). The mean CAVI was the significant difference between each age group. The ROC results showed that the best diagnostic point was 8.350, where the sensitivity was 72.2% and the specificity was 72.3%. The positive rate of the CAVI was higher than normal blood pressure for those over 60 years of age.
CONCLUSION: Compared with normal blood pressure measurements, CAVI measurements are relatively reliable for predicting hypertension in those over the age of 60. More attention should be paid to the CAVI $\geqslant$ 8.350, which may be regarded as a simple and noninvasive reference index of hypertension diagnosis for middle-aged and elderly.

Keywords: Hypertension, cardio-ankle vascular index, cardiovascular diseases; middle-aged and elderly, diagnosis validity

1. Background

Cardiovascular disease is a major human disease. The high incidence, high morbidity and high mortality of cardiovascular disease have become a major public health and safety problem, and increasing numbers of younger people are now tending to become afflicted with this disease [1,2]. Hypertension is the most common condition associated with cardiovascular disease, and its etiology and pathogenesis is complex and has not been fully clarified [3]. Hypertension is a systemic condition associated with the pathological development of a small amount of arteriosclerosis that occurs most often in middle-aged

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and elderly people. Atherosclerosis is four times more prevalent in patients with hypertension than in patients with normal blood pressure [4]. Therefore, intervening in cardiovascular disease with hypertension at the subclinical stage and identifying asymptomatic patients at high risk at such an early stage are fundamental measures to ward off and control cardiovascular events.

Currently, effective control of hypertension is only 6.1%, the major causes of low control is due to the patient can not accurately measure their blood pressure. The cardio-ankle vascular index (CAVI) is a recently developed measure method involving a comprehensive analysis of limb blood pressure, ECG, PCG, and many other parameters based on the PWV [5–9]. The CAVI calculation is based on the stiffness parameter β, which does not depend on changes of blood pressure. The equation for this parameter, $\beta = \ln(Ps/Pd)*(D/\Delta D)$, was proposed by Hayashi et al. in 1980 [10], where Ps and Pd are the systolic and diastolic blood pressures, respectively, D is the diameter of the artery, and ΔD is the change in the arterial radius per cardiac cycle that occurs when the blood pressure changes. The CAVI was developed to properly measure arterial stiffness for some length of the arterial, according to the theory underlying the stiffness parameter. Therefore, the CAVI has good reproducibility and it is also more independent of blood pressure than the PWV [11,12].

Several studies have shown the CAVI to be significantly increased in hypertension patients, but few reports are available that describe how valid it is to use the CAVI to diagnose hypertension in middle-aged and elderly patients [13–16]. Is CAVI feasible for the diagnosis of hypertension? The current study proposes a hypothesis that CAVI would diagnose hypertension to a certain extent. Therefore, we measured CAVI and collected information of subjects to analyze the diagnostic validity of the CAVI for hypertension for different age groups, and to uncover relationships between the CAVI and relevant factors. The overall aim of this study was to determine the applicability of the CAVI for diagnosing hypertension, and especially for providing a simple and noninvasive way to detect masked hypertension at an early stage.

2. Methods

2.1. Subjects

One hundred and ninety-five subjects (69 males and 126 females; mean age of 56.06 $\pm$ 12.08 years), from the staff of Beijing University of Technology were enrolled in this study. All subjects answered questionnaires and provided the following basic information: name, gender, medical history, medication history, allergies, diet history and exercise. All subjects who had experienced heart failure, coronary artery diseases, stroke, renal function impairment, liver function impairment, infectious disease, or cancer (or other such diseases) were excluded. Although smoking, drinking or salt habits interfere with the CAVI, those factors were not excluded from the present subjects. Every subject signed a written informed consent before participating. This study was approved by the Ethics Committee of School Hospital in Beijing University of Technology, and College of Life Science and Bioengineering in Beijing University of Technology.

2.2. Measurement of the CAVI

The CAVI was measured with a Vasera VS-1000 arterial function detection instrument (Fukuda Company, Beijing, China). All subjects were made to lie in a supine position, with the head held at the midline position, and the palms of the hands turned upwards from the subject's sides. After resting for

10–20 minutes, the measurement was made. Electrocardiograph electrodes were placed on both wrists in order to collect the ECG waveform, a minitype recorder for detecting heart sounds was placed over the fourth rib at the left edge of the sternum, and blood pressure cuffs were wrapped around both the arms and ankles. CAVI values were automatically measured by the instruments, and the data were then analyzed computationally.

The CAVI was calculated by using Eq. (1),

$$CAVI = a\left[\left(\frac{2\rho}{Ps - Pd}\right) * \left(ln\frac{Ps}{Pd}\right) PWV^2\right] + b \quad (1)$$

where Ps is systolic blood pressure, Pd is diastolic blood pressure, *PWV* is pulse wave velocity, ΔP is $Ps - Pd$, ρ is blood density, L is the length from aortic valve to ankle, T is the time taken for the pulse wave to propagate from the aortic valve to the ankle, and a and b are constants. *PWV* was obtained by dividing the vascular length by the propagatione time of the pulse wave from the aortic valve to the ankle.

2.3. Relevant factors

The pulse rate, blood pressure and ankle brachial index (ABI) were simultaneously measured with the measurement of the CAVI, all at rest and at the appropriate room temperature to ensure that the test results of the subjects were not affected by the environment. Note that the ABI is the ratio of the highest blood pressure values of the ankle to the highest blood pressure values of the upper arm, and evaluates stenosis or occlusion of the lower limb caused by atherosclerosis. The pulse pressure index (PPI) was calculated using the equation (PPI = ΔP/Ps, where ΔP is Ps – Pd) as a clinical influencing factors of cardiovascular abnormalities with hypertension patients. The full-time staff measured the height, weight, waist circumference and hip circumference of each subject, and the body mass index (BMI = weight/height^2, kg/m^2) was calculated to assess the degree of obesity. Blood viscosity samples were collected from an elbow vein, with an empty stomach condition in the early morning and were inspected by using an LG-R-80 rotary viscometer (Beijing Steellex Scientific Instrument Company, China). A diagnosis of hypertension was defined as a systolic blood pressure of equal to or greater than 140 mmHg and a diastolic blood pressure of equal to or greater than 90 mm Hg for adults take the measure of their blood pressure three times not in the same day according to the World Health Organization and International Society of Hypertension (WHO/ISH) standards of 1999 and 2010 and “The regulations on prevention and control of hypertension in China” of 2010 [17].

2.4. Statistical analysis

Data were stored in Excel 2013 and statistical analysis was performed with SPSS 15.0. Data values were expressed as percentages and meanSD.195 patients were classified into 2 groups (healthy group and hypertension group) according to the hypertension, and then they were stratified by 10-year layers into 5 subgroups (30–39, 40–49, 50–59, 60–69, 70 above). The data were statistically analyzed using the independent sample T-test, Pearson Correlations, Multivariate Linear Regression, One-way Analysis of Variance and ROC curve statistical methods to evaluate the relevant factors and diagnosis validity of CAVI for middle-aged and elderly population with hypertension. A difference was considered significant if the P value was < 0.05.

Table 1
Comparison of clinical characteristics in different groups

Characteristics	Healthy (N =141)	Hypertension (N = 54)	t	P	95%CI
Age (years)	53.1 ± 11.10	63.8 ± 11.16	−6.01	0.000	−14.21 ∼ −7.19
Male/female	40/101	29/25	3.39	0.001	0.11 ∼ 0.40
Height	163.74 ± 7.02	167.26 ± 6.20	−3.23	0.001	−5.66 ∼ −1.37
Weight	63.57 ± 9.97	70.54 ± 9.91	−4.37	0.000	−10.11 ∼ −3.82
BMI	23.59 ± 2.81	25.14 ± 3.09	−3.35	0.001	−2.46 ∼ −0.64
SBP (mm Hg)	123.13 ± 9.80	149.44 ± 10.81	−16.31	0.000	−29.50 ∼ −23.13
DBP (mm Hg)	76.82 ± 6.61	89.52 ± 8.11	−11.25	0.000	−14.93 ∼ −10.48
PP (mm Hg)	46.31 ± 7.23	59.93 ± 11.38	−9.88	0.000	−16.33 ∼ −10.90
PPI	0.38 ± 0.04	0.40 ± 0.06	−3.20	0.002	−0.39 ∼ −0.01
Heart rate	68.76 ± 9.98	70.22 ± 11.46	−0.88	0.381	−4.75 ∼ 1.82
ABI	1.08 ± 0.09	1.09 ± 0.11	−0.52	0.616	−0.04 ∼ 0.02
Blood viscosity	4.50 ± 0.73	4.64 ± 0.90	−1.14	0.258	−0.39 ∼ 0.10
CAVI	7.75 ± 1.15	9.13 ± 1.62	−6.67	0.000	−1.79 ∼ −0.97

SBP: systolic blood pressure; DBP: diastolic blood pressure; PP: pulse pressure.

Table 2
Pearson correlations between the CAVI and relevant factors for the entire group, healthy group and hypertension group

Related factors	Entire group (n = 195)		Healthy group (n = 141)		Hypertension group (n = 54)	
	r	P	r	P	r	P
Age (years)	0.728**	0.000	0.693**	0.000	0.656**	0.000
Height	0.110	0.127	0.041	0.631	−0.045	0.749
Weight	0.109	0.130	0.089	0.291	−0.242	0.078
BMI	0.730	0.311	0.093	0.272	−0.249	0.070
SBP (mm Hg)	0.557**	0.000	0.394**	0.000	0.388**	0.004
DBP (mm Hg)	0.347**	0.000	0.245**	0.003	−0.107	0.443
PP (mm Hg)	0.522**	0.000	0.307**	0.000	0.445**	0.001
PPI	0.313**	0.000	0.145	0.086	0.376**	0.005
Heart rate	−0.26	0.714	−0.212*	0.012	0.189	0.170
ABI	0.219**	0.002	0.311**	0.000	0.101	0.467
Blood viscosity	0.132	0.066	0.016	0.847	0.248	0.071

**. Correlation is significant at the 0.01 level (2-tailed). *. Correlation is significant at the 0.05 level (2-tailed).

3. Results and discussion

3.1. Clinical baseline characteristics of the study participants

The selected groups were divided into healthy group ($n = 141$) and hypertension group ($n = 54$) according to the blood pressure levels. The differences between the groups were analyzed by an independent sample T-test. The clinical baseline characteristics of the patients are shown in Table 1. The results showed that there were significant differences ($P < 0.05$) in age, gender, height, weight, BMI, SBP, DBP, PP, PPI and CAVI between the healthy group and the hypertension group. Meanwhile, there were no significant differences ($P > 0.05$) in ABI, heart rate and blood viscosity. The mean of the CAVI in the hypertension group was obviously higher than that in the healthy group (9.13 ± 1.62 VS 7.75 ± 1.15, $P < 0.05$).

3.2. Pearson correlations between the CAVI and the relevant factors

Pearson correlations between the CAVI and the relevant factors are shown in Table 2. The CAVI was found to be positively and significantly correlated with age, SBP, DBP, PP, PPI and ABI in the entire

Table 3
Multiple linear regression analysis between the CAVI and relevant factors for the entire group, healthy group and hypertension group

Related factors	Entire group ($n = 195$)		Healthy group ($n = 141$)		Hypertension group ($n = 54$)	
	β	P	β	P	β	P
Age (years)	0.073	0.000	0.067	0.000	0.083	0.000
Height	0.046	0.526	−0.039	0.626	0.204	0.238
Weight	−0.036	0.682	0.075	0.448	−0.246	0.227
BMI	0.041	0.863	−0.242	0.362	0.574	0.305
SBP (mm Hg)			0.064	0.404	0.311	0.044
DBP (mm Hg)	−0.058	0.091	−0.073	0.556	−0.494	0.047
PP (mm Hg)	0.140	0.009				
PPI	−24.857	0.037	−9.405	0.551	−69.465	0.060
Heart rate	2.628	0.026	−0.001	0.896	0.041	0.005
ABI	0.015	0.001	2.907	0.004	2.955	0.066
Blood viscosity	0.011	0.906	−0.079	0.429	0.033	0.875

Table 4
CAVI reference range in the middle-aged population

Age	Number	CAVI value		
(years)	($n = 195$)	$\bar{x} \pm$ S	$S_{\bar{x}}$	95%CI
30 ∼ 39	17	6.447 ± 1.081	0.262	5.89 ∼ 7.00
40 ∼ 49	47	7.191 ± 0.840	0.123	6.94 ∼ 7.44
50 ∼ 59	56	7.979 ± 0.886	0.118	7.74 ∼ 8.22
60 ∼ 69	47	8.768 ± 1.148	0.167	8.43 ∼ 9.11
70 above	28	9.954 ± 1.237	0.234	9.47 ∼ 10.43

There were significant difference ($P < 0.05$) between each age group.

Table 5
Area under the curve of the CAVI variable

Variable	AUC	$X_{\bar{x}}$	P	95%CI
CAVI	0.770	0.041	0.000	0.690 ∼ 0.850

AUC: The area under the curve.

group ($r = 0.728$, 0.557, 0.347, 0.522, 0.313, 0.219; all $P < 0.05$). For the healthy group, the CAVI was found to be positively correlated with age, SBP, DBP, PP and ABI ($r = 0.693$, 0.394, 0.245, 0.307, 0.311; all $P < 0.05$), and negatively correlated with heart rate ($r = -0.212$, $P = 0.012 < 0.05$), with all these correlations being significant. For the hypertension group, the CAVI was found to be positively and significantly correlated with age, SBP, PP and PPI ($r = 0.656$, 0.388, 0.445, 0.376; all $P < 0.05$), and negatively, but not significantly, correlated with DSP ($r = -0.107$, $P = 0.443 > 0.05$).

3.3. Multiple linear regression analysis between the CAVI and the relevant factors

A multiple linear regression analysis between the CAVI and the relevant factors are shown in Table 3. The independent factors positively correlated with the CAVI were found to be age, PP, heart rate and ABI ($\beta = 0.073$, 0.140, 2.628, 0.015; all $P < 0.05$) and the only independent factor of the entire group found to be negatively correlated with the CAVI was PPI ($\beta = -24.857$, $P = 0.037$). For the healthy group, the independent factors positively correlated with the CAVI were age and ABI ($\beta = 0.067$, 2.907; all $P < 0.05$). For the hypertension group, the independent factors positively correlated with the CAVI were age, SBP and heart rate ($\beta = 0.083$, 0.311, 0.041; all $P < 0.05$), and DSP was the one independent factor found to be negatively correlated with the CAVI ($\beta = -0.494$, $P = 0.047$).

3.4. CAVI reference range in middle-aged and elderly

Based on the above analysis, age was the main factor influencing the CAVI. As mentioned above, all subjects were divided into five age-dependent groups, and the data were analyzed by the One-way

Table 6
ROC curvilinear coordinates points of the CAVI variable

Variable	Diagnostic point	Sensitivity	Specificity	Youden index
CAVI	......	......	......	......
	8.150	0.741	0.681	0.422
	8.250	0.741	0.695	0.436
	8.350	0.722	0.723	0.446
	8.450	0.704	0.738	0.441
	8.550	0.667	0.745	0.411
	......	......	......	......

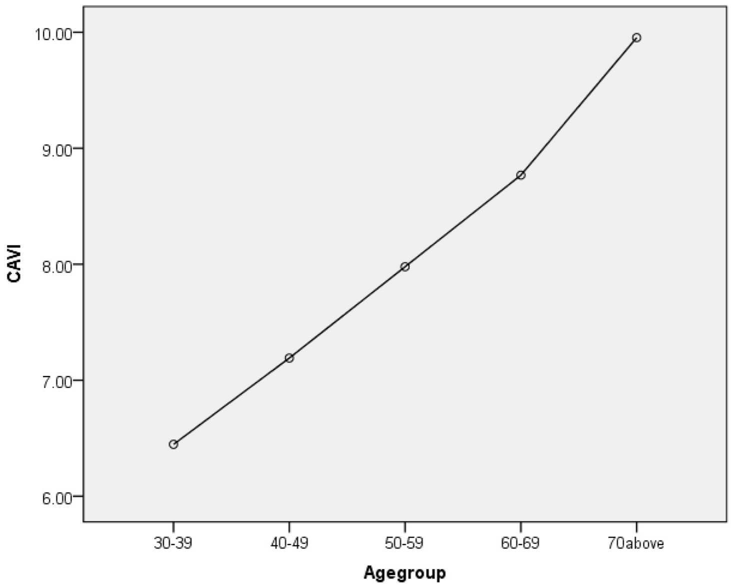

Fig. 1. Change curve of CAVI values between each age group.

Analysis of Variance. The mean CAVI of these 30 $\sim$ 39, 40 $\sim$ 49, 50 $\sim$ 59, 60 $\sim$ 69 and 70 above age groups were observed to be 6.447, 7.191, 7.979, 8.768 and 9.954, respectively (Table 4 and Fig. 1), presenting a steadily increasing trend. The differences between these CAVI values were determined to be significant ($P < 0.05$) according to an LSD test.

3.5. The relationship between the CAVI and hypertension

The diagnostic criterion of hypertension mentioned above is considered to be the gold standard. The CAVI was determined to have a certain predictive value for hypertension because the AUC value was 0.77 (0.7 $\sim$ 0.9) (Table 5). The ROC results in Table 6 and Fig. 2 showed that the maximum value of the Youden index was 0.446, the best diagnostic point was 8.350, the sensitivity was 72.2%, and the specificity was 72.3% according to the maximum value of the Youden index.

3.6. Comparison of the positive rate in different age groups

In this study, the subjects were divided into five groups by age, and converted the CAVI into positive (CAVI $\geqslant$ 8.350) and negative (CAVI $<$ 8.350) based on the best bound values of the ROC curve (CAVI

Table 7
Comparison of the positive rate between CAVI and normal blood pressure measurements in each age group

Age (years)	Number ($n = 195$)	CAVI positive rate	Normal positive rate	P
30 ∼ 39	17	1(5.9%)	2(11.8%)	0.545
40 ∼ 49	47	3(6.4%)	3(6.4%)	1.000
50 ∼ 59	56	17(30.4%)	13(23.2%)	0.393
60 ∼ 69	47	31(66.0%)	19(40.4%)	0.013
70 above	28	26(92.3%)	17(60.7%)	0.004

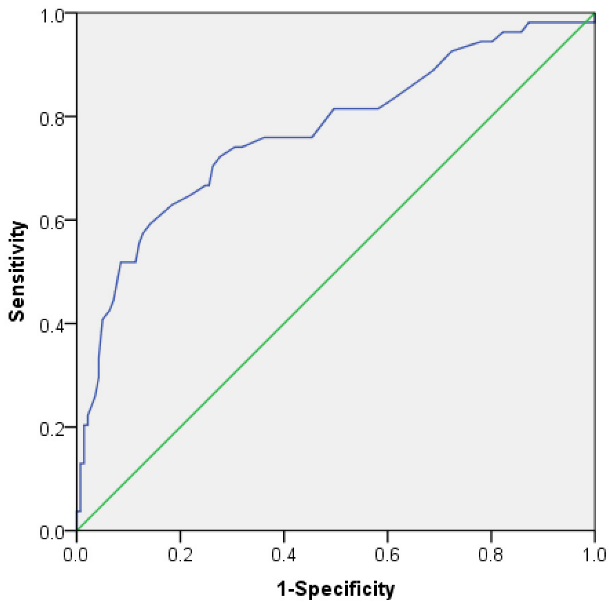

Fig. 2. ROC curve for forecasting hypertension by the CAVI.

$\geqslant$ 8.350) as the standard. The results of the positive rate between CAVI and normal blood pressure measurement are shown in Table 7. In the 30 ∼ 39 year age group, the positive rate of CAVI was less than the normal blood pressure measurement, but insignificantly so. The positive rate of CAVI was equal to the normal blood pressure measurement in the 40 ∼ 49 year age group. The positive rate of CAVI was higher than the normal blood pressure measurement in the 50 ∼ 59 year age group, but again insignificantly so. Only for those over 60 years of age was the positive rate of CAVI found to be higher than the normal blood pressure measurement, and there was significant ($P < 0.05$).

3.7. Discussion

The CAVI, due to its stability and independence of blood pressure, serves as an indicator of arteriosclerosis [18]. The CAVI has shown a tendency to increase with increasing age, suggesting that there should be different CAVI reference ranges for different ages [19]. In this study, CAVIs of the subjects with hypertension were found to be significantly greater than the healthy subjects, and increased with age, the positive correlation was found to be significant ($P < 0.05$) and to be stronger for hypertensive than healthy individuals. Of the factors tested, age was found to be the main factor influencing the CAVI, which is especially important because the elderly have a higher hypertension risk than do younger people. The statistical analysis of the reference range of all ages in this study showed that the CAVI was different from the evaluation standard of atherosclerosis (normal CAVI defined as 9.0) for those aged 60 years or more, and the positive rate of CAVI were significantly increased than normal blood pressure for this age group. This result suggests that we should pay particular attention to patients whose change of cardiovascular disease status was caused by hypertension at about 60 years of age.

Hypertension is an independent risk factor for cardiovascular and cerebrovascular disease, and long-term high blood pressure can cause systemic arteriole lesions, and increased arterial stiffness. This study showed the mean CAVI to be significantly ($P < 0.05$) higher in the hypertension group than in the healthy group, with the CAVI value increasing with increasing blood pressure. Okura [20], Takaki [21], Kadota [22], etc. reported the CAVI to be closely related to blood pressure. This report first showed the relationship between blood pressure and arterial stiffness – that the CAVI was observed to start increasing before blood pressure did so [23]. The CAVI could therefore be used to predict the occurrence of hypertension, but further detailed studies are needed on this point. This study discussed the predictive value of CAVI in hypertension. The ROC curve showed an area under the curve of 0.77 (0.7 $\sim$ 0.9), and showed 8.35 to be the best CAVI value for predicting hypertension. The results showed that CAVI values were greater than or equal to 8.350, which was also the typical CAVI value found for the subjects who were more than 60 years old, the ability of CAVI to predict hypertension was much higher than the ability of normal blood pressure measurements to do so. Therefore, for elderly people, CAVI appears to have a higher predictive value for hypertension than does normal blood pressure measurements. Furthermore, regarding the scope of the CAVI for atherosclerosis: a CAVI is considered normal when it is less than 8, a CAVI is considered a critical value when it is greater than or equal to 8 and less than 9, and a CAVI is considered to be a diagnosis of atherosclerosis when it is greater than or equal to 9 [24]. The best diagnostic point was just in the critical range of arteriosclerosis in this study, which accounts for the potential possibility of atherosclerosis and hypertension at the same time. The CAVI assessment boundary value of arterial stiffness may also vary because the current diagnostic criterion of CAVI was derived from a large study in Japan [25]. Therefore, the normal standard abroad (CAVI < 9.0) may not be suitable for Chinese people. According to this study, the domestic elderly population might develop an early change of atherosclerosis or the occurrence of hypertension when CAVI is greater than or equal to 8.35. In other words, more attention should be paid to this phenomenon that the CAVI has reached or exceeded 8.35 at about 60 years of age, it will be improve the early detection of vascular lesions because the masked hypertension has already occurred in this period.

In principle of measurement of the CAVI, CAVI is associated with the pulse wave velocity, pulse wave velocity is associated with the blood vessels elasticity, arterial elasticity affects the change of blood vessel radius, and then which will affect the changes of blood pressure in turn. It is alike confirmed that CAVI is feasible to predict high blood pressure according to the principle of measurement of the CAVI. To improve on the current study, future studies should consider a large sample size, a sample that extends beyond a single group (i.e., beyond university teachers), and influencing factors beyond the traditional risk factors studied here, more importantly, the follow-up survey should be carried out to validate this study by epidemic statistics.

4. Conclusions

As you can see from above, CAVI has a greater statistical significant difference in hypertension patients, and measurement of the CAVI predicted hypertension much more reliably than did the measurement of normal blood pressure when the CAVI value was greater than or equal to 8.350 for people older than 60 years. We should pay more attention to this diagnosis point (CAVI $\geqslant 8.350$) because arterial functionality may have changed or masked hypertension may have occurred at this stage. Based on our findings, we conclude that CAVI has a certain application value in the prediction of hypertension, and it can be regarded as a diagnosis indicator, and that CAVI measurements are relatively reliable than normal blood pressure measurements for predicting hypertension in those over the age of 60, especially for elderly individuals who are without symptoms of hypertension. In addition, CAVI has important clinical value for the diagnosis and treatment of cardiovascular disease and the evaluation of sub-health to realize the early prevention, early treatment and early control of the development of cardiovascular disease.

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Conflict of interest

None to report.

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