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Review Article

Arterial Stiffness as a Predictor of Future Cardiovascular Events: Methods of Measurement and Clinical Implications

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ABSTRACT

Recent studies have shown that arterial stiffness is an important predictor of cardiovascular events including heart attacks and strokes. The cardio-ankle vascular index (CAVI) is an innovative metric for gauging arterial stiffness at the point where the artery divides from the aorta and approaches the foot. CAVI's ability to provide accurate results regardless of the patient's blood pressure now of measurement is, without a doubt, its most valuable characteristic. CAVI is associated with cardiovascular risk factors such as dyslipidemia, diabetes, hypertension, and smoking. It also rises with age and in many arteriosclerotic disorders, including coronary artery disease, carotid artery disease, and chronic kidney disease. CAVI also increases in patients who have cerebrovascular disease. Controlling conditions such as hypertension and diabetes and quitting smoking may also reduce the risk of CAVI. This indicates that CAVI is a physiological surrogate measure of atherosclerosis, and it also implies that it might be a signal of lifestyle change. Recent research has shown that CAVI and numerous functions of the left ventricle are linked, which points to a link between vascular function and the heart muscle. This study discusses the fundamentals of CAVI as well as our preunderstanding of the measurement, with a particular emphasis on its functions and potential future use.

1. Introduction

Cardiovascular diseases are the primary cause of mortality and morbidity worldwide. According to data provided by the WHO, cardiovascular diseases accounted for the deaths of 17.9 million people worldwide, which is equivalent to 32 percent of all fatalities. The majority of these fatalities (85%) are caused by cardiovascular conditions such as heart attacks and strokes.[1] It is possible to avoid developing cardiovascular disease by addressing modifiable risk factors, such as obesity, dyslipidemia, smoking, or hypertension. It is of the utmost importance to perform early detection of cardiovascular disease in order to initiate counseling and pharmaceutical care as soon as is practically practicable. In addition, it is possible to forecast future cardiovascular events by employing a scoring system that considers the classic atherosclerotic risk factors. However, in recent years, it has been hypothesized that various vascular markers such as endothelial function, carotid ultrasonography, ankle-brachial index, and arterial stiffness might be screening tools and predict future cardiovascular events.

Arterial Stiffness

Arterial stiffness has been linked to cardiovascular events including heart attacks in several studies. Arterial stiffness is a problem with the artery's tunica media. The arterial wall is a highly organized structure composed of endothelial cells, smooth muscle cells, matrix proteins (cross-linked collagen fibers and elastic lamellae orientated in opposite directions), and glycosaminoglycans in the intima.[2] From the aortic arch to the periphery, there is a transition in the arterial wall's composition. Elastic lamellae and smooth muscle cells form the interdigitating connective tissue layers that make up the tunica media of large elastic arteries. This microstructure slowly deteriorates in arteries of medium and smaller sizes, such as arterioles, with less elastic lamellae and more soft muscle cells.[2]

Elastin and collagen play crucial roles in vascular elasticity and flexibility. It is the natural distensibility of the vessel's elastin and the undulating, undulating nature of the collagen that allow a young, healthy artery to dilate under physiological stresses

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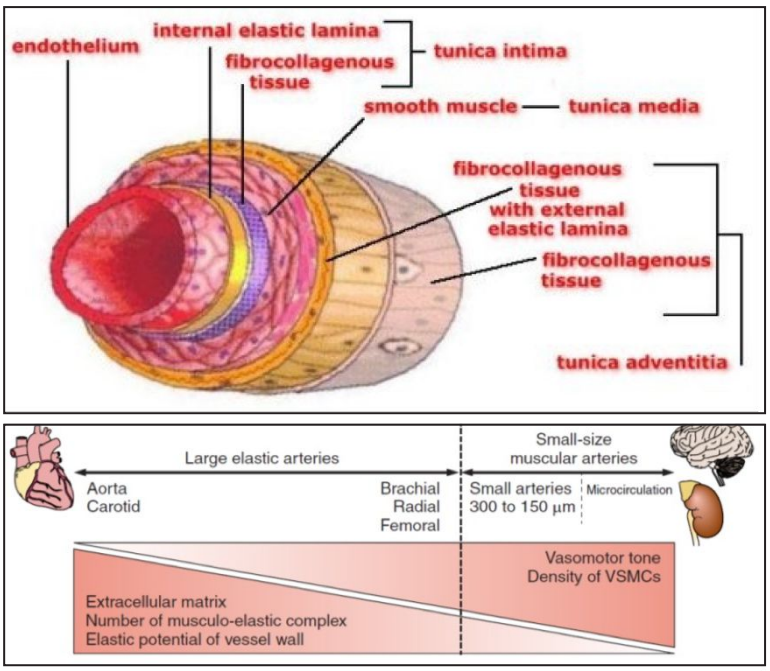

Figure 1. Structure of artery.[2]

Elastin is not replaced after it has been deposited in the arterial wall media throughout development and childhood. Somatic growth causes tensional strain in both the circumferential and longitudinal directions to be applied uniformly to the elastin within the arterial wall. To adapt to the mechanical and biological changes in their environment, blood vessels undergo a constant process of collagen destruction and deposition thanks to mechano-biological homeostasis. The progressive functional stiffening of the artery at higher pressures is due to the progressive recruitment of collagen fibers as the pressure or stretch level increases. This explains the striking nonlinearity in the mechanical response of an artery when stretched or compressed across a wide range.[3] Large, elastic arteries are predisposed to contract with age because elastin has a half-life of 40 to 50 years, which has negative health consequences. As these arteries mature, the strain is transferred from the low-stretch bearing component to the more rigid matrix components (collagen), which are less elastic. At the same time, arteries become less elastic and more rigid along their lengths, which causes them to elongate and twist more. As people get older, their vessels become more stiff and longer, increasing their cross-sectional area. Large Artery Stiffening (LAS) can be caused by a number of factors interacting with one another and with pathways such as endothelial dysfunction and inflammation. These factors include increased smooth muscle cell stiffness, elastin and collagen cross-linking, replacement fibrosis, and media calcification4.

LAS has many negative effects on the body. The inability of the central arteries to inflate and store elastic energy during systole, which is then released during diastole to improve blood flow, is known as the Windkessel function, and its loss can lead to a reduction in blood pressure and other cardiovascular problems. Since the ejecting left ventricle's less distensible aorta stores less blood locally in systole, more blood must be transported over longer distances in systole, necessitating higher driving pressures and increasing energy demands on the heart, resulting in wider pulse pressure. Significant links have been shown between LAS and organ damage because to the increased mechanical stress on the arteries and organs brought on by elevated arterial pressures and pulsatility. Arterial hemodynamics are altered when the stiffness gradient between the central and peripheral arteries is reduced. This is because the peripheral arteries are less prone to stiffening (perhaps due to their lower elastin concentration). LAS is largely considered a crucial indicator of vascular health due to its consistent demonstration of increased mortality and morbidity prediction in the context of other traditional cardiovascular risk factors. LAS is theorized to incorporate the age-related and insult/mechanochemical stressor-related effects on the vascular system.[2]

The atherosclerotic changes that come with aging make the arteries stiffer. There is an increase in wall thickness due to the thickening of the intima. Even in the absence of atherosclerotic disease, aging frequently brings to increased stiffness and a rise in wall thickness. However, the mechanical features of the artery wall may be altered by other atherosclerotic risk factors such as dyslipidemia, diabetes mellitus, hypertension, and smoking, all of which can contribute to arterial stiffness. Patients' arterial stiffness can be evaluated in numerous ways, both invasive and non-invasive, such as cardio-ankle vascular index (CAVI) and pulse wave velocity (PWV).[5]

Pulse wave velocity

A parameter known as pulse wave velocity (PWV) is regarded as the gold standard for arterial stiffness assessment. It is also the most commonly used. This parameter may be calculated by monitoring the speed at which pulse pressure waves move through the arterial tree. Especially in Western nations, calculating the carotid-femoral pulse wave velocity (cfPWV) is a common and verified technique. cfPWV remained a predictor of CHD, stroke, and CV events despite accounting for more traditional risk variables such h as age, systolic BP, serum cholesterol, HDL-C, smoking history, diabetes status, and antihypertensive drug use. There have been many meta-analyses that demonstrate its usefulness in enhancing the prediction of CV events beyond the use of traditional risk variables.[6]

However, the measurement of cfPWV is rarely used in clinical practice because it requires exposing the inguinal region and having the necessary technical expertise to measure the carotid and femoral pulses. One potential alternate method of determining arterial stiffness is using the brachial-ankle pulse wave velocity, which is more often abbreviated as baPWV.[7] When determining the baPWV, it is necessary to wrap blood pressure cuffs around all four limbs. Because of this, it is an ideal method for determining arterial stiffness in a normal clinical setting or research based on a population. A greater baPWV was related to a higher risk of cardiovascular disease, according to a meta-analysis that included prospective studies with participants from Japan who did not already have cardiovascular disease.[8] Additionally, incorporating baPWV into a patient's Framingham risk score (FRS) improved the accuracy of the Framingham risk score's ability to forecast cardiovascular illness.[9] The value of baPWV at a threshold of 18 meters per second has been proposed as the value to use to describe an artery as being stiff. According to the KSH 2018 guidelines for the therapy of arterial hypertension, a baPWV that is more than 18 meters per second indicates subclinical damage to the target organs caused by hypertension.[10] On the other hand, the majority of baPWV implementations have taken place in Japan in addition to a few other East Asian countries.[11] The therapeutic usefulness, clinical outcomes, and cost-effectiveness of the baPWV have not been thoroughly confirmed in other countries. Determining wave propagation distance using a height-based formula is yet another issue that has to be tested over a wide range of cultural groups.[12]

There are a lot of techniques to demonstrate the baPWV's worth as a vascular biomarker, including by comparison to other multivariate risk-predicting algorithms. There are other approaches besides this one, though. Rhee et al. found that four different risk-scoring methods all had a similar connection with baPWV. Recent articles have focused on these discoveries.[13] They compared baPWV to the FRS in its inceptional form, to the FRS as revised by the Adult Treatment Panel III, to the FRS in its generalized form, and to the CVD risk equation recently proposed by the American College of Cardiology and the American Heart Association. The investigators set out to determine whether or not baPWV is a valid predictor of cardiovascular disease. In their estimates, they include in the possibility of experiencing cardiovascular issues or a stroke. This study could not establish a precise cut-off value for identifying persons at high risk for future cardiovascular events; nevertheless, it did demonstrate a substantial association between baPWF and the risk scores of multiple algorithms, suggesting its potential predictive relevance as a vascular biomarker. Additionally, there was no threshold value given to distinguish persons at low risk for future cardiovascular events. They also discovered that the link was stronger in women than in men, indicating that the baPWV was more accurate at predicting cardiovascular risk in women than in men among healthy populations.[13]

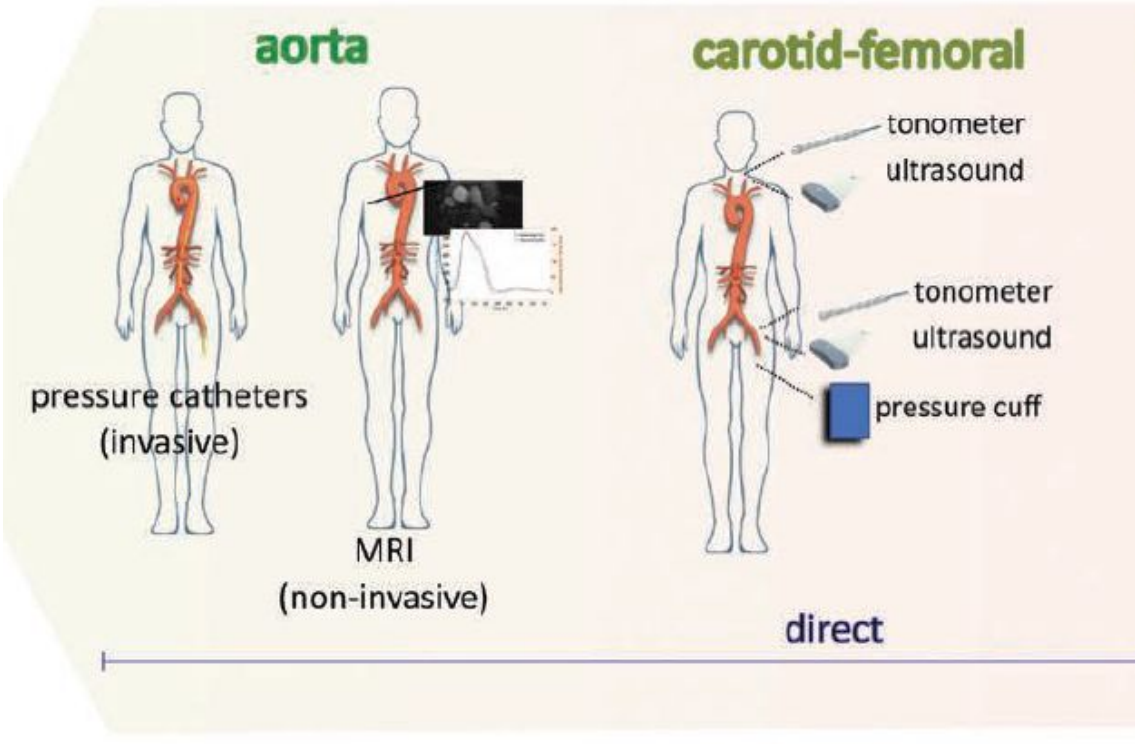

Figure 2. PWV Measurement. Invasive pressure catheter recordings are only occasionally used in technical validation studies because of their complexity, cost, and ethical constraints. Magnetic resonance imaging (MRI) is the only imaging modality to provide, within one examination, the 3D aorta and path length (anatomic imaging) and transit times (phase-contrast sequences). The most widely used proxy for aortic PWV is carotid-femoral PWV, with transit times assessed from signals measured at the carotid and femoral arteries.[3]

Many different points of view have been recorded, and one of them is the debate about whether there are gender differences in arterial stess.[12] Age is one of the most critical elements in determining the baPWV, therefore this finding was expected given the average age of the women in the study. The baPWV was found to be higher in females than males by Rhee et al. Researchers in Japan found that, up until age 60, women had a lower baPWV than men did, and that the effect of age on baPWV was more pronounced in females than in males. The coefficients of correlation between baPWV and other common CV risk factors were equally greater in women than in men, as reported by Rhee et al.[9] This held true in analyses comparing mean values for a variety of cardiovascular risk factors. All the aforementioned conditions were met. The strength of the association between baPWV and a CV risk score is also seen to vary by gender. However, the mechanism responsible for these differences remains unclear.[10]

The slope of the age-related increase in cfPWV was comparable across men and women, and CV risk factors made this slope steeper without sex differences, according to a population-based study done in Brazil. This remained true even after accounting for variations in mean BP.[11] This finding contradicts the idea that men's cfPWV is higher than women's at all age intervals. The previous study discovered that the slope of the age-related increase in cfPWV was the same for men and women. As a result, our conclusion contradicts the previous research's conclusions. It was possible to directly examine sex differences in baPWV and cfPWV with age in a single research by utilizing the same equipment to assess baPWV and cfPWV in the same people. This was made achievable by testing both baPWV and cfPWV in the same people.[12] This enabled a comparison between the baPWV and the cfPWV in persons of similar ages. The most important takeaways from this research were that both baPWV and cfPWV rose with age and were lower in women than in males. After the age of 50, men and women had values that were comparable to one another. However, males of all ages had a higher cfPWV. In addition, it d that the baPWV was lower in women up to the period in question, but that beyond that age, it was the same in both sexes. Between the ages of 30 and 70, a more significant rise in baPWV was seen in women compared to an increase in cfPWV in males; nevertheless, the surge in cfPWV was comparable in both sexes. According to these results, a more significant correlation with cardiovascular risk-prediction scores in women may only apply to the baPWV; this issue has to be investigated further by means of more study.[13]

The early return of reflected waves during systole rather than diastole is made possible by the high velocities of both the backward reflection wave and the forward flow in a stiff arterial system. Because reflected waves go in the opposite direction of forward-moving waves, this is the case. This causes the afterload on the left ventricle to rise while simultaneously decreasing blood supply to the coronary arteries. In addition, both the central systolic and pulse pressures (PP) rise. The ratio of the peripheral PP to the central PP, or PP amplification, is also decreased. Because of the decline, this ratio is now lower. Despite the fact that men and women have the same PWV, women are more likely to experience these phenomena because of their smaller stature, smaller main artery diameter, and lower large and small artery elasticity. Despite the fact that the PWV is identical between the sexes, this is the case. Although the PWV is the same for both sexes, women tend to exhibit these behaviors more openly. Women may be more at risk since their arteries tend to be narrower but longer than those of men. Only in female patients was there an interaction between those indices and left ventricular diastolic function or ventricular-arterial coupling. This may account for the greater prevalence of heart failure in female patients who had their ejection fraction preserved. In addition, it has been shown that while having lower total arterial compliance than men, women have a higher average aortic impedance.[10]

It has been highlighted how the measurement of PWV is subject to several restrictions and potential causes of imprecision11. First, it is possible that the actual length of the arterial segment cannot be reliably determined by determining the transit distance of pressure waves by using measurements taken on the body's surface. This is particularly true in cases of obesity and when the arteries become more tortuous with age.[12] Second, the carotid-femoral PWV is not a straightforward unidirectional route length for the pulse wave; as a result, the actual traveled path length approximates the true value. In addition, several potentially confusing physiological and technological aspects have been documented about PWV. Blood pressure and heart rate are the two physiological parameters that have the most significant impact on PWV. Technical confounders include the algorithm of the device utilized and the arterial route considered (carotid-femoral, brachial-ankle, etc.).[13]

Cardio ankle vascular index.

There is also anecdotal evidence that blood pressure does not influence the Cardio Ankle Vascular Index (CAVI), which measures arterial stiffness over the entire aortic, femoral, and tibial segments.[14] CAVI can be diagnosed by comparing the diastolic and systolic blood pressure readings recorded at the upper brachial artery with the pressure waveform from the aortic origin to the tibial artery just above the ankle.[15]

Many studies have shown that CAVI is less reliant on blood pressure than PWV. However, this does not mean that CAVI is independent of blood pressure when it is measured.[16] Metoprolol is a selective beta-blocker, meaning that it lowers blood pressure and slows the contraction of heart muscle without affecting the tone of the artery wall. It is one of the most prescribed drugs because of these properties. In the context of therapeutic medicine, all of these outcomes are positive. Treatment with metoprolol for six hours resulted in a reduction of baPWV in 12 male subjects. Even so, the lack of a correlation between blood pressure and the CAVI provides conclusive evidence that the CAVI is independent of blood pressure. This inference is warranted because this outcome was discovered.[17]

The effects of age and gender on CAVI in otherwise healthy people living in Japan's major cities were investigated in this study18. The participants included 32,627 individuals who were currently undergoing yearly health checks and 32,627 healthy individuals who did not have any risk factors. Their ages varied anywhere from 20 to 79. To measure CAVI, a Fukuda Denshi Co. Tokyo VaSera VS-1500 was used. CAVI in males are otherwise healthy and free of cardiovascular risk factors rose linearly with increasing age from 20 to 70.

Diseases related to CAVI and arteriosclerosis

It is not simple to confirm that CAVI is a sign of arteriosclerosis since the quantitative evaluation of arteriosclerosis is complex in vivo. However, this does not mean that it cannot be done. The physical appearance of the aorta at postmortem was compared with the CAVI, which was assessed while the individuals were still alive. This was done so that it could be determined whether or not CAVI accurately represents the degree of arteriosclerosis. A woman's aorta that was 50 years old revealed very little evidence of atheroma, and her CAVI score was 7.0. Arteriosclerosis was found at an advanced stage in both men's aortas, despite their ages of 74 and 76. The CAVI was the same in both cases, 11.0. The CAVI cutoff value is set at 9.0, as will be explained further on. The physical appearance of the aortas after death at the postmortem supports the hypothesis that The development of CAVI mirrors the evolution of atherosclerosis.[19]

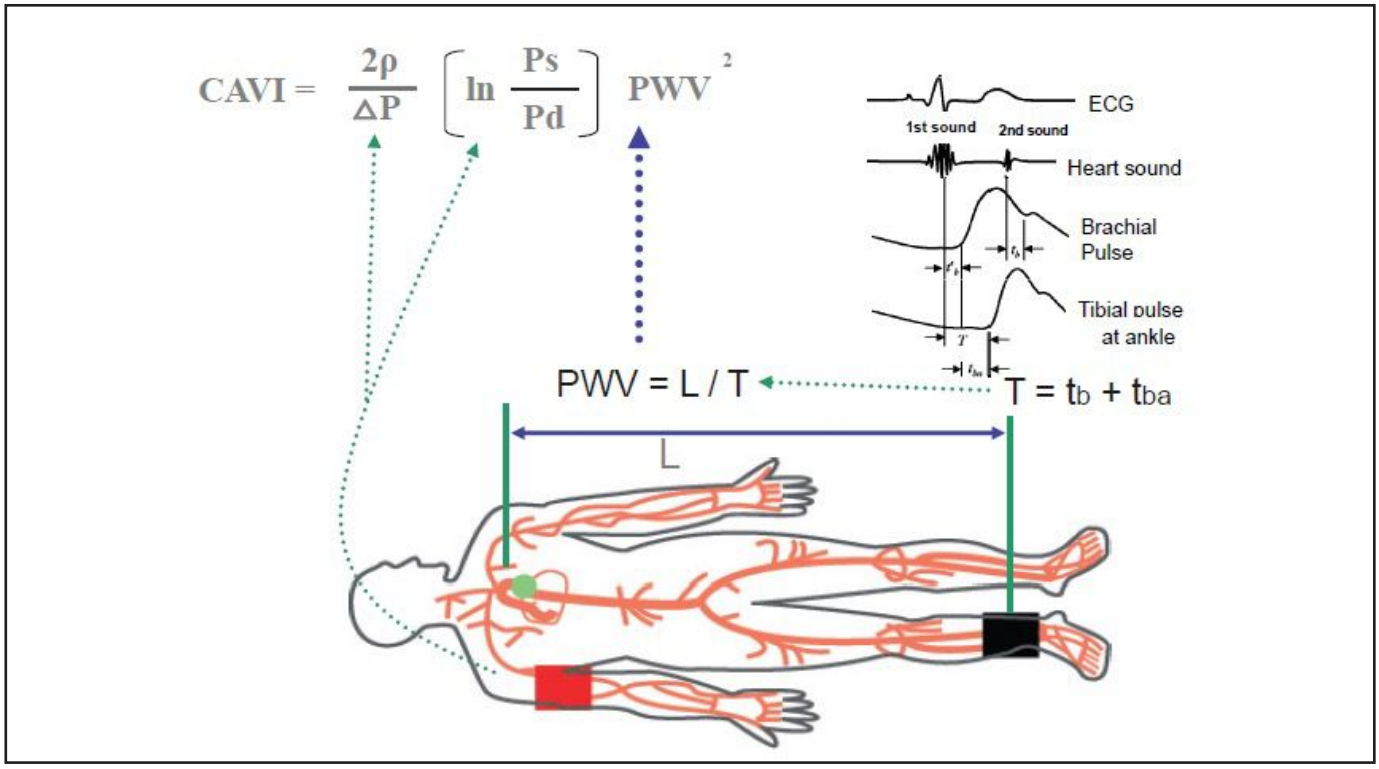

Figure 3. CAVI Measurement. With the patient lying supine, electrocardiogram, and heart sounds are monitored. PWV from the heart to the ankle is obtained by measuring the length from the origin of the aorta to the ankle and calculating T= tb+tba. Blood pressure is measured at the brachial artery. Ps: systolic blood pressure, Pd: diastolic blood pressure, PWV: pulse wave velocity, ΔP: Ps−Pd, ρ: blood density, ΔP: pulse pressure, L: length from the origin of the aorta to the ankle, T: time taken for the pulse wave to propagate from the aortic valve to the ankle, tba: time between the rise of the brachial pulse wave and the rise of the ankle pulse wave, tb: time between aortic valve closing sound and the notch of the brachial pulse wave, tb: time between aortic valve opening sound and the rise of brachial pulse wave.[15]

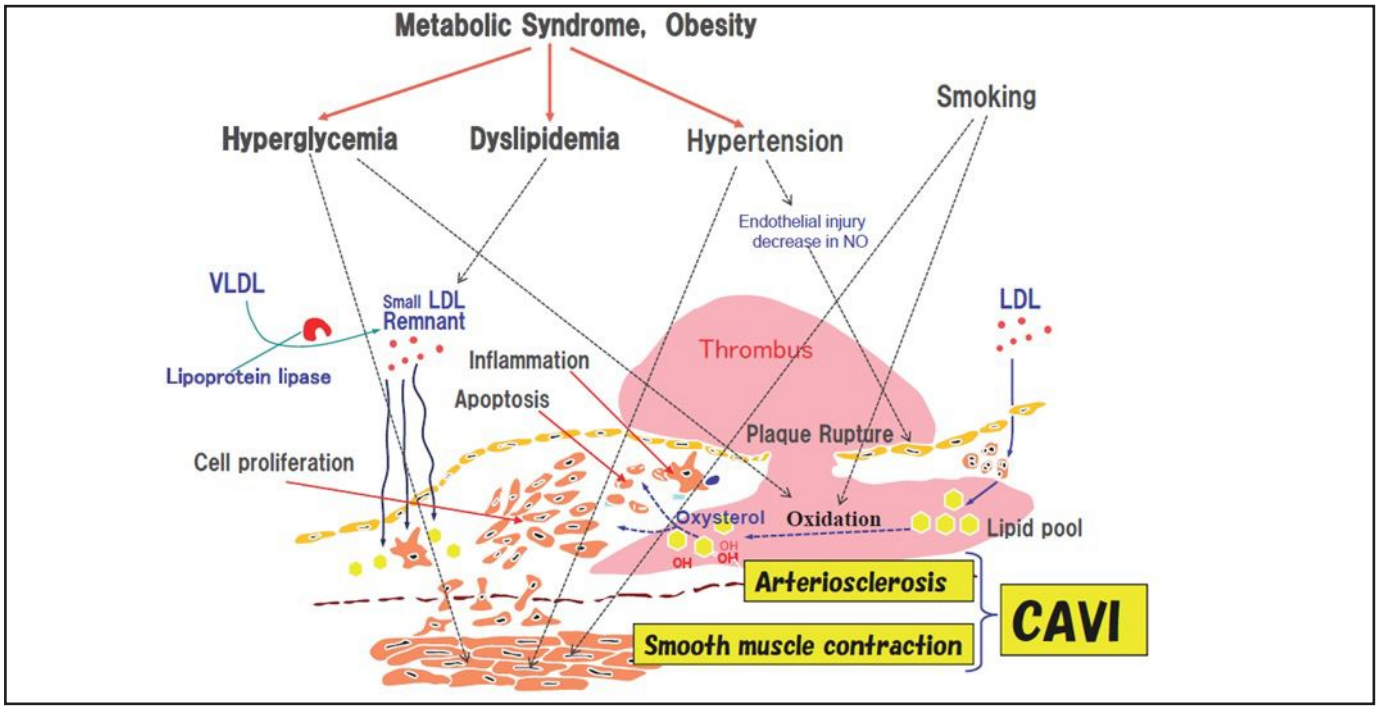

Figure 4. Atheroma formation with coronary risk factors and CAVI. The process of athero- and arteriosclerosis is supposed as follows. A lipid pool is formed with infiltration of LDL, small dense LDL, and remnants. Oxidation of lipids provokes inflammation. Then, smooth muscle cells proliferate to develop intimal thickening. Inflammatory reaction gathers macrophages, which degrade the matrix and also induce smooth cell apoptosis. Then, plaque rupture occurs, and thrombus is formed. Risk factors are involved in various steps. Some target the endothelial cells and produce injuries. Some promote oxidation stress in the arterial wall. Others target medial smooth muscle cells, increasing contraction or provoking cell proliferation. Interestingly, all these injurious reactions seem to be integrated into CAVI.

The results of a study by Nakamura and colleagues indicate that CAVI increases along with the fraction of substantially constricted vessels (more than 75 percent). According to the stepwise ordinal logistic regression analysis findings, CAVI was the only factor shown to have a positive association with the extent of coronary atherosclerosis. Mean and maximum intima-media thickness (IMT), plaque score, and carotid atherosclerotic vasculopathy were additional independent factors investigated. CAVI had the biggest area under the receiver operating characteristic (ROC) when compared to maximum IMT, mean IMT, plaque score, and CAVI. The ability of CAVI to differentiate between the presence and absence of coronary atherosclerosis utilizing high-resolution B-mode ultrasonography may be improved. In order to diagnose coronary stenosis, the CAVI cutoff threshold of 8.91 was applied.[20]

Izuhara et al.[21] found that coronary artery vessel inflammation (CAVI) is independently linked with the severity of coronary atherosclerosis. Recent research conducted by Miyoshi and colleagues22 lends credence to the idea that CAVI and coronary atherosclerosis are linked. According to Horinaka and colleagues[24] findings, CAVI is a more accurate predictor of coronary artery disease than baPWV. According to Takaki et al., findings[24] CAVI is superior to baPWV for determining whether or not there is atherosclerosis in the coronary and cervical arteries.

When comparing those with acute coronary syndrome to those with stable angina pectoris, those with CAVI have a higher prevalence. Cardio-ankle vascular index accurately predicts cardiovascular events in persons with risk factors for cardiovascular disease, according to recent prospective cohort research by Miyoshi and colleagues.[25] The cardio-ankle vascular index was shown to be related to an increased risk of death from cardiovascular disease, nonfatal stroke, death from all causes, and heart failure that required hospitalization.

According to the findings of Nakamura and colleagues,[20] CAVI is positively correlated with both the carotid plaque score and the maximal IMT. CAVI was found to have a positive connection with both IMT ($r = 0.360$, $p = 0.0022$) and the stiffness parameter ($r = 0.270$, $p = 0.0239$) in a sample of 70 hypertension patients analyzed by Okura et al. CAVI and IMT were found to have a statistically significant correlation ($r = 0.48$, p 0.01) by Takaki et al. According to Izuhara et al.,[21] elevated CAVI is associated with worsening carotid arteriosclerosis. This research also suggests that CAVI may have a stronger association with atherosclerosis than baPWV. A conclusion was drawn from these results. Individuals with severe atherosclerotic cardiovascular disease may benefit from a more precise prediction of thrombosis using a combination of CAVI and IMT.

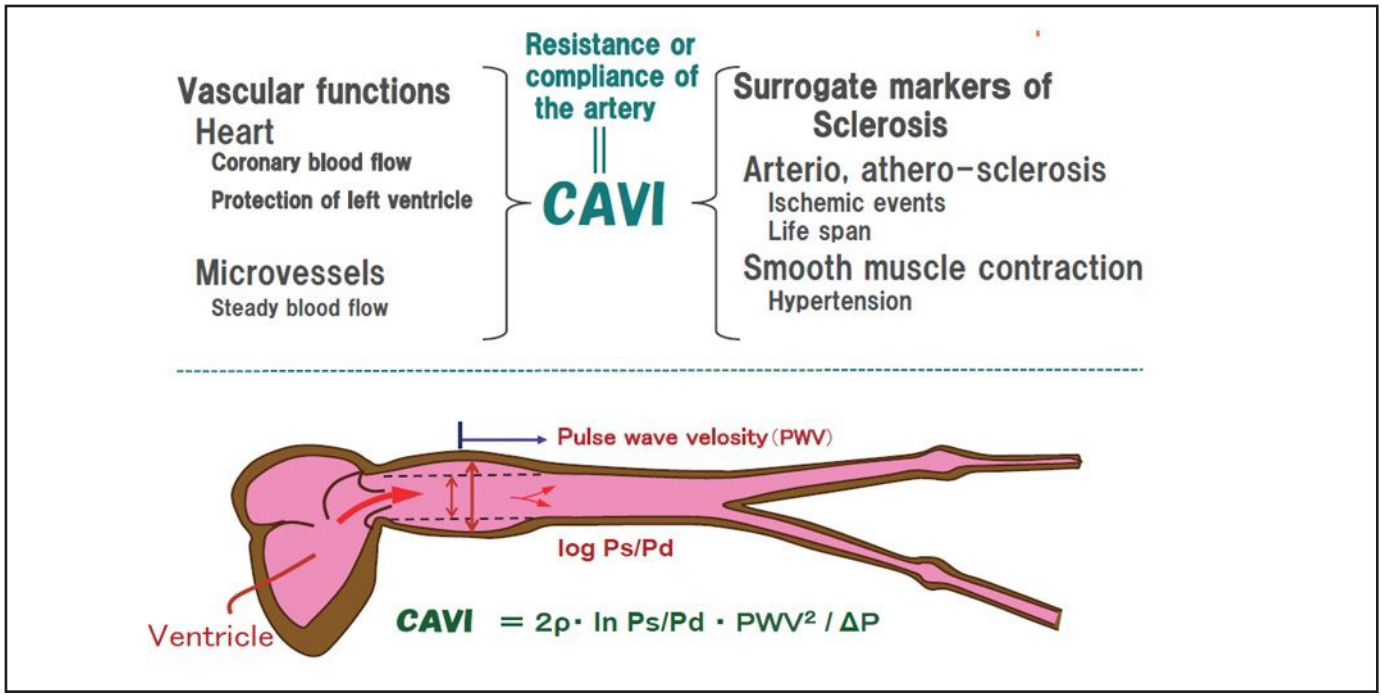

Figure 5. Roles of CAVI in resistance or compliance of the artery as a surrogate marker of arteriosclerosis and vascular function. CAVI reflects the resistance or compliance of the artery; therefore, CAVI indicates the degree of sclerosis of the artery and also reflects vascular function, which keeps the heart functioning and maintains peripheral steady blood flow as a Windkessel. The former is a surrogate marker of arteriosclerosis and smooth muscle contraction. The latter might protect or improve left ventricular function and maintain steady blood flow. To confirm this, many more basic and clinical studies are required.[26]

The correlation between CAVI and the cardiac functions

In people with cardiovascular risk factors, new research reveals a connection between arterial stiffness and left ventricular diastolic performance.[26] Researchers found a positive correlation between CAVI and both the peak E/A and the deceleration time of early diastolic transmitral flow velocity.

They also found that CAVI correlated positively with velocities in the trans-mitral region at the apex of the early diastolic phase. They also found a correlation between CAVI and a decrease in transmitral flow velocity during early diastole (E-DT). Patients with poor left ventricular (LV) diastolic function had a significantly higher incidence of CAVI compared to those with normal LV diastolic function

Sakane et al. found that even in patients with maintained systolic function, an increase in CAVI is independently linked with LV diastolic impairment. Tissue Doppler echocardiography was utilized in another investigation to measure the early diastolic peak mitral annular velocity (E') to assess LV diastolic function. CAVI was shown to have a negative correlation with E' ($r = -0.518$, $p < 0.001$). Aortic annular velocity, measured by tissue Doppler echocardiography, was also considered as a potential marker of arterial stiffness.[27] These findings point to a relationship between the malleability of the blood arteries and the diastolic chamber's function in the heart's left ventricle, indicating a link between the two. In other words, having a high CAVI of the elastic and muscular artery wall may worsen the diastolic function of the left ventricle. As a direct result of hiring, CAVI may be required to contemplate diagnostic and therapeutic operations to preserve the heart's health.

Future direction

Coronary artery disease, cerebrovascular disease, carotid artery disease, and chronic kidney disease all have significant CAVI. There is some clinical evidence that CAVI can serve as a surrogate indicator for other forms of arteriosclerosis. Numerous risk factors, such as high blood pressure, high blood sugar levels, abnormal lipid profiles, and smoking, all have detrimental effects on arterial walls. Some of the harmful effects include endothelial dysfunction, oxidative stress, and inflammatory response activation. Both organic sclerosing and smooth muscle cell contraction can be sped up with different techniques. A high CAVI score indicates this. CAVI has the potential to be used in the future to assess the prevalence and severity of atherosclerosis in populations from various geographic locations and to discover risk factors associated with this disease. In addition, CAVI may serve as a useful physiological surrogate marker of lifestyle changes like giving up tobacco, lowering blood cholesterol levels, and keeping glucose levels stable. Thus, CAVI's potential to aid in the avoidance of atherosclerotic disorders can be anticipated. Clinical applications of CAVI include the estimation of the risk of cardiovascular events in patients with cardiovascular disease risk factors.

4. Declarations

4.1. Ethics Approval and Consent to participate
This study was approved by local Institutional Review Board, and all participants have provided written informed consent prior to involvement in the study.

4.2. Consent for publication
Not applicable.

4.3. Availability of data and materials
Data used in our study were presented in the main text.

4.4. Competing interests
Not applicable.

4.5. Funding source
Not applicable.

4.5. Funding source
Not applicable.

4.6. Authors contributions
Idea/concept: AG, CT. Design: AG, CT. Control/supervision: CT, MSR, NK. Literature search: AG, CT. Study quality assessment: CT, MSR, NK. Data extraction: AG, CT. Statistical analysis: AG, CT. Results interpretation: AG, CT. Critical review/discussion: CT, MSR, NK. Writing the article: AG, CT. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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