PSYCHOLOGY AND EDUCATION (2023) 60(2): 1813-1828
ISSN: 1553-6939

Cardio-ankle vascular index (CAVI) is a potential new parameter independent of blood pressure at the time of measurement for arterial stiffness estimation

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ABSTRACT

The cardio-ankle vascular index (CAVI) is a robust predictor of cardiovascular events. An innovative, non-invasive approach to measuring arterial stiffness. The (CAVI) approach was developed to overcome the limitations of carotid-femoral pulse wave velocity (cf-PWV), the gold standard indicator of arterial stiffness. The present study aims to propose a new algorithm to calculate the cardio-ankle vascular index (CAVI) parameter from Pulse Wave Database (PWDB), that contains the pulse waves of 500 virtual subjects aged between 25 and 75 years, generated from cardiovascular characteristics. The results obtained are promising in terms of sensitivity (SEN) and accuracy (ACC). The sensitivity values are (95.18 %, 95.71%, 92.70 %, 90.33%, 89.28%, and 89.05%), and accuracy (ACC) are (91%, 89.4%, 86.4 %, 80.4%, 80 %, and 81.4%) for normal values of (CAVI, cf-PWV, a-PWV, PPamp, AIx, and ABI) respectively. We confirmed the value of (CAVI) as an indicator of cardiovascular disease by investing the relationship between (CAVI) and several parameters of arterial stiffness including carotid-femoral pulse wave velocity (cf-PWV, r=0.66), arterial stiffness index (AIx, r=0.72), and aortic pulse wave velocity (a-PWV, r=0,96). Pulse pressure amplification showed a negative correlation (PPamp, r=-0.67). A moderate negative correlation was observed with ankle brachial index (ABI, r=-0.38). A weak dependence on different blood pressures at the time of measurement was confirmed, by the coefficients of determination r^2 (systolic SBP, 0.08, diastolic DBP, 0.11, mean MBP, 0.10, and pulsed pressures PP, 0.16). The influence of age on arterial stiffness was found with a strong positive correlation between age and cardio-ankle vascular index (CAVI, r=0.88).

Keywords
Cardio-ankle vascular index (CAVI), arterial stiffness (AS), pulse wave velocity (PWV), cardiovascular disease (CVD), algorithms.

Introduction

Detection and diagnosis of early signs of cardiovascular disease (CVD) are essential for effective prevention and treatment [1]. Arterial stiffness (AS) refers to the first change in arterial structure or function [2] and represents a loss of the artery's ability to dilate under pressure [3]. It is a significant risk factor for cardiovascular disease [4, 5, 6]. Several parameters assess central and peripheral arterial stiffness [7, 8]. Central arterial stiffness parameters: central blood pressure [9], pulse pressure amplification ratio (PPamp) [10]. Peripheral parameters: pressure strain [8], elastic modulus (Ep) [11], augmentation index (β) [12], augmentation index (AIx) [13], stiffness index (SI) [14], ankle brachial index (ABI) [15], arterial distensibility [16], peripheral vascular compliance (V_C) [17], and arterial impedance [18]. Pulse wave velocity (PWV) is the speed of pulse wave propagation between two points in the arterial tree [19, 20, 21]. There are different types of pulse wave velocity (PWV), depending on the location of the arteries. Pulse wave velocity includes brachial-ankle (ba-PWV) [23, 24], aortic (a-PWV) [25], heart-femoral (hf-PWV) [26], carotid-radial (cr-PWV) [27], aorta-branch PWV ratio (cf-PWV/cr-PWV) [28], femoral-ankle (fa-PWV) [29], and finger-toe (ft-PWV) [30, 31]. The measurement of carotid-femoral stiffness (cf-PWV) [22] is the "gold standard" for arterial stiffness [19]. The (cf-PWV) is robust and reproducible but has some disadvantages. It's dependent on blood pressure at the time of measurement [32]. A new powerful parameter developed in the 1980s is the cardio-ankle vascular index (CAVI). It was developed by Hayashi et al. [31] in Japan and has the advantage of being independent of blood pressure at the time of measurement. It is based on the β-stiffness parameter, which reflects the arterial stiffness from the aortic origin (aortic valve pressure) measured at the brachial level, and the pressure wave at distal points (ankle) [35]. Various non-invasive techniques are used to obtain information for (CAVI) calculation, cardiac phonograms [36], electrocardiograms [37], and pressure cuffs [38]. (CAVI) has been widely used to assess cardiovascular diseases [39, 40], such as hypertension [42], hyperlipidemia [43], dyslipidemia [41], coronary heart disease [44], renal disease [45, 46], diabetes mellitus [42], metabolic syndrome [47], left ventricular function [48], and sleep apnoea syndrome [49]. Risk factors such as smoking [50], obesity [51], and stress influence this parameter [52]. (CAVI) increases with age, and is generally higher in men than in women [53]. Kubota et al. reported that the group with (CAVI) above 10 had a high incidence of cardiovascular and renal disease [54]. Standard values for (cf-PWV) <12m/s [55], (a-PWV<10m/s) [56], (ba-PWV<14m/s) [57]. An augmentation index (Aix) greater than 30% indicates increased arterial stiffness [58]. The pulse pressure amplification ratio (PPamp) is generally between 1.2 and 1.4 [59]. Various algorithms are used to measure (CAVI) [60, 61, 62], ranging from simple mathematical formulae: The Bramwell-Hill equation, assumes a linear relationship between (PWV) and blood pressure (BP) [21], which calculates (CAVI) using only brachial and ankle BP measurements. More sophisticated machine learning models and multiple regression analysis have been used to incorporate additional factors such as age, height, and weight. Machine learning approaches have also been explored for (CAVI) analysis [63, 64]. A widely used algorithm for measuring (CAVI) is the Matsudo method, which uses a formula to calculate (CAVI) from the beta stiffness parameter (β) and age [65]. It has shown a strong correlation with invasive pulse wave velocity measurements. Katakami et al. [66] used a combination of brachial (ba-PWV) and ankle rotation velocity, age, and mean arterial pressure to predict (CAVI). Shirai et al. [67] investigated the reproducibility and blood pressure dependence using VaSera. (CAVI) was weakly correlated with systolic and diastolic blood pressure in 482 hemodialysis patients, while brachial-ankle (PWV) was strongly correlated with systolic and diastolic blood pressure. Kubozono et al. [68] studied a total of 1,333 consecutive subjects with (CAVI) automatically calculated from records of pulse volume, blood pressure, and vessel length from the heart to the ankle. The results showed that (ba-PWV) and (CAVI) were positively correlated with age. The (CAVI) is a reproducible and useful index of arterial distensibility that is not influenced by changes in blood pressure during measurement. The cardio-ankle vascular index (CAVI) was used in our study because it is non-invasive, quantitative, reproducible, and objective. It allows healthcare professionals to estimate arterial stiffness and assess cardiovascular health accurately.

Methodology

Principle of the cardio-ankle vascular index (CAVI) parameter

The (CAVI) index reflects the stiffness of the entire arterial segment, including the aorta, femoral, and tibial arteries (as shown in Figure 1). It was originally derived from the βeta stiffness parameter proposed by Hayashi [31] and Kawasaki et al. [53] and extended to a certain length of the artery by applying the modified Bramwell-Hill equation [21]. The formula for the beta parameter is:

$$\beta\text{-stiffness} = \ln(Ps/Pd) \times D/\Delta D \quad (1)$$

Where Ps is systolic blood pressure, Pd is diastolic blood pressure, D is the diameter of the artery, and ΔD is changes in the diameter.

The Bramwell-Hill formula is determined by the following formula:

$$PWV^2 = \frac{\Delta P}{\rho} \times \frac{V}{\Delta V} \qquad (2)$$

Where: ΔP: pulse pressure, V: Blood vessel volume, ΔV: change of V, ρ: blood density of 1.05 g/ml.

Equation **(2)** describes the relationship between volume elastic modulus and pulse wave velocity. $\frac{V}{\Delta V}$ can be expressed by **D**, and ΔD, ($\mathbf{\Delta D^2}$ is small and negligible).

$$V/\Delta V = (\pi L(D/2)^2) / (\pi L ((D + \Delta D) /2)^2 - \pi L(D/2)^2) = D^2/ (2D\Delta D + \Delta D^2) \cong D/2\Delta D \quad (3)$$

$$CAVI = a\,(\beta\text{-stiffness}) + b \quad (4)$$

$$CAVI = a \times (2\rho \times \frac{\ln(\frac{P_s}{P_d})}{\Delta P} \times PWV^2) + b \quad (5)$$

Where a and b are mathematical model subject-specific constants, PWV: Arterial pulse wave velocity (branchial – ankle), ln (Ps/Pd): logarithm of ratio systolic (SBP) and diastolic (DBP) blood pressure, ρ: Blood density between 1.045 and 1.055 g/ml, ΔP: is pulse pressure, calculated by subtracting diastolic blood pressure (SBP) from systolic blood pressure (DBP).
According to equation **(5)**, (CAVI) can be measured from the blood pressure and (ba-PWV). The equation reflects the overall stiffness of the aorta to the ankle.

$$CAVI = a \times (2\rho \times \frac{\ln(\frac{P_s}{P_d})}{\Delta P} \times baPWV^2) + b \quad (6)$$

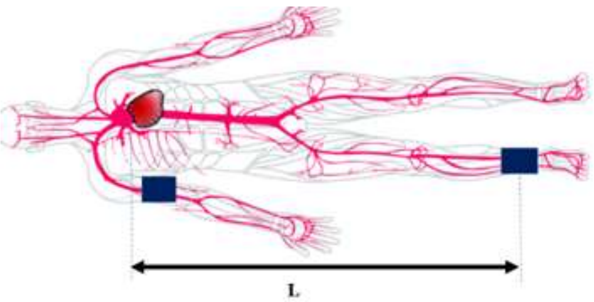


Figure 1. Calculation of branchial-ankle pulse wave velocity (ba-PWV)

For a given subject, the (ba-PWV) is calculated using the following equation:

$$baPWV = \frac{L}{T} \quad (7)$$

Where L length of the aorta origin to the ankle and T is the Branchial-ankle pulse transit time.

Arterial stiffness parameters algorithm

Our study algorithm is shown in (Figure 2). To evaluate the different parameters related to arterial stiffness.

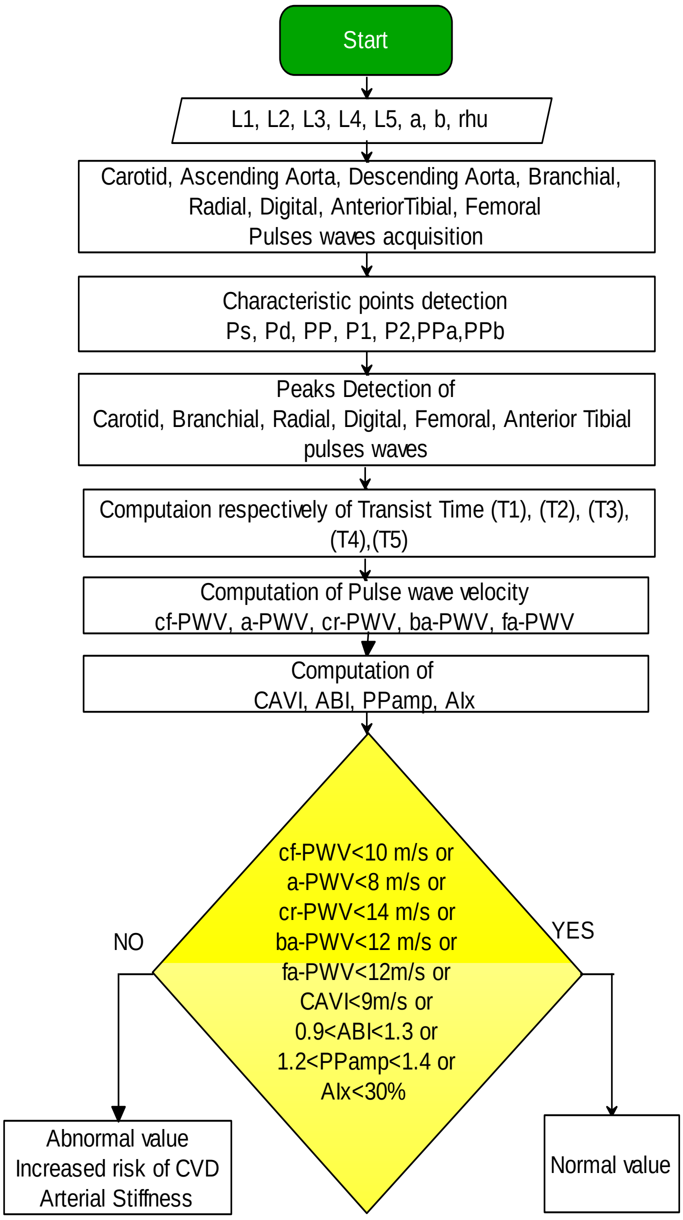


Figure 2. Arterial stiffness parameters algorithm from blood pressure pulse waves

L1: Carotid-femoral distance, L2: Ascending aorta-finger distance, L3: Carotid-radial distance, L4: Branchial-ankle distance, L5: femoral-ankle distance, a, b are constants specific to the mathematical model for each subject, rhu. : Blood density between 1.045 and 1.055 g/ml, Ps:

Systolic blood pressure, Pd: Diastolic blood pressure, P1: Systolic arterial pressure in the carotid artery, P2: Maximum arterial pressure in the femoral artery, PP: Pulse pressure, PPb: Brachial pulse pressure, PPa: Aorta pulse pressure. T1: Pulse transit time carotid-femoral, T2: PTT Ascending aorta-finger, T3: PTT carotid-radial, T4: PTT Branchial-ankle, T5: PTT Femoral-ankle, (a-PWV): Ascending aorta-finger pulse wave velocity, (cr-PWV): Carotid-radial pulse wave velocity, (ba-PWV): Branchial-ankle pulse wave velocity, (fa-PWV): Femoral-ankle pulse wave velocity, (ABI): Ankle brachial index, (AIx): Augmentation index, (PPamp): Pulse pressure amplification, (CVD): Cardiovascular diseases.

Pulse wave velocity (PWV)

The first step was data acquisition (carotid, ascending aortic, descending aortic, digital, femoral, and anterior tibial) PW. The database signals were filtered to remove noise and artifacts. The foot-to-foot algorithm is then used to identify the onset of the pulse wave, known as the onset of the characteristic pulse waveform. The MATLAB signal processing toolbox functions, findpeaks () [69] and detectPeaks () [70], are used to easily identify the systolic (Ps) and diastolic (Pd) peaks, corresponding to the first and second detected peaks. The pulse wave velocity is calculated as a function of the distances between the two measurement points divided by time, summarized by the following equations: cf-PWV=L1/T1, PWV=L2/T2, cr-PWV=L3/T3, ba-PWV=L4/T4, fa-PWV=L5/T5. Where: L1, L2, L3, L4, and L5 are carotid-femoral, ascending aorta-finger, carotid-radial, arm-ankle, and femoral-ankle distance respectively. T1, T2, T3, T4, and T5 are carotid-femoral, ascending aorta-finger, carotid-radial, branchial-ankle, and femoral-ankle pulse transit times respectively.

Brachial-ankle pulse wave velocity (ba-PWV)

The following equation, known as the Bramwell-Hill equation [71], relates the (cf-PWV) to the (ba-PWV) as follows:

$$\mathbf{baPWV = 0.8\times(cf\text{-}PWV) + 0.07} \qquad \mathbf{(8)}$$

Where (cf-PWV) and (ba-PWV) are expressed in m/s.

Cardio ankle vascular index (CAVI)

To calculate the value of the parameter (CAVI), we use equation **(4)**, where a and b are constants that can be determined to correspond to the age-related change, the values of the coefficient "a" were 0.850, 0.658, and 0.432, respectively, and the values of coefficient "b" were 0.695, 2.103, and 4.441 [72].

Ankle brachial index (ABI)

Ankle brachial index (ABI) arterial pressure derived from upper arm arterial pressure has been determined from studies [73]. The value (ABI) is obtained using the following equations :

$$ABI = \frac{PsAnk}{PsBr} \qquad \mathbf{(9)}$$

Where PsAnk is the arterial pressure at the ankle and Psbr is the systolic pressure at the upper arm.

Augmentation index (AIx)

The augmentation index (AIx) reflects the percentage difference between central and peripheral arterial pressure during cardiac rhythm [74]. It is calculated using the formula :

$$AIx = \frac{(P_2-P_1)}{PP*100} \qquad \mathbf{(10)}$$

Where P_1: is systolic arterial pressure in the carotid artery, P_2: is maximum arterial pressure in the femoral artery, and PP: is pulse pressure.

Pulse pressure amplification ratio (PPamp)

The formula for calculating pulse pressure amplification is as follows [75] :

$$PPamp = \frac{PPb}{PPa} \qquad \mathbf{(11)}$$

Where PPb: Pulse pressure measured at the brachial artery, PPa: Pulse pressure measured at the aorta artery.

Data Analysis

In this study, we used the open-access database that contains pulse waves from 500 virtual subjects aged between 25 and 75 years ('10-year increments'), created using cardiovascular properties (heart rate and arterial stiffness). Pulse waves are provided for measurement sites, including the aorta, carotid, brachial, radial, digital, femoral, and ankle arteries [76].

Table 1. Aortic and branchial blood pressure evaluated by mean ± standard deviation

Characteristics	All subjects	25	35	45	55	65	75
Aortic Pressure SBP[mmhg]	108.6±14.8	96.22±10.09	104.25±10.30	110.20±10.70	113.07±12.46	115.58±13.75	118.56±17
Aortic Pressure DBP[mmhg]	74.5±7.8	73.82±5.86	76.97±6.83	78.16±7.08	76.31±7.24	73.14±8,17	69.23±9.33
Aortic Pressure MBP[mmhg]	92.8±8	86.53±7.29	92.37±7.15	95.93±7.11	96.18±7,09	95.35±6,99	94.10±7.07
Aortic Pressure [mmhg]: PP	34.08±17.38	22.39±8.49	27.28±10.45	32.03±11.55	36.76±14.,61	42.43±17,61	49.33±23.2
Branchial Pressure SBP [mmhg]	117.63±13.87	107.55±11	115.28±11.33	120.53±10.93	121.75±12.13	122.05±13.30	123.59±16.3
Branchial Pressure DBP [mmhg]	72±7.76	71.24±5.51	74±6.86	75.58±7.17	73.85±7,34	70.56±8,02	67.15±9.27
Branchial Pressure MBP [mmhg]	92.63±8.06	86.18±7.16	91.88±7.47	95.81±7.10	96.07±7,07	95.02±7,12	94.02±7.05
Branchial Pressure PP [mmhg]	45,62±16.34	36.30±10.02	41.28±11.56	44.94±12.30	47.89±14,68	51.48±17,12	56.44±22.34

Results

Accuracy and sensitivity of cardio-ankle vascular index (CAVI) Algorithm

We evaluate the experimental results of the proposed algorithm in terms of sensitivity (SEN) and accuracy (ACC), using equations (12) and (13), respectively.

$$\mathbf{SEN = VP / (VP + FN) \times 100} \qquad \mathbf{(12)}$$

$$\mathbf{ACC = (VP) / (VP + FP + FN) \times 100} \qquad \mathbf{(13)}$$

Where: VP is the true positives (number of correct detections), FP is the false positives (number of false detections, and FN is the number of false negatives (missed detections), ACC: is accuracy, SEN: is sensitivity.

Table 2 shows the accuracy and sensitivity of the algorithm. The algorithm failed to detect (23, 20, 34, 43, 48, and 50 FN) for the (CAVI, cf-PWV, a-PWV, PPamp, AIx, and ABI) respectively out of 500 all subjects. The results obtained are promising in terms of sensitivity (SEN) and accuracy (ACC). The sensitivity values are (95.18 %, 95.71%, 92.70 %, 90.33%, 89.28%, and 89.05%), and accuracy (ACC) are (91%, 89.4%, 86.4 %, 80.4%, 80 %, and 81.4 %) for normal values of (CAVI, cf-PWV, a-PWV, PPamp, AIx, and ABI) respectively.

Table 2. Algorithm accuracy (ACC) and sensitivity (SEN).

	CAVI	cf-PWV	a-PWV	PPamp	AIx	ABI
VP	455	447	432	402	400	407
FP	22	33	34	55	52	43
FN	23	20	34	43	48	50
Sensitivity (SEN)%	95,18	95.71	92.70	90.33	89.28	89.05
Accuracy (ACC)%	91	89.4	86.4	80.4	80	81.4

Table 3. Arterial stiffness parameters evaluated by mean ± standard deviation.

Parameters	All subjects	25	35	45	55	65	75
cf-PWV	8.17±2.35	6±0.81	6.83±1.06	7.80±1.07	8.69±1.42	9.73±1.86	11.03±2.75
a-PWV [m/s]	7.65±2.11	5.69±0.65	6.45±0.94	7.32±1.02	8.16±1.39	9.10±1.71	10.19±2.37
ba-PWV [m/s]	6.68±1.9	4.93±0.65	5.60±0.86	6.39±0.86	7.11±1.15	7.95±1.51	9±2.22
fa-PWV [m/s]	10.37±2.03	8.55±0.86	9.28±1.04	9.98±1.21	10.78±1.44	11.77±1.54	12.77±2.14
AIx[%]	19.29±19.26	-0.27±10.55	16.26±14.36	16.34±12.07	25.85±11.68	34.65±11.32	42.26±11.68
Pankle	137.63±13.87	127.55±11.06	135.28±11.33	140.53±10.93	141.75±12.13	142.05±13.30	143.26±16.20
ABI	1.18±0.018	1.17±0.0175	1.16±0.015	1.165±0.016	1.17±0.02	1.16±0.01	1.16±0.02
PPamp [ratio]	1.43±0.25	1.68±0.18	1.57±0.21	1.45±0.18	1.35±0.17	1.26±0.15	1.19±0.14
CAVI	10.64±3.25	6.98±0.68	7.14±0.74	10.83±0.43	11.23±0.695	14.61±0.59	14.38±1.16

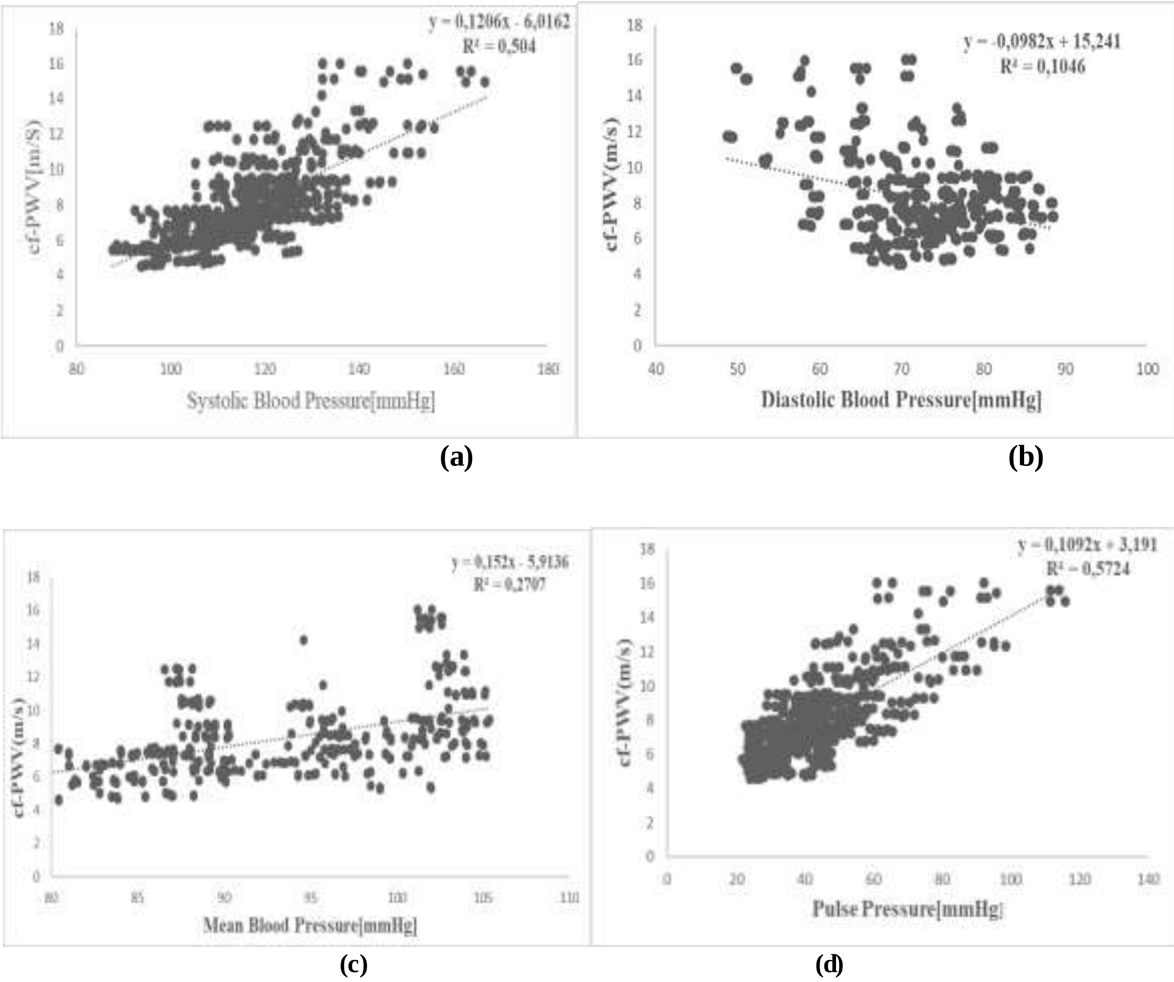
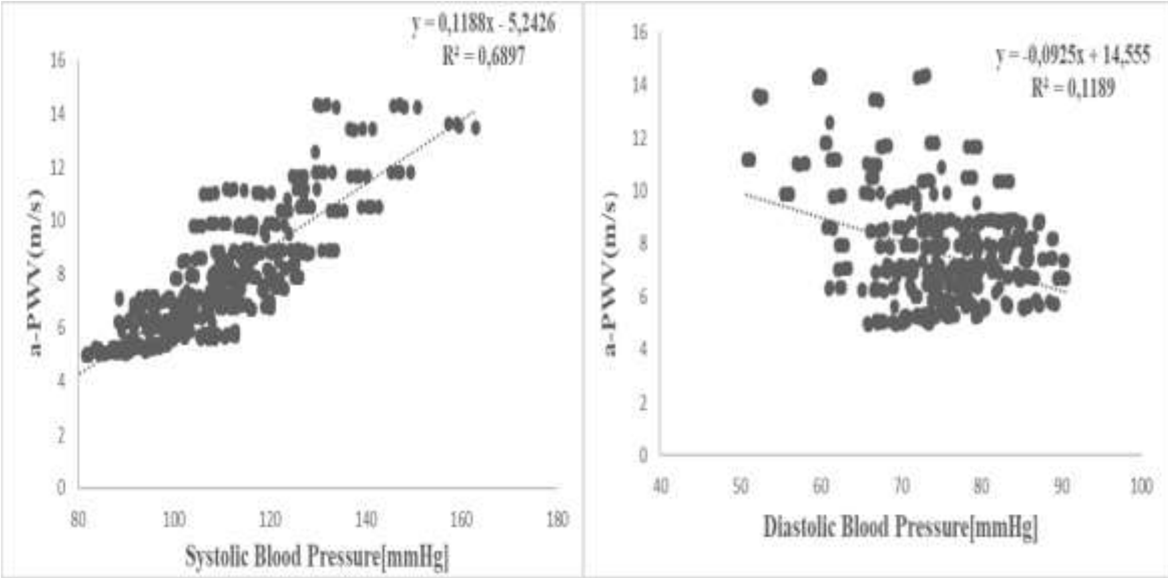
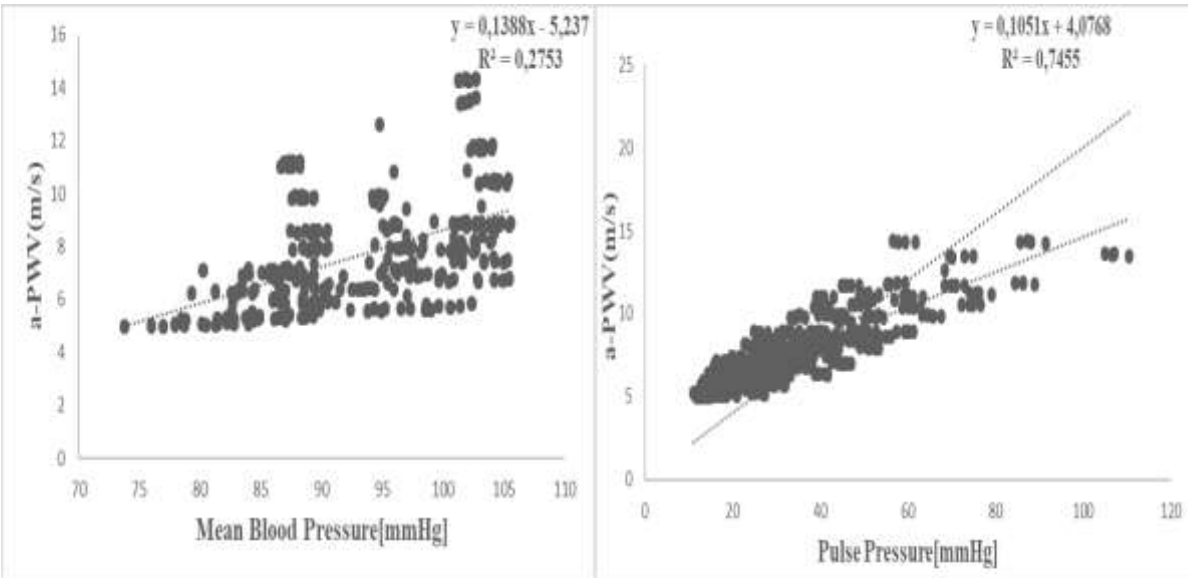


Figure 3. Coefficient of determination (r^2) values indicate the strength of the relationship between carotid-femoral pulse wave velocity (cf-PWV) and different measures of blood pressure. (a) 50% of the variance between (cf-PWV) and systolic blood pressure (SBP, r^2 = 0.50). (b) 10% of the variance between (cf-PWV) diastolic blood pressure (DBP, r^2= 0.10). (c) 27% of the variance of between (cf-PWV) mean arterial blood pressure (MBP, r^2 = 0.27). (d) 57% of the variance between (cf-PWV) is explained by pulse pressure (PP, r^2 = 0.57).



(a) **(b)**



(c) **(d)**

Figure 4. Coefficient of determination (r^2) values indicate the strength of the relationship between aortic-finger pulse wave velocity (a-PWV) and different measures of blood pressure. (a)- 69% of the variance between (a-PWV) and systolic blood pressure (SBP, r^2 = 0.69). (b)- 11% of the variance between (a-PWV) and diastolic blood pressure (DBP, r^2= 0.11). (c)- 27% of the variance in (a-PWV), and mean blood pressure (MBP, r^2 = 0.27). (d)- 74% of the variance in (a-PWV) can be explained by pulse pressure (PP, r^2 = 0.74).

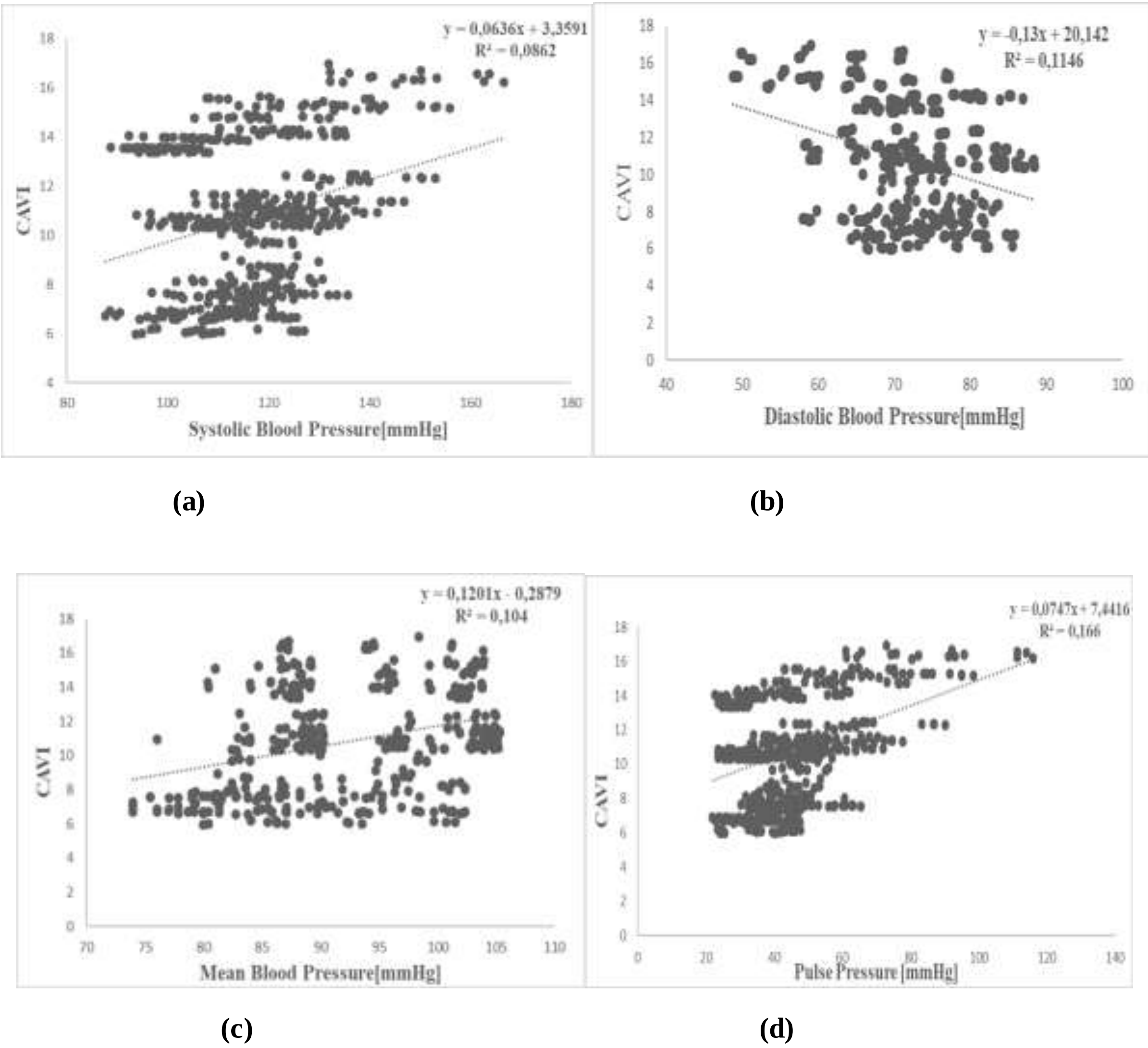


Figure 5. The relationship between the cardiovascular ankle index (CAVI) and different measures of blood pressure. (a) 8% of the variance between (CAVI) and systolic blood pressure (SBP, r^2 =0.08). (b) 11% of the variance between (CAVI) and diastolic blood pressure (DBP, r^2 = 0.11). (c) a variance of 10% between (CAVI) and mean arterial pressure (MBP, r^2 = 0.10). (d) a variance of 16% between the (CAVI) and pulse pressure (PP, r^2 = 0.16)

Discussions

The results obtained with our algorithm are promising in terms of sensitivity (SEN) and accuracy (ACC). Sensitivity values are (95.18 %, 95.71%, 94.52 %, 90.33%, 88.08%, and 89.03%), and accuracy (ACC) are (91%, 89.4%, 86.4 %, 80.4%, 80 %, and 81.4%) for normal values of (CAVI, cf-PWV, a-PWV, PPamp, AIx, and ABI) respectively. On the other hand, we confirmed the value of (CAVI) as an indicator of cardiovascular disease by investing the relationship between (CAVI) and several parameters of central and peripheral arterial stiffness including carotid-femoral pulse wave velocity (cf-PWV, r=0,91), which is the gold standard of arterial stiffness, and aorta-finger pulse wave velocity (a-PWV, r=0,96). A moderate correlation with branchial-ankle pulse wave velocity (ba-PWV, r= 0,66), and (fa-PWV r=0,65). A strong positive correlation between (CAVI) and (Aix, r=0,72). A moderate negative correlation between (CAVI) and pulse pressure amplification (PPamp, r=-0,67) An inverse correlation was found between (CAVI) and (ABI, r=-0,38). Our results indicate that (CAVI) is less dependent on the blood pressure at the time of measurement than the pulse wave velocity. This is demonstrated by the coefficient of determination (r^2) (systolic SBP, 0.08, diastolic DBP, 0.11, mean MBP, 0.10, and PP pulsed pressures, 0.16), as shown in Figures (3, 4, and 5). The influence of age on arterial stiffness was found with a strong positive correlation between age and cardio-ankle vascular index (CAVI, r=0.88). Our results are in line with those of the following studies [68, 69, 84].

Limitations and Future Studies

Simulated data cannot reproduce individuals' health conditions, medical histories, and drug treatments, leading to less relevant results. doming.

1-(CAVI) measurements can be analyzed accurately and efficiently, using machine learning algorithms.

2-Integration of (CAVI) algorithms into clinical practice improves personalized treatment plans for patients at reduced risk of cardiovascular events.

3-Validation of the (CAVI) algorithm through large-scale clinical trials to ensure its accuracy and usefulness in the diagnosis and monitoring of atherosclerosis.

4-Telemedicine platforms improve the accessibility of (CAVI) algorithm implementation, an essential measure for patients living in remote areas with limited access to healthcare resources.

5- A combination of algorithms (CAVI) and non-invasive imaging techniques for a global assessment of cardiovascular health.

Conclusion

In this study, we developed a new cardio-ankle vascular index (CAVI) algorithm to assess cardiovascular health and estimate arterial stiffness. The (CAVI) is a non-invasive indicator of arterial stiffness that increases linearly with age. The results of the algorithm were good in terms of sensitivity and accuracy. A correlation was found between this parameter and several central and peripheral arterial stiffness parameters, that (CAVI) is indicative of overall arterial stiffness. We showed a low dependence on different blood pressures at the time of measurement: systolic (SBP), diastolic (DBP), mean (MBP), and pulse pressure (PP) over carotid-femoral pulse wave velocity (cf-PWV).

Acknowledgment

Not applicable.

Funding Information

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Competing Interest Declaration

The authors declare that they have no conflict of interest.

Data access statement

Not applicable.

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