ARTERIAL STIFFNESS AND CORONARY ARTERY DISEASE

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ABSTRACT

Although there have been marked improvements in both diagnostic and therapeutic interventions over several decades, coronary artery disease (CAD) remains the leading cause of death worldwide. Intensive modification of classic risk factors such as hypertension, diabetes mellitus, dyslipidaemia, and cigarette smoking has significantly reduced the development of CAD. The high prevalence of residual cardiovascular events does however require improvements in identification and risk stratification strategies. In this context, arterial stiffness, which reflects arterial ageing, damage, and arteriosclerosis has emerged as an important risk factor for cardiovascular disease. The measurements of arterial stiffness are easy to make using several non-invasive methods such as pulse wave velocity. The clinical utility of the measures has been validated in many prior studies. Recent evidence has suggested that the measures of arterial stiffness are correlated with the presence and extent of CAD. More importantly, increased arterial stiffness is an independent predictor of CAD-related morbidity and mortality beyond classic risk factors. Considering its non-invasiveness, simplicity, and reliability, arterial stiffness could serve as a useful marker of CAD and help identify high-risk patients who may benefit from more aggressive management.

Keywords: Arterial stiffness, coronary artery disease (CAD), pulse wave velocity (PWV), non-invasive.

INTRODUCTION

Coronary artery disease (CAD) remains one of the leading causes of death and disability worldwide. The underlying pathophysiology of most CAD is atherosclerosis, a complex process governed by multiple factors. Classic risk factors such as hypertension, diabetes mellitus, dyslipidaemia, cigarette smoking, and obesity, have been well-documented as significant contributors to the development of atherosclerosis and CAD. In fact, aggressive treatment of these factors has significantly reduced the risk of future cardiovascular events. By the strength of evidence supporting their role in the pathogenesis of CAD, these classic risk factors have usually been a primary therapeutic target in patients with known or suspected CAD. Indeed, with many efforts focussed on these classic risk factors, there has been significant progress and improvement in prevention, diagnosis, and therapy however, the burden of CAD is still substantial. It is now generally accepted that classic risk factors cannot fully explain the increasing burden of CAD and that more than 50% of patients with CAD do not have any of these risk factors. Although several risk prediction models using a combination of individual classic risk factors have been suggested, they have a low diagnostic yield in the prediction of future cardiovascular events, depending on population and ethnicity. These findings suggest that other factors are clearly involved and raise the need for another tool to improve prevention and management of CAD beyond classic risk factors.

Arterial stiffness is accelerated by ageing, arterial damage, and arteriosclerosis. Arterial stiffness is an important reflection of degeneration of the arterial wall as a consequence of repetitive cyclic stress. From the pathologic point of view, arterial stiffening is characterised by the loss of elastic fibres and increases collagen deposition and cross-
linking within arterial walls. Emerging evidence suggests that arterial stiffness is one of the earliest detectable signs of functional and structural changes in the arterial wall. The measurement of arterial stiffness could be advantageous in early detection and prevention of vascular disease. More importantly, arterial stiffness can predict adverse cardiovascular events beyond classic risk factors, in patient groups with different diseases and in the general population. Recent studies have reported that arterial stiffness is associated with the presence and extent of CAD and cardiovascular outcomes. Special attention has been focussed on the measurement of arterial stiffness as a reliable and useful non-invasive tool to improve detection and risk stratification of patients with CAD. The present review summarises how to assess arterial stiffness and provides clinical evidence for the detection of CAD and the prediction of CAD-related outcomes based on arterial stiffness.

**Measurements of Arterial Stiffness**

**Pulse Wave Velocity**

Arterial stiffness can be assessed using several non-invasive and invasive methods. Among them, pulse wave velocity (PWV) is the most widely and frequently used tool to quantify arterial stiffness, because its measurement is non-invasive, simple, and reproducible. Of note, there has been much data indicating the clinical values of PWV in the prediction of cardiovascular events. PWV is the measure of the speed of the arterial pressure waves travelling along the aorta and large arteries. Therefore, PWV can be determined by dividing distance with transit time of pressure waveforms at the two recording sites. PWV is inversely correlated with arterial compliance; it is faster in a more stiffened artery. According to arteries measured, there are several types of PWV. Carotid-femoral PWV (cfPWV), which is made by recording pressure waveforms at the carotid artery followed by the femoral artery, is most validated, and has been considered a reference standard technique to assess arterial stiffness. However, the wide use of cfPWV in clinical practice is hindered by the need for technical skills during the carotid and femoral pulse acquisition. In addition to this, cfPWV measurement causes some discomfort to subjects and is time-consuming. To overcome these drawbacks of cfPWV, the newly developed and simpler measurement, brachial-ankle PWV (baPWV), has been used in research and clinical fields. The baPWV measurement does not require technical expertise and it can be done by simply wrapping blood pressure cuffs around the four extremities. Therefore, the measurement of baPWV is simple and timesaving. Furthermore, baPWV is well-correlated with cfPWV and invasive parameters, and the diagnostic and prognostic values of baPWV have been proven in many clinical studies and in a meta-analysis. There has been some criticism that baPWV cannot reflect pure central arterial stiffness because it includes a much more peripheral component. However, considering its simplicity and clinical values, baPWV is expected to be more widely used in clinical practice, especially for the purpose of mass screening.

**Pulse Pressure and Augmentation Index**

Pulse pressure (PP) is defined as the difference between systolic blood pressure and diastolic blood pressure. Augmentation index (Alx) is defined as augmented pressure divided by PP. Elevated PP and Alx are regarded as a manifestation of increased arterial stiffness, although Alx is a more complex measure of wave forms propagated during systole with the reflected waves from peripheral arteries. In a stiffened artery, a reflected wave from the periphery returns faster and arrives earlier at the central aorta during myocardial systole which increases PP and the pressure at the late systolic phase (equalling augmentation pressure). PP and Alx are closely related to target organ damage, and they are important predictors of cardiovascular events. However, it should be considered that PP and Alx are potentially confounded by factors related to cardiac function such as heart rate and stroke volume. In addition, Alx has been found to have limited value as a marker of arterial stiffness in older individuals, particularly after 60 years of age.

**Central Aortic Pressure**

An invasively measured aortic pulsatile component is considered the gold standard for assessing central arterial stiffness. Anatomically, the central aorta is closer to the brain, heart, and kidneys, therefore the impact of aortic pulsatile stress is more pronounced to these vital organs than that of peripheral artery. It has been reported that the stiffness of the central elastic artery is more strongly correlated with cardiovascular and all-cause mortality than that of the peripheral artery. Indeed, intra-aortic haemodynamic parameters, as recorded
during invasive coronary angiography (ICA), have been shown to be a valuable measure of aortic stiffness.\textsuperscript{37-40} Therefore, measurement of central aortic pressure has been emphasised.\textsuperscript{37} However, difficulty in performing this invasive examination limits its use in clinical practice. Although current non-invasive techniques can estimate central pressure by analysing radial or carotid pulse waves using a mathematical relationship to peripheral pressure,\textsuperscript{41,42} the possibility of calculation error is not negligible.\textsuperscript{43}

**Other Modalities**

Magnetic resonance imaging and echocardiography can assess arterial stiffness of deep large arteries such as the aorta.\textsuperscript{12,44} However, these methods are expensive, time-consuming, and technically difficult. Therefore, they are impractical for wide clinical use.

**ASSOCIATION BETWEEN ARTERIAL STIFFNESS AND THE PRESENCE AND EXTENT OF CORONARY ARTERY DISEASE**

Prior studies have documented a direct relationship between arterial stiffness and the presence or extent of CAD. Recently, our study group investigated 470 patients who underwent both baPWV measurement and coronary computed tomography angiography (CCTA), and showed good correlations between baPWV and the CCTA parameters of CAD extent.\textsuperscript{25} Xiong et al.\textsuperscript{22} also used baPWV as a measure of arterial stiffness in 321 patients and reported an independent association between baPWV and CAD severity as assessed by ICA and SYNTAX (SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery) score. Alarhabi et al.\textsuperscript{19} demonstrated in a study of 92 patients undergoing ICA, that arterial stiffness measured through cfPWV is independently associated with multivessel disease. In accordance with these findings, Lim et al.\textsuperscript{21} performed a prospective study of 326 consecutive patients undergoing ICA and showed that cfPWV was significantly associated with the severity of CAD, expressed as one, two, or three-vessel disease. Invasive measurement of aortic pressure is feasible and parameters of central haemodynamics have provided useful information in patients undergoing ICA. A study by Nakayama et al.\textsuperscript{39} has indicated the usefulness of invasively measured pulsatility index of the ascending aorta as a predictor of in-stent restenosis after percutaneous transluminal coronary angioplasty. Philippe et al.\textsuperscript{23} invasively measured aortic PP in 99 patients undergoing ICA and showed that aortic PP is independently correlated with the CAD extent. Jankowski et al.\textsuperscript{40} measured aortic pulsatile components in 423 consecutive patients undergoing ICA and also demonstrated that aortic PP, fractional PP, and pulsatility index are risk factors for three-vessel disease.

**ARTERIAL STIFFNESS AND CORONARY ARTERY DISEASE-RELATED OUTCOMES**

Recent longitudinal studies have suggested that arterial stiffness is an important predictor for CAD-related morbidity and mortality in patients with different diseases as well as in the general population. In those studies, the prognostic value of arterial stiffness persists even after controlling for potential confounding effects by classic risk factors such as age, hypertension, diabetes mellitus, and dyslipidaemia. Boutouyrie et al.\textsuperscript{14} measured cfPWV in 1,045 hypertensive subjects and showed that cfPWV is significantly associated with the occurrence of coronary events during a mean follow-up of 5.7 years even after adjustment for the Framingham Risk Score or classic risk factors. Blacher et al.\textsuperscript{13} investigated 241 patients with end-stage renal disease undergoing haemodialysis, and reported that increased aortic stiffness measured by aortic PWV is a strong independent predictor for all-cause and cardiovascular mortality. Another study of 2,231 patients with acute myocardial infarction accompanied by left ventricular (LV) dysfunction over a 42-month follow-up period, documented that there is a close link between PP and subsequent cardiovascular events.\textsuperscript{16} Kim et al.\textsuperscript{15} studied 1,765 patients with acute ischaemic stroke during a mean follow-up period of 3.3 years and showed an independent association between baPWV and all-cause and vascular death. In a recently published article, with 2 years of clinical follow-up in 1,126 subjects >80 years old, it has been found that increases in carotid and brachial PP amplification is associated with reduction of total mortality and cardiovascular events.\textsuperscript{18} A more recent study performed by our study group, involving 350 subjects undergoing myocardial perfusion imaging, showed that baPWV provided additional prognostic value to classic risk factors and myocardial perfusion imaging in predicting cardiovascular events during the 441 days of...
Accordingly, the clinical importance of arterial increased arterial stiffness and CAD is incidental. It can be postulated that the association between and progression of CAD. For these reasons, on both arterial stiffening and the development dyslipidaemia, and smoking. including ageing, hypertension, diabetes mellitus, are considered to share many risk factors, with age. Therefore, arterial stiffening and CAD are considered to share many risk factors, including ageing, hypertension, diabetes mellitus, dyslipidaemia, and smoking. These risk factors for atherosclerosis may have a worse impact on both arterial stiffening and the development and progression of CAD. For these reasons, it can be postulated that the association between increased arterial stiffness and CAD is incidental. Accordingly, the clinical importance of arterial stiffness is frequently underestimated in patients with CAD because arterial stiffness changes with age. However, considering that the prognostic value of arterial stiffness does not change even after adjustment for age and other classic risk factors, it is evident that arterial stiffness is an independent predictor for future atherosclerotic cardiovascular events beyond classic risk factors. Finally, recent evidence has shown that inflammation can affect arterial stiffness. Given that chronic systemic inflammation is also closely related to cardiovascular risk, the association between increased arterial stiffness and CAD may be at least partially mediated by inflammation.

POSSIBLE MECHANISMS UNDERLYING THE LINK BETWEEN ARTERIAL STIFFNESS AND CORONARY ARTERY DISEASE

Precise mechanisms underlying the link between arterial stiffness and CAD have not been clearly established. Multiple complicated factors may be involved and interact with each other to a greater or lesser extent. There are however several accepted explanations of the association between increased arterial stiffness and CAD. First, increased arterial stiffness is the main cause of premature return of reflected waves in the late systole which is associated with increased PP and the afterload of LV. Increased LV load subsequently increases in LV mass and oxygen demand. In addition to increased load on the LV, increased arterial stiffness decreases diastolic pressure which is closely linked to impaired coronary perfusion and myocardial ischaemia. These unfavourable pathophysiological changes may lead to the progression of coronary atherosclerosis. Considering the fact that PP increases significantly only after the fifth decade, it is a natural hypothesis that the role of arterial stiffness in the evaluation of CAD is more valuable, especially in elderly people. Secondly, arterial stiffness itself reflects the burden of underlying systemic atherosclerosis and the presence of end-organ damage, both of which are associated with CAD and CAD related outcomes. Thirdly, arterial stiffness changes mainly with age. The prevalence of traditional risk factors for CAD is also increased with age. Therefore, arterial stiffening and CAD are considered to share many risk factors, including ageing, hypertension, diabetes mellitus, dyslipidaemia, and smoking. These risk factors for atherosclerosis may have a worse impact on both arterial stiffening and the development and progression of CAD. For these reasons, it can be postulated that the association between increased arterial stiffness and CAD is incidental. Accordingly, the clinical importance of arterial stiffening is frequently underestimated in patients with CAD because arterial stiffness changes with age. However, considering that the prognostic value of arterial stiffness does not change even after adjustment for age and other classic risk factors, it is evident that arterial stiffness is an independent predictor for future atherosclerotic cardiovascular events beyond classic risk factors. Finally, recent evidence has shown that inflammation can affect arterial stiffness. Given that chronic systemic inflammation is also closely related to cardiovascular risk, the association between increased arterial stiffness and CAD may be at least partially mediated by inflammation.

MANAGEMENT STRATEGY REDUCING ARTERIAL STIFFNESS

Several prior studies have shown that some pharmacological and non-pharmacological interventions may improve arterial stiffness. Although the degree of arterial stiffness reduction is different according to drug classes, doses, and treatment duration angiotensin converting enzyme inhibitor has been shown to be the most effective drug in reducing both peripheral and central arterial stiffness in long-term treatment. Recent studies have also reported that non-pharmacological interventions, including aerobic exercise training and continuous positive airway pressure in patients with sleep apnoea, improve arterial stiffness. However, whether the reduction of arterial stiffness by these pharmacological and non-pharmacological interventions can lead to a favourable clinical outcome remains to be determined in further studies.

CLINICAL IMPLICATIONS

Although there has been a marked improvement in both diagnostic and therapeutic interventions over several decades, CAD remains the leading cause of death worldwide. Intensive modification of classic risk factors has significantly reduced the development of CAD, however the high residual prevalence of cardiovascular events requires further improvements in identification and risk stratification strategies. Recent cardiovascular risk scoring strategies are not sufficient to identify patients at a high risk of CAD. Accurate assessment of CAD and its complications remains problematic for clinicians. Arterial stiffening is one of the earliest manifestations of vascular damage and atherosclerosis. However, it is difficult to recognise
such subclinical changes in routine medical practice. Simple and non-invasive measurement of arterial stiffness, such as PWV, can detect functional and structural changes in arterial wall even in early stages. As mentioned above, many cross-sectional and longitudinal studies have confirmed that arterial stiffness is closely related to CAD and CAD-related outcomes. Therefore, arterial stiffness measurement could serve as an important tool to identify patients at a high risk of CAD. Improved ability to identify such patients would lead to better risk stratification and more effective preventive therapy. Additionally, arterial stiffness can be a target or monitoring tool for therapeutic intervention. Appropriate medications reducing arterial stiffness may offer potential advantages in the management of patients at a high risk of CAD.

CONCLUSIONS

The measures of arterial stiffness are well-correlated with the presence and extent of CAD. More importantly, arterial stiffness is an independent predictor for CAD-related mortality and morbidity in various populations which are beyond prediction, based on classic risk factors. Considering its non-invasiveness, simplicity, and reliability, arterial stiffness could serve as a useful marker of CAD and help detect high-risk patients who may benefit from more aggressive management.

REFERENCES

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