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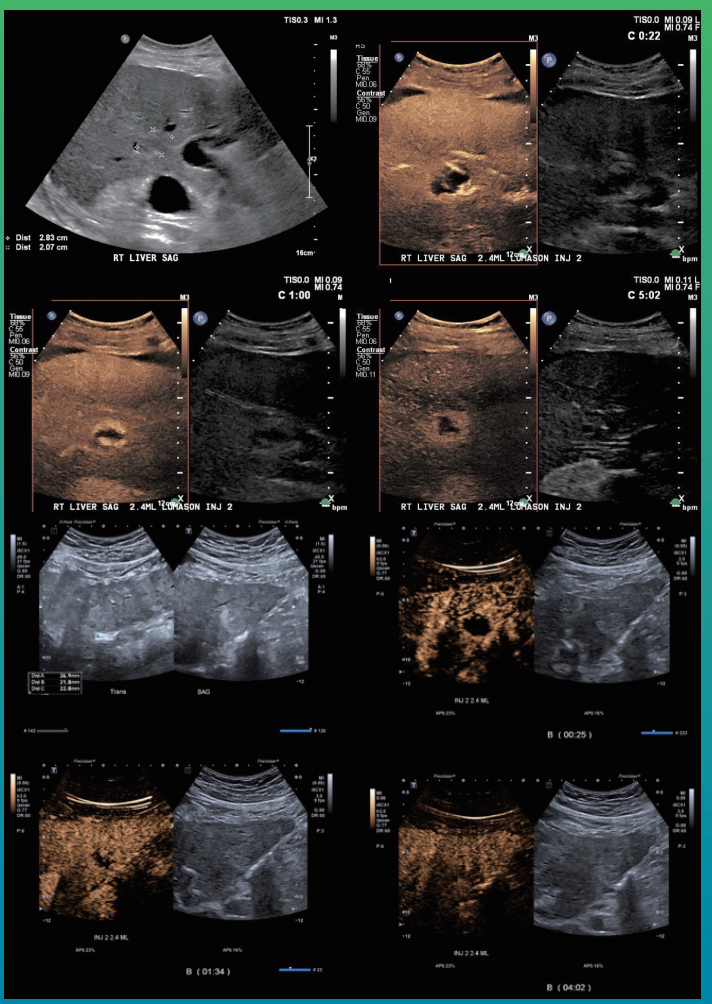

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Case Reports

REVIEW ARTICLE

Arterial Stiffness and Cardiovascular Risk: The Role of Brachial Cuff-measured Index

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Abstract: Early detection of vascular disease is fundamental to the prevention and treatment of systemic vascular lesions. The timely identification of vascular damage can be achieved by comprehensively assessing the structural anomaly and/or functional degeneration of the vasculature. The assessment may to some extent indicate the long-term detrimental effects of cardiovascular disease (CVD) risk factors on vascular health. A key aspect in the evaluation of vascular function is the measurement of arterial stiffness. In 2012, the arterial velocity-pulse index (AVI) and arterial pressure-volume index (API) were introduced, which are noninvasively measured with a brachial cuff, and can reflect the status of arterial stiffness in both the aorta and the brachial artery. A large number of relevant studies have demonstrated the strong associations between AVI/API and various CVD risk factors, underlining the substantial relevance of the indices in CVD risk assessment. In this review, we provide a systematic review of the progresses made in brachial cuff-based measurements of arterial stiffness. In addition, we summarize the results of the recent studies focused on exploring the associations of AVI/API with relevant risk factors as well as their roles in CVD assessment.

Key words: Arterial stiffness; Cardiovascular risk; Brachial cuff; Arterial velocity-pulse index; Arterial pressure-volume index

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Arterial stiffness is a well-established biomarker of vascular aging [1]. Centuries ago, physicians identified its predictive role in cardiovascular disease (CVD). Atherosclerotic diseases often progress silently, but may deteriorate abruptly to cause severe clinical events, such as acute coronary syndromes and acute cerebral infarction. Therefore, early assessment of arterial stiffness combined with aggressive intervention is crucial to the prevention and treatment of cardiovascular diseases.

What is Arterial Stiffness?

Arterial stiffness, known as the reciprocal of arterial elasticity or arterial compliance, reflects the changes in arterial structure and function [2]. The arterial tree within the human body spans from the aorta, which is about 3 cm in diameter, down to small precapillary arteries of about 50 micrometers in diameter. While arterial wall has a heterogeneous structure composed of complex materials, its intrinsic stiffness is determined mainly by the proportion, arrangement and mechanical

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properties of elastic fibers [3,4], which change during aging and are subjected to the influence of various factors like hypertension, diabetes mellitus and lipidemia [5]. Increased arterial stiffness can appear prior to the development or manifestation of permanent vascular damage or cardiovascular disease. Therefore, early detection of increased arterial stiffness holds the possibility to identify high-risk asymptomatic subjects who might benefit from early intervention. Even for patients with diagnosed cardiovascular diseases, measuring arterial stiffness can also provide useful information for predicting prognosis or guiding post-operative management and medication [6].

Methods of Arterial Stiffness Measurement

Various invasive and non-invasive methods and indices have been developed to estimate arterial stiffness [7]. Among these, pulse wave velocity (PWV) stands as the most commonly utilized technique and currently serves as the gold standard for assessing central arterial stiffness, particularly in Western countries. The first direct measurement of arterial stiffness using pulse wave velocity (PWV) was reported in the 1920s [8]. PWV represents the speed at which a pulse wave travels along the arterial tree and is determined by dividing the distance between two specific points by the time it takes for the wave to traverse that distance [9]. One commonly used method for measurement is carotid-femoral pulse wave velocity (cfPWV), which is well-established and validated. However, its integration into routine clinical practice has been limited due to the need for intricate techniques to obtain precise pulse wave measurement [10].

Current Non-invasive Brachial Cuff-measured Indices of Arterial Stiffness

Arterial velocity-pulse index (AVI) and arterial pressure-volume index (API) are non-invasive indices for assessing arterial stiffness, which are noninvasively measured using a single brachial oscillometric cuff operating similarly to that used in blood pressure measurement [11,12]. Previous studies have extensively demonstrated the significant correlations between AVI and API and PWV in healthy individuals [11], which suggests that AVI and API hold the potential to serve as viable alternatives to PWV for assessing arterial stiffness [13]. The device used to measure AVI and API (i.e., Portable Arterial Pulse Wave Detector (PASESA AVE-2000 Pro, DAIWA Healthcare, Shenzhen, China) has been certificated and put on the market in China since 2016. The measurement is easier to implement than traditional arterial stiffness measurements, requires less time, and is more comfortable in terms of postural requirements. These merits make the device well-suited for wide use in clinical settings and large-scale community screening [13,14].

Measurement Principles of AVI and API

The main feature of the device is the replacement of multipoint signal acquisition with single-point signal acquisition. The measurement principles of AVI and API are briefly introduced as follows.

AVI is an index calculated based on the characteristics of the cuff oscillation wave under high cuff pressures that exceed the systolic blood pressure (SBP). A computational model-based study has revealed that the oscillation wave measured by a suprasystolic cuff closely resembles the blood pressure wave in the brachial artery and is characterized by the presence of two systolic peaks [12]. In particular, it was found that the secondary peak in the systolic portion of the cuff oscillation wave increased significantly following the increase in aortic stiffness, which was accompanied by a steeper descent of pressure in late systole [12]. Relatively, the wave component in early systole was less affected by aortic stiffness. The biomechanical mechanism underlying the phenomena is the timing of the arrival of the reflected waves originated from peripheral arteries at the brachial artery. Under the condition of high aortic stiffness, the high PWV causes most reflected waves to arrive at the brachial artery in early or middle systole, which increases the secondary peak, but simultaneously reduces the intensity of reflected waves in late systole. AVI is an index used to quantify the changes in wave characteristics with aortic stiffness. Specifically, the cuff oscillation wave is first-order time differentiated, yielding a wave exhibiting one peak in early systole and two valleys in middle to late systole. AVI is defined as the ratio of the magnitude of the second valley ($|V_2|$) to that of the peak ($|P|$) multiplied by a constant (A): AVI= $A \times |V_2|/|P|$, where A is a dimensionless constant set to 20. Theoretically, AVI will increase with the stiffening of the aorta and central arteries. It may also increase if |P| decreases significantly as a consequence of severe impairment of the systolic function of the left ventricle.

API is derived from the time series cuff oscillation waves monitored during the decompression of cuff from a supra-systolic pressure to a value lower than the diastolic pressure [11]. The time series information is processed to construct the transmural pressure-vessel volume characteristic curve (Fig. 1). The shape of the transmural pressure-area (or volume) curve of an artery is related closely to the stiffness of arterial wall. Specifically, the slope of the curve is steeper in the case of softer arterial wall, which is especially evident when

the transmural pressure is close to zero [15].

In general, the curve can be fitted using an arctangent function ($f(x) = a \arctan(bx + c) + d$), where b is the main determinant of the curve slope in the low transmural pressure zone. Given the fact that b is reversely related to the stiffness of the brachial artery under the cuff, API is, defined as API = $X \times 1/b$, is positively related to brachial arterial stiffness. X is a constant expressed in the physical unit of mm Hg (in contrast to the physical unit of B) to ensure that API is a dimensionless index [16]. It is noted that API is affected by arterial pulse pressure because arterial pulse pressure is directly used to construct the the transmural pressure-vessel volume characteristic curve.

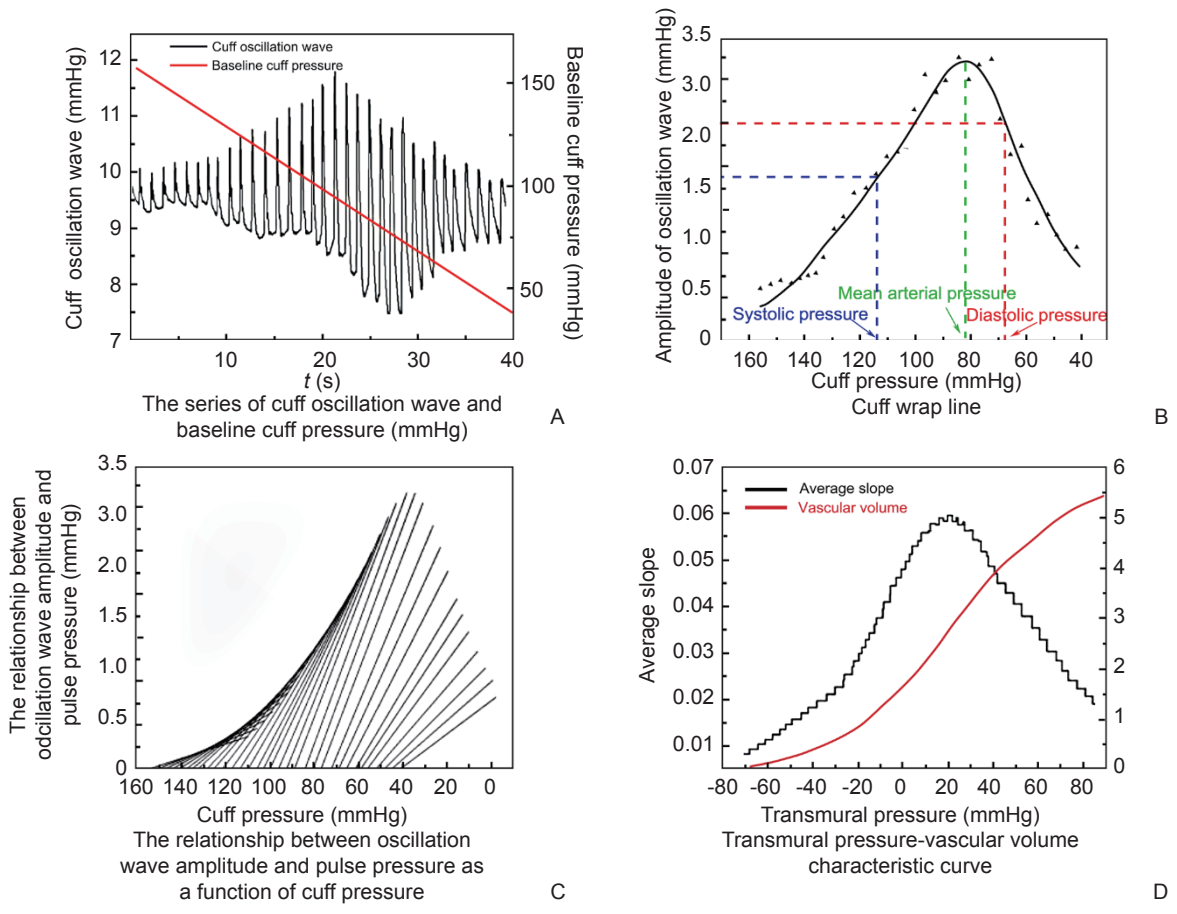

Figure 1 The procedure of deriving a pressure-vascular volume characteristic curve from measured time series cuff pressure. (A) Cuff oscillation wave extraction; (B) Envelope construction and blood pressure (including pulse pressure) estimation; (C) Local slopes of the cuff pressure-arterial volume characteristic curve; (D) Transmural pressure-vessel volume characteristic curve construction, and curve fitting [40].

Central Blood Pressure

In clinical studies, central blood pressure (CBP), which reflects the load on the heart as well as the coronary and cerebral vessels, has demonstrated superior predictive value for clinical outcomes in CVD compared to brachial BP [17]. Furthermore, there is enormous evidence supporting the measurement of central systolic blood pressure (CSBP) and central artery pulse pressure (CAPP) as good indicators of CVD risk [10]. PASESA AVE-2000 (DAIWA Healthcare, Shenzhen, China) also outputs the values of CSBP and CAPP. The device employs embedded algorithms to derive CSBP and CAPP based on acquirable information. Specifically, the algorithms utilize empirical functions to transfer age, brachial systolic pressure, brachial diastolic pressure, AVI and API into CSBP and CAPP [18].

Arterial Stiffness with CVD Risk Score

Assessing CVD risk is a fundamental component of CVD prevention [19]. The Framingham Heart Study has played a pivotal role in identifying CVD risk factors since 1976 [20]. In the Framingham Heart Study, aortic arterial stiffness was found to be predictive of the development of cardiac events, following adjustment for gender, SBP, lipid profile, anti-hypertensive medication, smoking and diabetes mellitus [21]. In clinical practice,

the Framingham Cardiovascular Disease Risk Score (FCVRS) is widely used in clinical practice. Similarly, the prediction for Atherosclerotic Cardiovascular Disease Risk in China (China-PAR) project, developed in 2016, is a recent addition to CVD risk prediction models. It's based on data gathered from several contemporary Chinese adult cohorts [22].

AVI and API contain information not only related to arterial stiffness but also pertaining to cardiac systolic function, thus serving as potential indicators to alert about impending cardiovascular events [23]. Several studies have confirmed the clinical significance of AVI and API and their relevance to CVD [13,24]. Sasaki-Nakashima et al. reported that API was independently associated with the FCVRS, suggesting that API is a valuable predictor of forthcoming CVD events [25]. Interestingly, a J-shaped association has been identified between AVI and API with both FCVRS and China-PAR [26,27]. For the lowest FCVRS, AVI was 8 units, and API was 18 units, respectively. In the case of China-PAR, the risk score was lowest when AVI was 85 units, and API was 19 units, respectively, with the risk increasing most evidently when AVI was 14 units or API was 26 units. These associations provide a new perspective on early treatment or lifestyle modifications aimed at preventing cardiovascular diseases. Figure 2 illustrated the correlations of API and AVI with FCVRS.

Arterial Stiffness with CVD Risk Factors

Arterial stiffness is associated with a variety of CVD risk factors, including increasing age [28], overweight [29], smoking [30], hypertension [31], diabetes mellitus [32], dyslipidemia [33]. In addition, increased arterial stiffness has been correlated with the presence and severity of atherosclerosis in the general population.

Age

Studies on arterial stiffness have revealed that with increasing age, there are alterations in the proportion and structure of elastin and collagen in the arterial wall, resulting in decreased vascular elasticity and increased arterial stiffness [34,35]. AVI and API have been shown to increase with age [36,37], and age has been identified as an independent risk factor for high AVI [38]. Moreover, the relationship between age and arterial stiffness is better captured by a non-linear model rather than the traditional linear model approach [39]. One plausible explanation is that arterial walls exhibit viscoelastic biomechanical properties and display nonlinear stress-strain relationships that change complicatedly with age [3]. Chen et al. [40] reported a J-shaped relationship between API and age, with the J-shaped curve displaying a complex pattern of change across age groups. Among women, API began to increase at the age of 31, followed by a rapid rise after 54 years. In men, API began to increase at age 38, with a sharp increase after 53 years.

Gender

CVD displays sex-specific differences in occurrence, progression, and outcomes, particularly concerning the degree and timing of arterial stiffening [41]. Previous studies have indicated that men exhibit greater arterial stiffness from early adulthood, with arterial stiffness increasing almost linearly across their lifespan. In contrast, women experience a notable acceleration in age-related arterial stiffness after menopause [42]. In a substantial population-based study comprising 7,620 subjects, a significant age-sex interaction in small-to-medium-sized arterial stiffness was observed. This entailed a higher API in men than in young women, but conversely, a higher API in middle-aged and older women compared to men [40]. Moreover, it's worth noting that the repercussions of arterial stiffening are more pronounced in women [43]. In a study by Jin et al. [44], it was reported that among women, AVI exhibited a significant association with both the Framingham and China-PAR risk scores. Notably, in both FCVRS and China-PAR models, AVI demonstrated relatively high importance in predicting CVD risk, as illustrated in Figure 3.

Overweight

Obesity is closely associated with hypertension and is a significant risk factor for increased arterial stiffness [45]. However, there is a lack of consistent conclusions regarding the correlation between body mass index (BMI) and arterial stiffness, assessed through API and AVI.

Several studies have identified a positive correlation between BMI and API. For instance, Xu et al. [46] reported notable differences in API values between overweight and normal-weight individuals. They observed that the API values increased with greater body weight, consequently leading to a an increased risk of high arterial stiffness among overweight individuals.

Similarly, Jin et al. [47] reported that API and BMI are correlated with 10-year cardiovascular risk across various age groups in females. Regardless of age, overweight females exhibited a higher risk of increased API. However, it's worth noting that some researchers have suggested a negative correlation between BMI and AVI. In a study involving 2,418 subjects, being overweight was identified as an independent protective factor against high arterial stiffness, with notable gender differences observed. High AVI incidence was more prevalent in overweight and obese females but less common in overweight and obese males [29]. This may be due to the fact that the measurement principles of AVI

and API are different. AVI, which is derived from the morphology of cuff oscillation wave, is more prone to the influence of the thickness of soft tissue in the upper arm. Thicker upper arm tissue in overweighted subjects may blunt the transmission of brachial arterial lumen deformation (induced by blood pressure pulsation) to cuff bladder volume change leading to an underestimation of AVI [13,16,38].

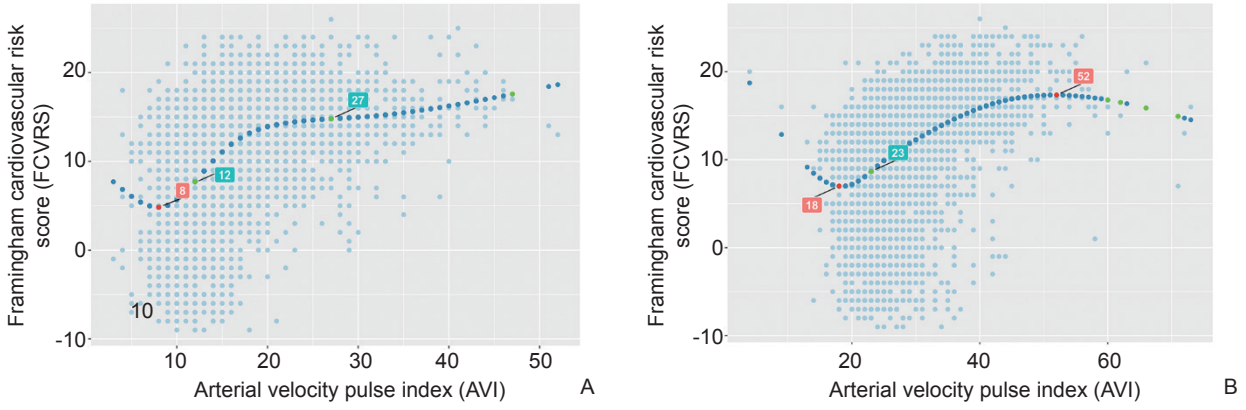

Figure 2 Correlations of API and AVI with FCVRS. (A) AVI have a J-shaped relationship with FCVRS. The value associated with the lowest risk score of CVD was 8 units; (B) API have a J- shaped relationship with FCVRS, and the API value associated with the lowest risk score of CVD was 18 units [26].

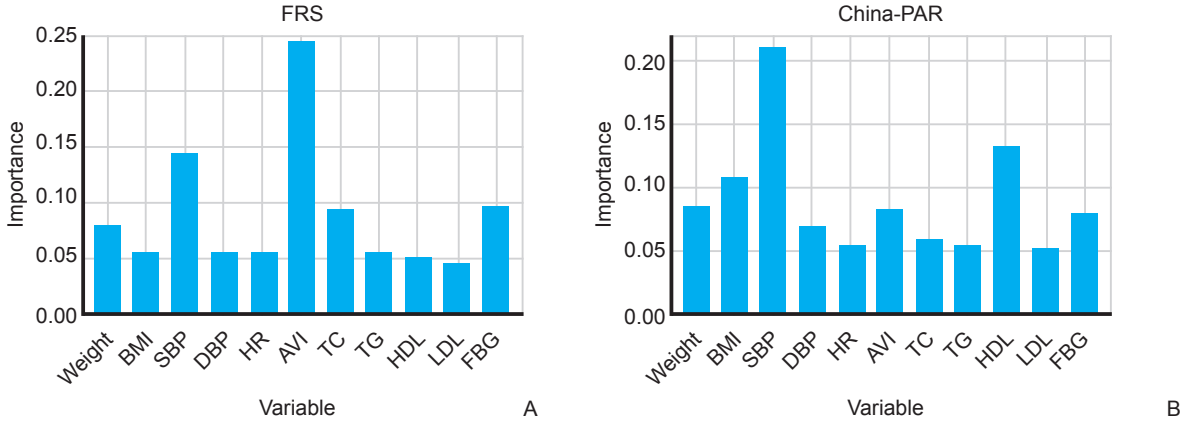

Figure 3 Relative importance of AVI in predicting the CVD risk score. (A) Relative importance of AVI in predicting the high FRS; (B) In predicting the high China-PAR as analyzed in random forest analysis [44].

Hypertension

Arterial stiffness serves as a significant marker of hypertension risk [48]. However, the bidirectional relationship, specifically whether arterial stiffness causes hypertension or hypertension causes arterial stiffness, remains a subject of controversy in the field [49]. In their assessment of the relationship between arterial stiffness, central hemodynamics, and the 10-year risk score of CVD in a Chinese cohort, Jin et al. [50] found that individuals with uncontrolled hypertension exhibited elevated values of CAPP, CSBP, API, AVI, and CVD risk score. Importantly, CAPP emerged as one of the key variables independently associated with high CVD risk stratification. Additionally, CAPP demonstrated significant J-shaped relationships with China-PAR and FCVRS, as illustrated in Figure 4. The study also noted that central hemodynamics (CAPP) tended to be lower in younger age groups, gradually increasing and becoming more variable in middle and old ages. These findings offer valuable insights for further investigations into the interactions between BP and arterial stiffness in the context of CVD risk scores.

Diabetes mellitus

It has been found that the likelihood of heart and macrovascular disease in diabetic patients is 3 to 5 times higher than in the general population, and this risk is further elevated in individuals with hypertension [32].

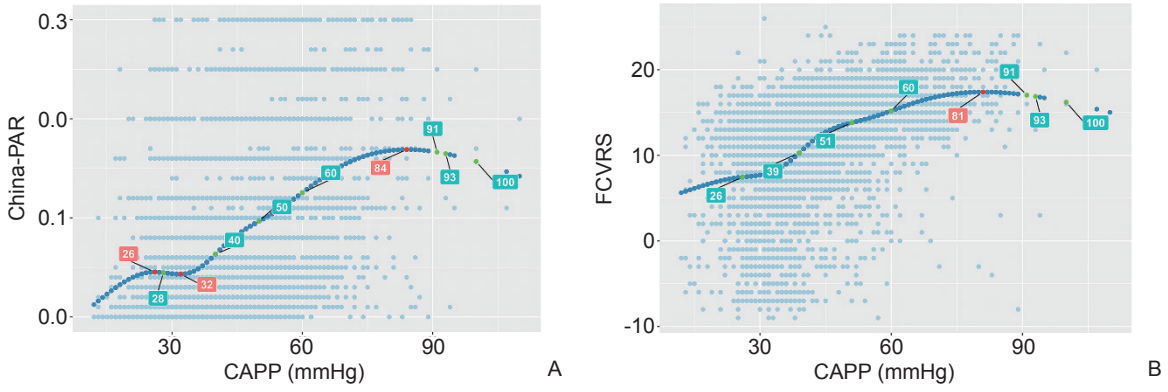

Figure 4 The association between CAPP and China-PAR, FCVRS. (A) J-shaped relationship between CAPP and China-PAR score; (B) J-shaped relationship between CAPP and FCVRS [44].

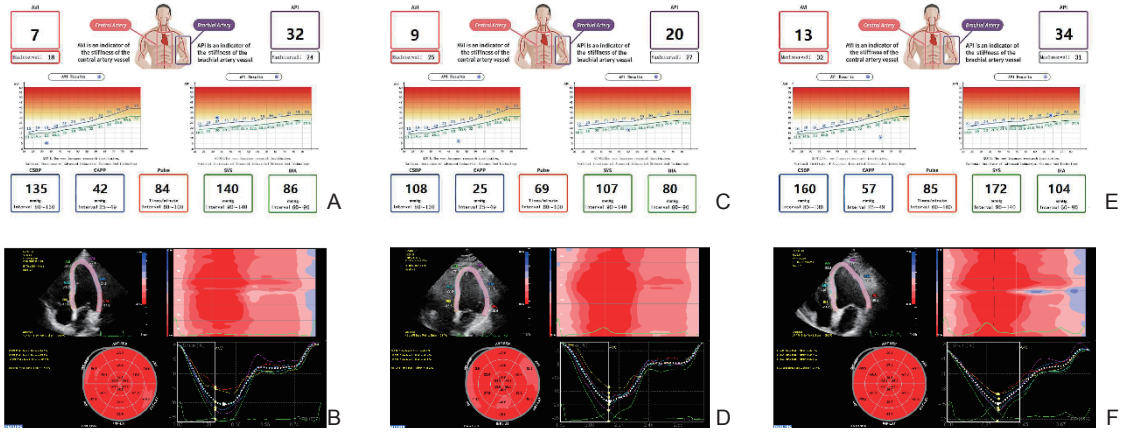

Figure 5 Analysis of AVI and LVGLS. (A and B) Male, 39 years, AVI = 7, LVGLS = -21.5%, AVI/LVGLS = -32.56; (C and D) Female, 48 years, AVI = 9, LVGLS = -22.4%, AVI/LVGLS = -40.18; (E and F) Female, 65 years, AVI = 13, LVGLS = -24.9%, AVI/LVGLS = -34-52.21 [59].

T2DM (type II diabetes mellitus) can lead to a simultaneous increase in parameters reflecting myocardial elasticity, such as left ventricular end-systolic elasticity (Ees) and effective arterial elasticity (Ea). This phenomenon, known as cardiovascular coupling, involves the functional coupling of cardiac and vascular elasticity. Conversely, it can also lead to a sequential increase in both parameters, resulting in elastance mismatch and functional decoupling [51]. Wu et al. reported that arterial elastance and ventricular elastance increase in parallel in diabetic patients with hypertension. Furthermore, they found that the increased arterial stiffness indices were positively correlated with the indices of ventricular-vascular coupling [52].

Heart failure

Increased arterial stiffness, which is associated with central blood pressure and wave reflections, plays a role in adverse cardiac outcomes [53]. Indeed, a previous study demonstrated that optimal heart stroke work is determined by the elastic and functional coupling of the heart and blood vessels [51].

The study revealed that AVI and API can serve as indicators of illness severity and mid-term prognosis in hospitalized patients. Among patients with acute heart failure, those with an AVI $\geqslant$ 26 at discharge had a 2.75-fold higher rate of all-cause death or heart failure recurrence compared to patients with an AVI < 26 (95%CI: 1.411 to 5.349) [54]. Additionally, patients with diastolic heart failure exhibited an elevated AVI, translating to a 3.12-fold higher risk of cardiovascular events in comparison to patients with normal diastolic function [55]. Furthermore, heart failure with preserved ejection fraction (HFpEF) patients may manifest increased arterial stiffness alongside reduced myocardial longitudinal contraction, and there exists a correlation between increased arterial stiffness and decreased myocardial longitudinal contraction [56].

Arterial Stiffness with Ventricular-Vascular Coupling

Ventricular-vascular coupling stands as one of the most significant determinants of cardiovascular function [57]. Global longitudinal strain of the left ventricle (LVGLS) serves as an early indicator of cardiac systolic function [58]. Wu et al. [59] employed the novel cardiovascular coupling index AVI/LVGLS to investigate

the impact of age on ventricular-vascular coupling function. Their findings indicated that AVI/LVGLS was more effective than traditional indices in discerning differences in cardiovascular function across various age groups. Figure 5 presented the analysis of AVI and LVGLS.

Conclusion

AVI and API can serve as markers of arteriosclerotic disease and exhibit a robust association with the occurrence of CVD events. Moreover, AVI and API display J-shaped associations with CVD risk scores. Consequently, the incorporation of arterial stiffness indices into CVD risk assessment could enrich the information for diagnosis and favor early identification of asymptomatic individuals who might benefit from more aggressive primary preventive therapy.

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Conflict of Interest

The authors have no conflict of interest to declare.

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