

State of the Art Review



Pulsatile Hemodynamics and Coronary Artery Disease



Received: Jun 28, 2021

Revised: Jul 22, 2021

Accepted: Jul 26, 2021

Correspondence to

Thomas Weber, MD


Department of Cardiology, Klinikum Wels-Grieskirchen GmbH, Grieskirchnerstrasse 42, 4600 Wels, Austria.


E-mail: thomas.weber3@liwest.at

Copyright © 2021. The Korean Society of Cardiology

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<https://creativecommons.org/licenses/by-nc/4.0>) which permits unrestricted noncommercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ORCID iDs

Hack-Lyoungh Kim 
<https://orcid.org/0000-0002-6703-1472>

Thomas Weber 
<https://orcid.org/0000-0003-0617-0417>

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Conflict of Interest

The authors have no financial conflict of interest.

Data Sharing Statement

Data sharing is not applicable as no datasets were created and/or analyzed for this study.

Hack-Lyoungh Kim , MD¹, and Thomas Weber , MD²

¹Division of Cardiology, Department of Internal Medicine, Seoul Metropolitan Government-Seoul National University Boramae Medical Center, Seoul National University College of Medicine, Seoul, Korea

²Department of Cardiology, Klinikum Wels-Grieskirchen GmbH, Wels, Austria

AUTHOR'S SUMMARY

The initiation and progression of coronary atherosclerosis, from subclinical plaque to plaque rupture and coronary events, and even to heart failure, seems to be driven to a large amount by hemodynamic factors. These factors, recently termed pulsatile hemodynamics, include central pressures, arterial stiffness (pulse wave velocity), and wave reflections, and can be measured invasively and non-invasively, even in clinical routine. The authors provide an overview of recent evidence on the interplay between these hemodynamic factors and coronary artery disease at all stages.

ABSTRACT

Coronary artery disease (CAD) is the leading cause of human death and has a high prevalence throughout the world. Therefore, it is important to detect CAD early and to apply individualized therapy according to the patients' risk. There is an increasing interest in pulsatile arterial hemodynamics in the cardiovascular area. Widely used measurements of arterial pulsatile hemodynamics include pulse pressure, pulse wave velocity and augmentation index. Here, we will review underlying pathophysiology linking the association of arterial pulsatile hemodynamics with CAD, and the usefulness of the measurements of pulsatile hemodynamics in the prediction of future cardiovascular events of CAD patients. Clinical and therapeutic implications will be also addressed.

Keywords: Arterial stiffness; Pulse wave velocity; Wave reflections; Coronary artery disease; Pulsatile hemodynamics

INTRODUCTION

Coronary artery disease (CAD) is a leading cause of morbidity and mortality worldwide.¹⁾ For early diagnosis and individualized therapy, it is of paramount importance to understand the mechanism of CAD development as well as the factors determining the prognosis of CAD patients. Over the past century, many risk factors associated with CAD development

Author Contributions

Conceptualization: Weber T; Writing - original draft: Kim HL; Writing - review & editing: Weber T.

have been identified and utilized for prevention and treatment.²⁾ However, the incidence of CAD is still high and the prognosis is poor.¹⁾ Given that substantial portion of individuals without traditional cardiovascular risk factors suffering from cardiovascular events,³⁾ more accurate risk predictions are needed. As the causes of initiation and progression of coronary atherosclerosis are multifactorial, there is still a room for improvement in the prognosis of CAD patients by identifying new modifiable risk factors.

Many epidemiologic studies have shown a close association between the level of blood pressure (BP) and cardiovascular events and mortality.⁴⁾ BP reduction is very effective way to reduced cardiovascular risk.⁵⁾⁶⁾ Specific levels of systolic and diastolic BPs have been used in the diagnosis and treatment of hypertension and to define cardiovascular risk.⁷⁾⁸⁾ However, BP is a periodic phenomenon that can be divided into 2 components: steady (mean arterial pressure) and pulsatile (pulse pressure [PP]). The steady component is determined by cardiac output and small resistance arterial function. The pulsatile component is mainly determined by left ventricular (LV) ejection, large artery compliance (the opposite of stiffness) and the speed and the intensity of the reflected waves returning toward the heart from arterial bifurcation points (due to impedance changes).⁹⁾ The large conduit arteries buffer the pulsating blood ejection generated by LV contraction by intermittent expansion according to the cardiac cycle. In the LV diastolic phase, when there is no blood ejection from the heart, the arteries maintain perfusion pressure to major organs and periphery by wall contraction through vascular recoil.¹⁰⁾ Many studies have shown that measurements of these pulsatile components of BP such as PP, augmentation index (AIx) and pulse wave velocity (PWV) are associated with the development of future cardiovascular events independent of BP and other risk factors.¹¹⁻²⁰⁾ Therefore, it is important to understand that BP is composed of pulsatile component as well as steady component, which may offer better insight into pathophysiology of the development of target organ damage and cardiovascular risk. Moreover, this in-depth understanding might help to evaluate and monitor patients' response to treatment, as well as to develop effective treatment strategies.

Here, we will review the role of arterial pulsatile hemodynamics in CAD, focused on the association between pulsatile hemodynamics and CAD, and prognostic value as well as clinical implications of pulsatile hemodynamics in CAD patients.

MEASUREMENT OF ARTERIAL PULSATILE HEMODYNAMICS

There are several non-invasive measures that allow assessment of arterial pulsatile hemodynamics.

Pulse pressure

PP is the result of a combination of the episodic nature of LV contraction and the elastic properties of the large arteries.²¹⁾ Brachial PP (brPP) is the simplest and most widely used indicator of arterial pulsatile hemodynamics. brPP is defined as the pressure difference between systolic and diastolic BP of at the site of brachial artery. Many studies have shown that brPP is associated with target organ damage and cardiovascular outcome.¹¹⁻¹⁵⁾ However, it should be noted that brPP does not adequately reflect central aortic PP (aPP) or aortic stiffness because there is PP amplification between central and peripheral arteries.²²⁾ Central aPP can be obtained using non-invasive methods by analyzing the waveforms of the brachial or radial arteries.²²⁾ Since central aorta is located closer to the heart, brain, and kidney than

brachial artery, aPP is more influential to these vital organs and may have a higher degree of clinical relevance than brPP.²²⁻²⁴⁾ In addition to arterial stiffness, PP is greatly affected by factors related to cardiac function such as stroke volume, heart rate and pattern of LV ejection.²¹⁾ Therefore, the effects of these factors should be considered and controlled during analysis. Moreover, PP is not a direct measure of arterial hemodynamics but just a mathematical difference between systolic and diastolic BP.

Wave reflections

Normally, when the pulse wave from the heart passes through the elastic arteries and reaches the muscular artery, a smaller reflected wave that goes backwards to the heart is generated, mainly at branch points or sites of impedance mismatch.²¹⁾ In a compliant arterial system, effectively timed wave reflections (i.e. with a maximum during diastole) enhance coronary perfusion, which mainly occurs during diastole.⁹⁾ In a stiffened arterial system, the velocity of reflected wave increases, thus reflected waves merge earlier with forward waves, leading to increase (augmentation) in late systolic BP and PP, and to a higher workload on the LV.²⁵⁾ Standard integrated measure of wave reflection is AIx, which is defined as the amount of pressure augmentation relative to PP. The most widely used method for evaluating central AIx is to first obtain a waveform by performing applanation tonometry on the radial artery, and then calculate the waveform and AIx of central aorta using a generalized transfer function (GTF).²³⁾²⁶⁾ The central AIx estimated by the GTF method is very well correlated with the values measured by invasive catheterization.²⁷⁾²⁸⁾ Many studies have shown that increased central AIx is associated with atherosclerotic burden and cardiovascular risk.¹⁶⁾¹⁷⁾ However, while AIx is a sensitive marker of arterial aging in young individuals, AIx may underestimate the degree of arterial stiffness and cardiovascular risk in older people, likely associated with reduced impedance mismatch.²⁹⁾³⁰⁾ Since several clinical factors such as age, height and heart rate affect AIx, it is important to consider the effects of these confounding variables when analyzing AIx-related data.³¹⁾ Given that AIx is highly affected by heart rate, it is sometimes used after calibrating to 75 heart rate per minute (AIx@75).³²⁻³⁴⁾ Also, LV function has a major influence of central waveforms and, thus, on AIx.³⁵⁾ For certain types of pulse waveforms, in particular in young healthy individuals, AIx can be calculated as negative.³⁶⁾

Pulse wave velocity

The pressure generated by the LV contraction is transmitted towards the periphery not only with the bloodstream but also in the arterial wall. Since the degree of stiffening of the arterial wall and the speed of the pulse wave traveling along the arterial wall are proportional, the pulse wave transmission speed (= PWV) is an important measure of arterial stiffness.³⁷⁾ PWV is defined as the distance between 2 specific arterial points divided by the time difference of the pulse wave passing through these 2 distances. The higher the PWV value, the greater the arterial stiffness. Of note, higher PWV is a risk factor for future cardiovascular events and all-cause mortality independent of traditional risk factors.¹⁸⁾¹⁹⁾ Because it is non-invasive, relatively easily quantitated, and well supported by a wealth of outcome data, PWV is considered to be the most useful clinical marker of arterial stiffness.³⁷⁾³⁸⁾ There are various PWVs depending on the measurement locations, but among them, aortic PWV (aPWV), carotid-femoral PWV (cfPWV) and brachial-ankle PWV (baPWV) are the most widely used. As cfPWV is the direct measures of arterial stiffness of central elastic arteries, it is considered as gold standard for the noninvasive measure of arterial stiffness.³⁹⁾ Compared to cfPWV, more recently developed baPWV is more simple to measure by just wrapping BP cuffs in both upper arms and legs, and is validated in many clinical studies.¹⁸⁾⁴⁰⁾⁴¹⁾ Thus, baPWV may be useful in mass screening, and it has been more commonly used in Asian countries in research and

clinical fields.⁴¹⁾ Main limitation of PWV is that it is highly affected by various clinical factors, mainly by age and BP.³⁹⁾⁴²⁾ When BP rises, the tension of the vessel wall increases, and the pulse wave transmission speed increases as if arterial stiffness increases.⁴³⁾ When interpreting PWV, the effect of these factors should be considered. In addition, for the accuracy of the PWV value, it is necessary to measure the distance between 2 points in the blood vessel. However, it is generally difficult to accurately measure the distance between these 2 points of vessel wall, so it is estimated by measuring the distance between 2 points on the surface of the human body, or by calculating with a predetermined equation.³⁷⁾⁴¹⁾

Invasive measurements

Direct measurement of pressure by inserting an intraarterial catheter is the most accurate method assessing arterial pulsatile hemodynamics. However, its use is hindered due to invasiveness and cost. Therefore, these measurements are primarily limited to patients undergoing invasive coronary angiography (CAG).⁴⁴⁻⁴⁶⁾ Although the invasive measurement can be performed in limited clinical conditions, information on central arterial hemodynamics measured invasively can be used for validation of non-invasively measured values.⁴⁶⁻⁴⁸⁾ It also provides diagnostic and prognostic value of patients with undergoing invasive CAG.⁴⁴⁾⁴⁹⁻⁵³⁾ Invasive hemodynamic measurement may be feasible in patients undergoing invasive CAG because it can be performed during the procedure, so there is no additional cost or risk, and the measurement time is short.

PATHOPHYSIOLOGY

In a recent animal model in hypercholesteremic, transgenic minipigs, the role of elevated BP in facilitating the accumulation of low-density lipoprotein-cholesterol (LDL-C) and plaque formation in coronary arteries was nicely illustrated.⁵⁴⁾ A closer look unveils that the cyclic strain of the arterial wall is mainly determined by the cyclic (pulsatile) change of BP,⁵⁵⁾ playing an important role on every stage of the development of atherosclerosis.⁵⁵⁾ For instance, at an early stage, elevated PP was the driver of the activation of C-reactive protein and of the influx of lipids into the arterial intima, leading to oxidized LDL-C.⁵⁶⁾ Later on, through various mechanisms, cyclic stretch promotes plaque progression,⁵⁵⁾⁵⁷⁾ weakening of the fibrous cap and plaque rupture.⁵⁸⁾ These findings may explain the consistent association between pulsatile hemodynamics and the presence and severity of coronary atherosclerosis outlined below. **Figure 1** shows that pulsatile hemodynamics are deeply involved in development and progression of coronary atherosclerosis, plaque rupture, and subsequent myocardial infarction and, ultimately, heart failure.

When clinicians estimate the severity of CAD, the anatomical extent of a coronary stenosis is typically considered. Based on animal experiments, at diameter stenosis of 50%, maximum coronary flow (coronary flow reserve [CFR]) begins to fall, and at 85% diameter stenosis resting coronary flow begins to fall.⁵⁹⁾ Recent advances take the functional severity of a coronary stenosis into account, using fractional flow reserve or related measurements, which are based on pressure measurements proximal (in the aorta or at a coronary ostium) and distal to a coronary stenosis (as a measure of relative CFR), the latter with dedicated intracoronary wires.⁶⁰⁾ These methods are now recommended by clinical practice guidelines from major Cardiology societies⁶¹⁾ and not the focus of this review. We rather address the impact of pulsatile hemodynamics of large arteries on coronary blood flow. A prerequisite of correct understanding of the physiology is the fact that—in contrast to other vascular beds in the body—perfusion

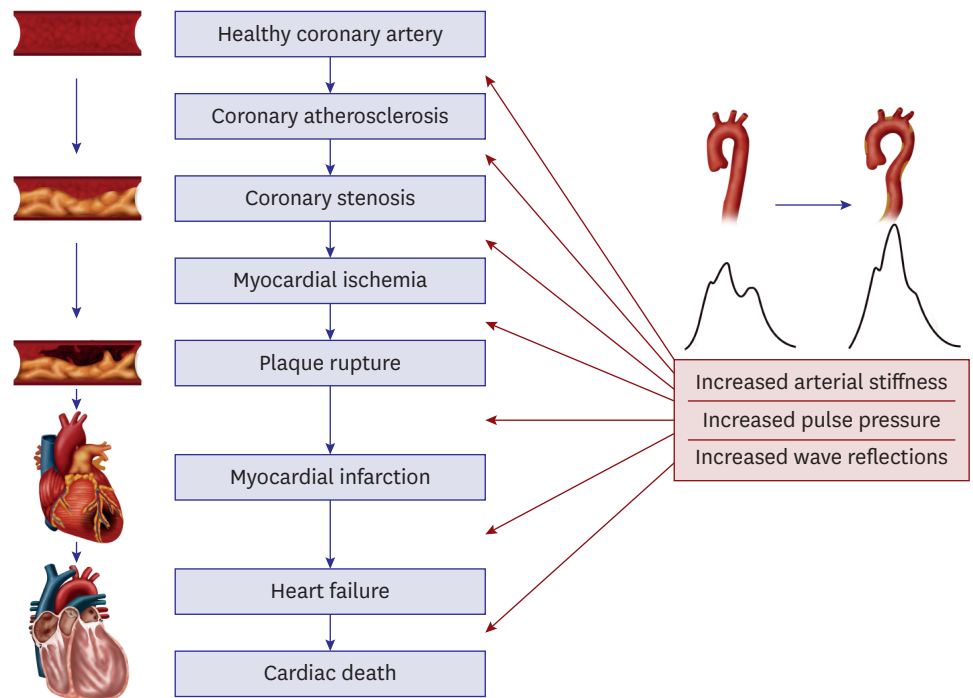


Figure 1. Pulsatile hemodynamics may promote the progression of coronary artery disease at every step.

of the myocardium (in particular the subendocardium) occurs predominantly during diastole, because during systole the contracting myocardium interrupts flow in intramyocardial arteries.⁶² The ratio between myocardial oxygen demand (tension time index in systole) and myocardial oxygen supply (diastolic pressure time index) can be approximated by the area under the aortic pressure waveforms in systole and diastole, respectively.⁶³ This ratio is well balanced in young, healthy individuals. With aging, arterial stiffness increases, shifting reflected waves towards systole, thus increasing systolic and decreasing diastolic BP, and distorting the above mentioned ratio to a tendency towards ischemia.⁶² The interplay between coronary stenosis and aortic stiffening was nicely shown in an animal experiment: in 10 mongrel dogs, a coronary stenosis was produced in the circumflex artery with a metal constrictor, while the left anterior descending coronary (LAD) artery was left healthy. This stenosis was not sufficient to induce ischemia at rest and with pacing, as long as the aorta remained elastic. When the aorta was stiffened with banding, however, the combination of exercise (pacing), stenosis and a stiffened aorta led to ischemia in the territory of the circumflex artery,⁶⁴ but not in the LAD. In humans, coronary blood flow was measured invasively following successful percutaneous coronary intervention (PCI) in 18 patients.⁶⁵ Resting, but more hyperemic coronary blood flow was strongly and inversely related to aPWV and central PP. Moreover, the gain in coronary blood flow following PCI was substantial in patients with a compliant aorta, but much less so in patients with a stiff aorta. These results were confirmed by non-invasive studies, showing inverse relationships between cfPWV,⁶⁶ baPWV,^{67/68} and AIx⁶⁸ and CFR in patients without severe coronary stenosis. As a clinical consequence, patients with established CAD and a high amount of wave reflections reach the ischemic threshold earlier, as proven in a study of 96 patients with CAD, undergoing treadmill exercise tests.⁶⁹

Furthermore, increased arterial stiffness and increased wave reflections may lead to LV hypertrophy, prolongation of mechanical systole⁷⁰ (with consecutive reduction of diastolic time)

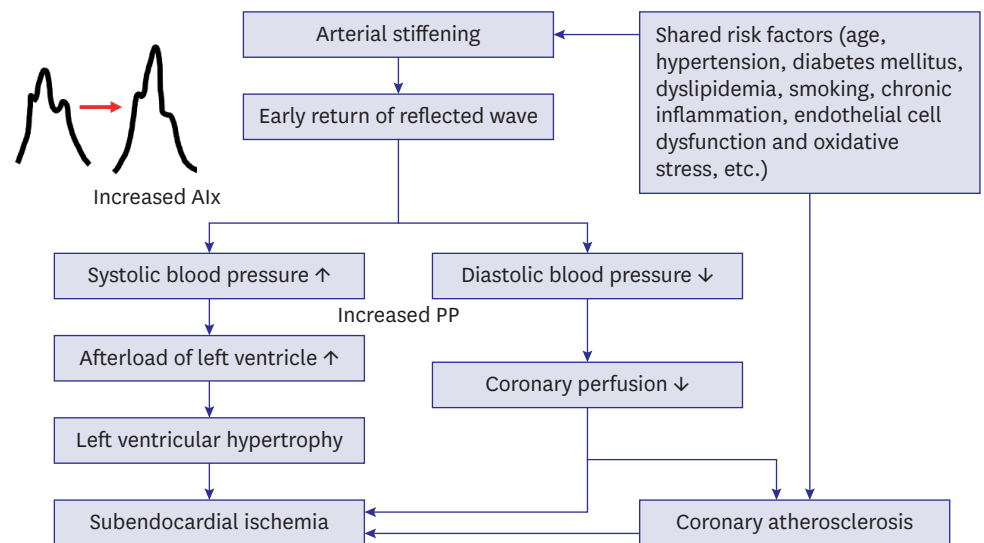


Figure 2. Mechanisms explaining the association between arterial stiffening and coronary atherosclerosis. AIx = augmentation index; PP = pulse pressure.

and impairment of diastolic function¹⁰⁾⁷¹⁾ (with increased LV diastolic pressures⁷²⁾, all of them further compromising myocardial perfusion and predisposing to (subendocardial) ischemia.

Another mechanism for the relationship between pulsatile hemodynamics/arterial stiffness and coronary atherosclerosis is that both share common risk factors, most prominent aging, but also including traditional cardiovascular risk factors, endothelial dysfunction, chronic inflammation and oxidative stress.³⁹⁾⁴¹⁾ A summary of the association of arterial stiffening and increased wave reflection with CAD is shown in **Figure 2**.

ASSOCIATION OF PULSATILE HEMODYNAMICS WITH THE PRESENCE AND EXTENT OF CORONARY ATHEROSCLEROSIS

Many clinical studies have shown that measures of arterial stiffness and wave reflections are associated with CAD (**Table 1**).⁵⁰⁾⁵²⁾⁵³⁾⁷³⁻⁹⁵⁾ Most studies were conducted with patients undergoing invasive CAG, and CAD was assessed by the analysis of invasive CAG. In some studies, CAD was assessed using coronary computed tomography angiography (CCTA).⁷⁴⁾⁷⁹⁾⁸⁸⁻⁹⁰⁾ Most of study subjects of these studies were with suspected or documented CAD, but one study included stroke patients.⁷⁹⁾ There were various methods of measuring arterial pulsatile hemodynamics used in these studies, which included brPP, cPWV, baPWV, aPWV, AIx and aPP. aPWV/cPWV and AIx, measured by tonometry, aPP measured invasively using intra-arterial catheter monitoring, and baPWV were the most widely applied measures for arterial pulsatile hemodynamics in these studies. In one study, aortic distensibility was assessed using aortic CTA.⁹⁰⁾ Most of these studies have shown consistent findings that measurements of arterial pulsatile hemodynamics were associated with the presence and severity of CAD even after controlling for potential confounders. In a longitudinal study with cardiac CTA, even the progression of aortic stiffness was associated with the progression of coronary

Table 1. Summary of studies showing the association of arterial pulsatile hemodynamics and CAD

Source (year)	Population test	Number of subjects	CAD assessment	Measure of arterial hemodynamics	Result	Summary of findings
Li et al. ⁷⁶⁾ (2020)	Patients	654	Invasive CAG	brPP	+	Risk of multivessel CAD ↑ with brPP ≥60 mmHg (multiple-adjusted OR 1.69).
Yannoutsos et al. ⁷⁸⁾ (2018)	Patients	42	Invasive CAG	aPWV by app tono	+	aPWV and CAD severity positively correlated (p=0.001).
Kim et al. ⁷⁵⁾ (2017)	Patients	632	Invasive CAG	brPP	+ (women)	Risk of obstructive CAD ↑ with brPP ≥50.5 mmHg in women (multiple-adjusted OR, 2.83), but not in men.
Kim et al. ⁷⁴⁾ (2015)	Patients	470	Coronary CTA	baPWV	+	Risk of obstructive CAD ↑ with baPWV ≥1.547 cm/sec (multiple-adjusted OR, 2.56).
Duman et al. ⁷³⁾ (2015)	Patients	103	Invasive CAG	aPWV by app tono	+	Highly positive correlation between CAD severity and aPWV (r=0.838).
Tanindi et al. ⁷⁷⁾ (2014)	Patients	145	Invasive CAG	Alx by app tono	+	Risk of moderate/severe CAD (SYNTAX Score >23) ↑ with Alx >24.45 (multiple-adjusted OR 2.94).
Hofmann et al. ⁸³⁾ (2014)	Patients scheduled for CABG	155	Invasive CAG	cfPWV	+	cfPWV associated with CAD extent after controlling for confounders.
Kim et al. ⁸⁴⁾ (2014)	Patients	201	Invasive CAG	baPWV	+	Significant correlation of baPWV and modified Gensini stenosis score.
Hayashi et al. ⁸²⁾ (2014)	Patients	120	Invasive CAG	Alx by app tono	-	No significant difference in Alx between CAD and non-CAD groups.
Calvet et al. ⁷⁹⁾ (2014)	Patients with ischemic stroke	300	Coronary CTA	cfPWV	+	Risk of ≥50% asymptomatic CAD ↑ with cfPWV >9.6 m/sec (multiple-adjusted OR 2.3).
Chung et al. ⁸¹⁾ (2014)	Patients	703	Invasive CAG	baPWV	+	baPWV significantly associated with SYNTAX score.
Cho et al. ⁸⁰⁾ (2013)	Patients	80	Invasive CAG	Alx and PP amplification by app tono	+ (<65 yrs)	Risk of triple-vessel CAD ↑ per 5% increase of Alx (multiple-adjusted OR, 2.15) and per 0.05 increase of PP amplification (multiple-adjusted OR, 2.02) in pts <65 yrs, but not in pts ≥65 yrs.
Bechlioulis et al. ⁸⁵⁾ (2013)	Male patients	303	Invasive CAG	cfPWV and Alx by app tono	+ (cfPWV) - (Alx)	Increased cfPWV associated with CAD in overweight and obese pts. No association of Alx with CAD.
Kotecha et al. ⁸⁷⁾ (2013)	Patients	531	Invasive CAG	Central Alx by radial artery tono	+	Lower central Alx (<24 mmHg) associated with angiographically normal coronary arteries (multiple-adjusted OR, 2.0).
Oberoi et al. ⁹⁰⁾ (2013)	Patients	164	Coronary CTA	Aortic distensibility index by CTA	+	Longitudinal evaluation: Decrease in aortic distensibility index associated with increase in segment involvement score.
Nam et al. ⁸⁹⁾ (2012)	Subjects health check-up	615	Coronary CTA	baPWV	+	Risk of significant occult CAD ↑ with baPWV ≥1,426 cm/s (multiple-adjusted OR, 3.3).
Xiong et al. ⁹¹⁾ (2012)	Patients	321	Invasive CAG	baPWV	+	baPWV associated with SYNTAX score in multiple regression analysis.
Liu et al. ⁸⁸⁾ (2011)	Subjects health check-up	654	Coronary CTA	baPWV	+	Risk of coronary stenosis ↑ with baPWV 1,400-1,800 cm/s (adjusted OR, 2.48) and baPWV >1,800 cm/s (adjusted OR, 3.16).
Fischer-Rasokat et al. ⁸⁶⁾ (2009)	Male patients	152	Invasive CAG	Radial Alx by radial artery tono	+ (<60 yrs)	Risk of CAD ↑ with radial Alx in multivariable regression analysis in patients ≤60 years but not in those >60 years.
Alarhabi et al. ⁹²⁾ (2009)	Patients	92	Invasive CAG	cfPWV	+	Significant association between the severity of CAD and cfPWV.
Koji et al. ⁹³⁾ (2007)	Patients	396	Invasive CAG	baPWV	+	baPWV significant determinant of the number of diseased coronary arteries in multiple regression analysis.
Nair et al. ⁹⁴⁾ (2005)	Postmenopausal women with angio-confirmed CAD	309	Invasive CAG	brPP	+	Longitudinal study: Progression of coronary stenosis independently associated with higher baseline brPP.
Guray et al. ⁵⁰⁾ (2005)	Female patients	262	Invasive CAG	Invasive aPP and aortic pulsatility	+	Risk of CAD ↑ per 10 mm Hg aPP (multiple-adjusted OR, 1.3) and per 0.1 aortic pulsatility (multiple-adjusted OR, 1.8).
Weber et al. ⁹⁵⁾ (2004)	Patients	465	Invasive CAG	Alx by app tono of radial artery	+	Risk of CAD ↑ with higher Alx (multiple-adjusted OR, 4.06 for comparison first vs. fourth quartile).
Philippe et al. ⁵³⁾ (2002)	Patients	99	Invasive CAG	Invasive aPP	+	Independent association between aPP and extent of CAD.
Nakayama et al. ⁵²⁾ (2000)	Patients underwent PTCA	53	Invasive CAG	Invasive PPF	+	Risk of restenosis after PCBA ↑ per 0.1 PPF (multiple-adjusted OR, 1.88) and per 0.1 aortic pulsatility (multiple-adjusted OR, 1.8).

Alx = augmentation index; aPP = aortic pulse pressure; app tono = applanation tonometry; aPWV = aortic pulse wave velocity; AUC = area under curve; baPWV = brachial-ankle pulse wave velocity; brPP = brachial pulse pressure; CABG = coronary artery bypass graft; CAD = coronary artery disease; CAG = coronary angiography; cfPWV = carotid-femoral pulse wave velocity; CI = confidence interval; CTA = computed tomography angiography; OR = odds ratio; PCBA = percutaneous coronary balloon angioplasty; PPF = fractional pulse pressure; SYNTAX = Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery.

atherosclerosis.⁹⁰⁾ However, another study showed a neutral result indicating that there was no significant difference in AIx in patients with and without CAD.⁸²⁾

PROGNOSTIC VALUE OF ARTERIAL PULSATILE HEMODYNAMICS IN CORONARY ARTERY DISEASE PATIENTS

The prognostic value of arterial pulsatile hemodynamics in CAD patients has been reported in several studies (Table 2).³⁴⁾⁴⁴⁾⁴⁹⁾⁵¹⁾⁹⁶⁻¹⁰⁸⁾ In these studies, non-invasive measurements for arterial pulsatile hemodynamics included AIx assessed by radial artery applanation tonometry, baPWV, cfPWV and brPP. Invasive assessment of aPP, aPWV, AP and AIx were also used as indicators of arterial pulsatile hemodynamics. During about 1–5 year of clinical follow-up, these measurements were independently associated with the occurrence of cardiovascular events or mortality in multivariable analyses. To be more specific, in recent a study of 1,040

Table 2. Summary of studies showing the prognostic value of arterial pulsatile hemodynamics in patients with CAD

Source (year)	Population	Number of subjects	Follow-up duration	Measure of arterial hemodynamics	Result	Summary of findings
Hametner et al. ⁴⁴⁾ (2021)	Patients with susp. CAD	1,040	4.3 years	Invasive aPWV	+	Risk of MACE ↑ with aPWV (multiple-adjusted HR per SD, 1.18).
Kaolawanich et al. ⁹⁹⁾ (2020)	Patients with susp. CAD	520	3.9 years	aPWV by CMR	+	Risk of MACE ↑ with aPWV ≥10.54 m/s (multiple-adjusted HR, 2.42).
Siasos et al. ¹⁰⁴⁾ (2018)	Patients with successful PCI	262	1 year	cfPWV	+	Risk of MACE ↑ with cfPWV (multiple-adjusted HR per SD, 1.29).
Hwang et al. ⁹⁷⁾ (2018)	Patients with susp. CAD/CCTA	523	1.8 years	baPWV	+	Risk of composite endpoint ↑ with baPWV ≥1,619 cm/sec (multiple-adjusted HR, 4.7).
Maruhashi et al. ¹⁰²⁾ (2018)	Patients/CAD	462	5.3 years	baPWV	+	Risk of coronary events ↑ with baPWV >1,731 cm/sec (multiple-adjusted HR, 1.86).
Feistritz et al. ⁹⁶⁾ (2017)	Patients with STEMI	160	1.2 years	aPWV by CMR	+	Risk of MACE ↑ with aPWV >7.3 m/sec (adjusted HRs, 3.5–5.3).
Lin et al. ⁵¹⁾ (2016)	Patients/PCI	1,126	2.5 years	Invasive aPP	+	Risk of repeated PCI ↑ with aPP (multiple-adjusted HR per mm Hg, 1.014).
Tokitsu et al. ¹⁰⁶⁾ (2015)	Patients/CAD	401	2.9 years	brPP	+	Risk of cardiovascular events ↑ with aPP >60 mm Hg m/sec (adjusted HR, 1.71).
Lee et al. ¹⁰¹⁾ (2015)	Patients susp. CAD/MPI	350	1.2 years	baPWV	+	Risk of cardiovascular events ↑ with baPWV ≥1,790 cm/s (multiple-adjusted HR, 2.03).
Ki et al. ¹⁰⁰⁾ (2014)	Patients/PCI	372	2 years	baPWV	+	Risk of cardiac death ↑ with baPWV ≥1,672 cm/s (multiple-adjusted HR, 6.77).
Sugamata et al. ¹⁰⁵⁾ (2014)	Patients with stable CAD	923	4.1 years	baPWV	+	Risk of coronary events ↑ with baPWV (multiple-adjusted HR per SD, 1.52).
Kaneko et al. ⁹⁸⁾ (2013)	Patients/PCI	275	6–12 months	baPWV	+	Risk of progression of new coronary lesion ↑ with baPWV (multiple-adjusted OR per 1 cm/sec, 1.02).
Weber et al. ¹⁰⁸⁾ (2010)	Male patients/invasive CAG	520	4.1 years	AIx, AIx@75, and PWTT by radial app tono	+	Risk of combined clinical endpoint ↑ with AIx (multiple-adjusted HR per 10%, 1.26), AIx@75 (multiple-adjusted HR per 10% 1.27), and ↓ with PWTT (multiple-adjusted HR per 10 msec, 0.84).
Nakamura et al. ¹⁰³⁾ (2010)	Diabetic patients/CAD	564	3 years	baPWV	+	Risk of MACE ↑ with baPWV ≥1,730 cm/s (multiple-adjusted HR, 1.97).
Chirinos et al. ⁴⁹⁾ (2005)	Male patients/invasive CAG	297	3.2 years	Invasive aPP and AIx	+	Risk of MACE ↑ with AIx (multiple-adjusted HR per 10%, 1.28) and AP (multiple-adjusted HR per 10 mm Hg, 1.19).
Weber et al. ³⁴⁾ (2005)	Patients/PCI	262	2 years	AIx@75 by app tono of radial artery	+	Risk of MACE ↑ with AIx@75 (multiple-adjusted HR per increasing tertile 1.8).
Tomiyama et al. ¹⁰⁷⁾ (2005)	Patients/ACS	215	1.1 years	baPWV	+	Risk of MACE ↑ with baPWV >1,700 cm/s (multiple-adjusted HR, 9.22).

ACS = acute coronary syndrome; AIx = augmentation index; AIx@75 = AIx corrected by heart rate 75 bpm; aPP = aortic pulse pressure; app tono = applanation tonometry; aPWV = aortic pulse wave velocity; baPWV = brachial-ankle pulse wave velocity; brPP = brachial pulse pressure; CAD = coronary artery disease; CAG = coronary angiography; CCTA = coronary computed tomography angiography; cfPWV = carotid-femoral pulse wave velocity; CI = confidence interval; CMR = cardiac magnetic resonance imaging; CTA = computed tomography angiography; HR = hazard ratio; MACE = major adverse cardiovascular event; MPI = myocardial perfusion imaging; OR = odds ratio; PCI = percutaneous coronary intervention; PWTT = pulse wave transit time; SD = standard deviation; STEMI = ST-elevation myocardial infarction; susp. = suspected.

patients undergoing invasive CAG, aPWV was invasively measured during CAG, and it was associated with cardiovascular events during the follow-up after CAG.⁴⁴ cfPWV could predict 1-year cardiovascular outcome in patients with successful PCI.¹⁰⁴ In patients after a first acute ST-elevation myocardial infarction, those with a higher aPWV measured by cardiac magnetic resonance imaging had a worse prognosis.⁹⁶ Higher value of baPWV was an independent predictor of adverse cardiovascular events in patients with or suspected CAD in Asian countries.^{97,98,100-103,105,107} Non-invasively measured AIx using radial artery tonometry were also useful in the prediction of cardiovascular events in patients undergoing invasive CAG.^{34,108} All this data suggests that the measurements of arterial pulsatile hemodynamics in CAD patients is valuable in the prediction of future cardiovascular events.

THERAPEUTIC CONSIDERATIONS

Since the measures of arterial pulsatile hemodynamics are closely related to the occurrence of cardiovascular events, efforts to find ways to improve arterial elastic properties have continued (examples are given in **Table 3**). The association between weight gain and arterial stiffness, as well as between weight loss and arterial stiffness regression has been suggested in healthy young adults.¹⁰⁹ Also, improved aortic distensibility by weight reduction

Table 3. Typical examples of studies on methods to improve arterial pulsatile hemodynamics

Source (year)	Population	Number of subjects	Intervention	Measure of arterial hemodynamics	Summary of findings
Ikonomidis et al. ¹⁰⁰ (2007)	Obese individuals (BMI ≥ 40 kg/m ²)	120	Bariatric surgery (gastric bypass)	Aortic root distensibility by echocardiography	Reduction in BMI at 3 months and 3 years after surgery was related to the concomitant increase in aortic root distensibility.
Wildman et al. ¹⁰⁹ (2005)	Healthy young adults	152	Weight change (observational study)	cfPWV	Weight change showed a direct relationship with cfPWV change.
Na et al. ¹⁰² (2009)	Subjects with never-treated hypertension	84	Sport index by questionnaire	hfPWV	Sport index was significantly correlated with hfPWV even after controlling for potential confounders.
Seals et al. ¹⁰⁹ (2001)	Postmenopausal women	35	Aerobic exercise (walking)	aPWV and carotid AIx by app tono	Three months of aerobic exercise did not alter aPWV and carotid AIx.
Ferrier et al. ¹⁰⁸ (2001)	Subjects with isolated systolic hypertension	20	Aerobic exercise training	cfPWV	Eight weeks of moderate intensity cycling did not reduce cfPWV.
Tanaka et al. ¹⁰¹ (2000)	Healthy men	151	Habitual exercise	Carotid artery compliance and β stiffness index by US and app tono	Correlations were observed of maximal oxygen consumption with carotid artery compliance and β stiffness index.
Lee et al. ¹⁰⁷ (2020)	Male subjects w/o CV disease	1,169	Cigarette smoking	Radial AIx by app tono	Dose-response elevation of smoking cessation and AIx.
Takami et al. ¹⁰⁵ (2011)	Subjects/smoking cessation treatment	70	Cigarette smoking	Radial AIx@75 by app tono and baPWV	radial AIx@75 and baPWV showed greater decrease in the smoking cessation group.
Jatoi et al. ¹⁰⁶ (2007)	Subjects with never-treated hypertension	554	Cigarette smoking	Aortic AIx and PWTT by app tono and cfPWV	Significant multiple-adjusted linear relationship between smoking status and cfPWV, AIx, and PWTT.
van den Berkortel et al. ¹²⁰ (2004)	Smokers	127	Cigarette smoking	Carotid distensibility by US	Two years of smoking cessation did not reduce carotid distensibility.
Mahmud et al. ¹⁰⁴ (2003)	Healthy young subjects	185	Cigarette smoking	Aortic AIx and PP amplification by app tono	AIx was significantly higher in smokers, and was significantly increased within 15 minutes after smoking.
Ikonomidis et al. ¹⁰⁵ (2020)	Subjects with type 2 diabetes mellitus	160	Liraglutide and empagliflozin	cfPWV	Empagliflozin (+/- liraglutide) showed greater decrease of cfPWV than insulin or liraglutide alone.
Ait-Oufella et al. ¹²⁴ (2010)	Pts with treated hypertension	97	Routine clinical practice	Carotid PP by app tono and cfPWV	During 5.3 years FU cfPWV decreased by 3.17 m/s (22%) in parallel with only minor decrease in brachial BP.
Williams et al. ¹²³ (2009)	Subjects with untreated hypertension	891	Atorvastatin vs. placebo	aPP and aortic AIx by radial app tono	Atorvastatin did not influence aPP and AIx.
Mitchell et al. ¹²¹ (2007)	Patients with stable CAD	300	Perindopril vs. placebo	cfPWV	Perindopril was associated with decreased cfPWV.

AIx = augmentation index; AIx@75 = AIx corrected by heart rate 75 bpm; aPP = aortic pulse pressure; app tono = applanation tonometry; aPWV = aortic pulse wave velocity; baPWV = brachial-ankle pulse wave velocity; BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; cfPWV = carotid-femoral pulse wave velocity; CV = cardiovascular; FU = follow up; hfPWV = heart-femoral pulse wave velocity; PP = pulse pressure; PWTT = pulse wave transit time; SBP = systolic blood pressure; US = ultrasound.

after bariatric surgery in obese patients has been reported.¹¹⁰⁾ Exercise training has been suggested as another effective way to improve arterial stiffness in healthy individuals,¹¹¹⁾ hypertensives,¹¹²⁾ and in patients with CAD.¹¹³⁾ The beneficial effect of exercise training on arterial stiffness may be additive to the effect of medication in CAD patients.¹¹³⁾ Arterial stiffness is increased in smokers,¹¹⁴⁾ and smoking cessation decreases arterial stiffness.¹¹⁵⁻¹¹⁷⁾ Therefore, healthy lifestyle habits such as weight loss, exercise, and smoking cessation can help reduce arterial stiffness, although there were some studies showing that such lifestyle modifications have little effect on arterial stiffness.¹¹⁸⁻¹²⁰⁾ Healthy lifestyle therapy is a basic and important treatment method that should be emphasized for the primary and secondary prevention of CAD. In particular, for subjects with high arterial stiffness, these lifestyle modifications should be better followed to lower arterial stiffness and further reduce cardiovascular risk. Although study sample size was small and the results are still inconsistent, several studies have reported that renin-angiotensin system blocker or statin have favorable effects on arterial pulsatile hemodynamics.¹²¹⁻¹²⁴⁾ Therefore, the use of these drugs should be actively considered in high-risk patients. Recently, there have been reports that new anti-diabetic drugs known to have protective effects on cardiovascular system (glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter-2 inhibitors) effectively lower arterial stiffness.¹²⁵⁻¹²⁷⁾ Additional studies on the effects of these drugs on lowering arterial stiffness should be followed. It has been suggested that continuous positive airway pressure in patients with sleep apnea was associated with a significant improvement in arterial stiffness measured by PWV or AIx.¹²⁸⁾

CLINICAL IMPLICATIONS

The onset of atherosclerosis occurs at an early stage and progresses to CAD over a period of decades.¹²⁹⁾ The speed of progress is determined by the individual risk factor burden of each person. Therefore, it is very effective to identify high-risk individuals for CAD early and implement strong primary preventive strategy. However, risk prediction based on traditional cardiovascular risk factors is limited,³⁾ requiring additional risk prediction tools. Measurements of arterial pulsatile hemodynamics are correlated with the presence and extent of CAD. Also, these measurements are good surrogate markers for future cardiovascular events and mortality in patients with CAD. Since information on arterial pulsatile hemodynamics can be obtained through non-invasive methods, it may be useful in predicting the occurrence of future cardiovascular events in both primary and secondary setting. Also, invasively measured indicators of arterial mechanics such as aPP, aPWV and AIx could predict cardiovascular events, and thus, it is worth considering measuring these parameters during the procedure of invasive CAG. However, we should keep in mind that it is not known to which extent such a strategy influences cardiovascular risk and clinical outcome. In this regard, additional studies should be supported.

CONCLUSIONS

Information on arterial pulsatile hemodynamics, such as arterial stiffness and wave reflections, is useful in the estimation of the risk of having coronary atherosclerosis. Also, it provides prognostic information on the development of future cardiovascular events in CAD patients. Noninvasive assessment of arterial pulsatile hemodynamics may be valuable tool in risk stratification. For patients undergoing invasive CAG, measuring pulsatile aortic

parameters requires little additional risk, cost, effort, or time, so it may be recommended to measure it during CAG. Further research is needed on whether nonpharmacologic and pharmacologic approaches that have favorable impact on arterial pulsatile hemodynamics improve the patients' clinical outcome.

REFERENCES

1. Virani SS, Alonso A, Aparicio HJ, et al. Heart disease and stroke statistics-2021 update: a report from the American Heart Association. *Circulation* 2021;143:e254-743.
[PUBMED](#) | [CROSSREF](#)
2. Berry JD, Dyer A, Cai X, et al. Lifetime risks of cardiovascular disease. *N Engl J Med* 2012;366:321-9.
[PUBMED](#) | [CROSSREF](#)
3. Khot UN, Khot MB, Bajzer CT, et al. Prevalence of conventional risk factors in patients with coronary heart disease. *JAMA* 2003;290:898-904.
[PUBMED](#) | [CROSSREF](#)
4. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R; Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002;360:1903-13.
[PUBMED](#) | [CROSSREF](#)
5. Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet* 2016;387:957-67.
[PUBMED](#) | [CROSSREF](#)
6. SPRINT Research Group, Wright JT Jr, Williamson JD, et al. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med* 2015;373:2103-16.
[PUBMED](#) | [CROSSREF](#)
7. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J* 2018;39:3021-104.
[PUBMED](#) | [CROSSREF](#)
8. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2018;71:2199-269.
[PUBMED](#) | [CROSSREF](#)
9. Safar ME, Levy BI, Struijker-Boudier H. Current perspectives on arterial stiffness and pulse pressure in hypertension and cardiovascular diseases. *Circulation* 2003;107:2864-9.
[PUBMED](#) | [CROSSREF](#)
10. Weber T, Chirinos JA. Pulsatile arterial haemodynamics in heart failure. *Eur Heart J* 2018;39:3847-54.
[PUBMED](#) | [CROSSREF](#)
11. Zhao L, Song Y, Dong P, Li Z, Yang X, Wang S. Brachial pulse pressure and cardiovascular or all-cause mortality in the general population: a meta-analysis of prospective observational studies. *J Clin Hypertens (Greenwich)* 2014;16:678-85.
[PUBMED](#) | [CROSSREF](#)
12. Chae CU, Pfeffer MA, Glynn RJ, Mitchell GF, Taylor JO, Hennekens CH. Increased pulse pressure and risk of heart failure in the elderly. *JAMA* 1999;281:634-9.
[PUBMED](#) | [CROSSREF](#)
13. Domanski MJ, Davis BR, Pfeffer MA, Kastantin M, Mitchell GF. Isolated systolic hypertension : prognostic information provided by pulse pressure. *Hypertension* 1999;34:375-80.
[PUBMED](#) | [CROSSREF](#)
14. Mitchell GF, Moyé LA, Braunwald E, et al. Sphygmomanometrically determined pulse pressure is a powerful independent predictor of recurrent events after myocardial infarction in patients with impaired left ventricular function. SAVE investigators. Survival and Ventricular Enlargement. *Circulation* 1997;96:4254-60.
[PUBMED](#) | [CROSSREF](#)
15. Mitchell GF, Vita JA, Larson MG, et al. Cross-sectional relations of peripheral microvascular function, cardiovascular disease risk factors, and aortic stiffness: the Framingham Heart Study. *Circulation* 2005;112:3722-8.
[PUBMED](#) | [CROSSREF](#)

16. Rosenbaum D, Giral P, Chapman J, et al. Radial augmentation index is a surrogate marker of atherosclerotic burden in a primary prevention cohort. *Atherosclerosis* 2013;231:436-41.
[PUBMED](#) | [CROSSREF](#)
17. Nürnberger J, Keflioglu-Scheiber A, Opazo Saez AM, Wenzel RR, Philipp T, Schäfers RF. Augmentation index is associated with cardiovascular risk. *J Hypertens* 2002;20:2407-14.
[PUBMED](#) | [CROSSREF](#)
18. Ohkuma T, Ninomiya T, Tomiyama H, et al. Brachial-ankle pulse wave velocity and the risk prediction of cardiovascular disease: an individual participant data meta-analysis. *Hypertension* 2017;69:1045-52.
[PUBMED](#) | [CROSSREF](#)
19. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. *J Am Coll Cardiol* 2010;55:1318-27.
[PUBMED](#) | [CROSSREF](#)
20. Chirinos JA, Segers P, Hughes T, Townsend R. Large-artery stiffness in health and disease: JACC state-of-the-art review. *J Am Coll Cardiol* 2019;74:1237-63.
[PUBMED](#) | [CROSSREF](#)
21. Dart AM, Kingwell BA. Pulse pressure--a review of mechanisms and clinical relevance. *J Am Coll Cardiol* 2001;37:975-84.
[PUBMED](#) | [CROSSREF](#)
22. McEniery CM, Cockcroft JR, Roman MJ, Franklin SS, Wilkinson IB. Central blood pressure: current evidence and clinical importance. *Eur Heart J* 2014;35:1719-25.
[PUBMED](#) | [CROSSREF](#)
23. Safar ME. Pulse pressure, arterial stiffness and wave reflections (augmentation index) as cardiovascular risk factors in hypertension. *Ther Adv Cardiovasc Dis* 2008;2:13-24.
[PUBMED](#) | [CROSSREF](#)
24. Agabiti-Rosei E, Mancia G, O'Rourke MF, et al. Central blood pressure measurements and antihypertensive therapy: a consensus document. *Hypertension* 2007;50:154-60.
[PUBMED](#) | [CROSSREF](#)
25. O'Rourke MF, Nichols WW. Aortic diameter, aortic stiffness, and wave reflection increase with age and isolated systolic hypertension. *Hypertension* 2005;45:652-8.
[PUBMED](#) | [CROSSREF](#)
26. Van Bortel LM, Balkestein EJ, van der Heijden-Spek JJ, et al. Non-invasive assessment of local arterial pulse pressure: comparison of applanation tonometry and echo-tracking. *J Hypertens* 2001;19:1037-44.
[PUBMED](#) | [CROSSREF](#)
27. Chen CH, Nevo E, Fetis B, et al. Estimation of central aortic pressure waveform by mathematical transformation of radial tonometry pressure. Validation of generalized transfer function. *Circulation* 1997;95:1827-36.
[PUBMED](#) | [CROSSREF](#)
28. Sharman JE, Lim R, Qasem AM, et al. Validation of a generalized transfer function to noninvasively derive central blood pressure during exercise. *Hypertension* 2006;47:1203-8.
[PUBMED](#) | [CROSSREF](#)
29. Mitchell GF, Parise H, Benjamin EJ, et al. Changes in arterial stiffness and wave reflection with advancing age in healthy men and women: the Framingham Heart Study. *Hypertension* 2004;43:1239-45.
[PUBMED](#) | [CROSSREF](#)
30. McEniery CM, Yasmin , Hall IR, et al. Normal vascular aging: differential effects on wave reflection and aortic pulse wave velocity: the Anglo-Cardiff Collaborative Trial (ACCT). *J Am Coll Cardiol* 2005;46:1753-60.
[PUBMED](#) | [CROSSREF](#)
31. Shimizu M, Kario K. Role of the augmentation index in hypertension. *Ther Adv Cardiovasc Dis* 2008;2:25-35.
[PUBMED](#) | [CROSSREF](#)
32. Kim HL, Koo BK, Joo SK, Kim W. Association of arterial stiffness with the histological severity of nonalcoholic fatty liver disease. *Hepatol Int* 2020;14:1048-56.
[PUBMED](#) | [CROSSREF](#)
33. Stamatelopoulous KS, Kalpakos D, Protogerou AD, et al. The combined effect of augmentation index and carotid intima-media thickness on cardiovascular risk in young and middle-aged men without cardiovascular disease. *J Hum Hypertens* 2006;20:273-9.
[PUBMED](#) | [CROSSREF](#)
34. Weber T, Auer J, O'Rourke MF, et al. Increased arterial wave reflections predict severe cardiovascular events in patients undergoing percutaneous coronary interventions. *Eur Heart J* 2005;26:2657-63.
[PUBMED](#) | [CROSSREF](#)
35. Weber T, Auer J, Lamm G, O'Rourke MF, Eber B. Arterial stiffness, central blood pressures, and wave reflections in cardiomyopathy-implications for risk stratification. *J Card Fail* 2007;13:353-9.
[PUBMED](#) | [CROSSREF](#)

36. Hughes AD, Park C, Davies J, et al. Limitations of augmentation index in the assessment of wave reflection in normotensive healthy individuals. *PLoS One* 2013;8:e59371.
[PUBMED](#) | [CROSSREF](#)
37. Cavalcante JL, Lima JA, Redheuil A, Al-Mallah MH. Aortic stiffness: current understanding and future directions. *J Am Coll Cardiol* 2011;57:1511-22.
[PUBMED](#) | [CROSSREF](#)
38. Safar ME. Arterial aging--hemodynamic changes and therapeutic options. *Nat Rev Cardiol* 2010;7:442-9.
[PUBMED](#) | [CROSSREF](#)
39. Laurent S, Cockcroft J, Van Bortel L, et al. Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J* 2006;27:2588-605.
[PUBMED](#) | [CROSSREF](#)
40. Munakata M. Brachial-ankle pulse wave velocity in the measurement of arterial stiffness: recent evidence and clinical applications. *Curr Hypertens Rev* 2014;10:49-57.
[PUBMED](#) | [CROSSREF](#)
41. Kim HL, Kim SH. Pulse wave velocity in atherosclerosis. *Front Cardiovasc Med* 2019;6:41.
[PUBMED](#) | [CROSSREF](#)
42. Reference Values for Arterial Stiffness' Collaboration. Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors: 'establishing normal and reference values'. *Eur Heart J* 2010;31:2338-50.
[PUBMED](#) | [CROSSREF](#)
43. Lee HY, Oh BH. Aging and arterial stiffness. *Circ J* 2010;74:2257-62.
[PUBMED](#) | [CROSSREF](#)
44. Hametner B, Wassertheurer S, Mayer CC, Danninger K, Binder RK, Weber T. Aortic pulse wave velocity predicts cardiovascular events and mortality in patients undergoing coronary angiography: a comparison of invasive measurements and noninvasive estimates. *Hypertension* 2021;77:571-81.
[PUBMED](#) | [CROSSREF](#)
45. Kim HL, Seo JB, Chung WY, Kim SH, Kim MA, Zo JH. Association between invasively measured central aortic pressure and left ventricular diastolic function in patients undergoing coronary angiography. *Am J Hypertens* 2015;28:393-400.
[PUBMED](#) | [CROSSREF](#)
46. Weber T, Wassertheurer S, Hametner B, Parragh S, Eber B. Noninvasive methods to assess pulse wave velocity: comparison with the invasive gold standard and relationship with organ damage. *J Hypertens* 2015;33:1023-31.
[PUBMED](#) | [CROSSREF](#)
47. Kang J, Kim HL, Lim WH, et al. Relationship between brachial-ankle pulse wave velocity and invasively measured aortic pulse pressure. *J Clin Hypertens (Greenwich)* 2018;20:462-8.
[PUBMED](#) | [CROSSREF](#)
48. Yamashina A, Tomiyama H, Takeda K, et al. Validity, reproducibility, and clinical significance of noninvasive brachial-ankle pulse wave velocity measurement. *Hypertens Res* 2002;25:359-64.
[PUBMED](#) | [CROSSREF](#)
49. Chirinos JA, Zambrano JP, Chakko S, et al. Aortic pressure augmentation predicts adverse cardiovascular events in patients with established coronary artery disease. *Hypertension* 2005;45:980-5.
[PUBMED](#) | [CROSSREF](#)
50. Guray Y, Guray U, Altay H, et al. Aortic pulse pressure and aortic pulsatility are associated with angiographic coronary artery disease in women. *Blood Press* 2005;14:293-7.
[PUBMED](#) | [CROSSREF](#)
51. Lin MJ, Chen CY, Lin HD, Lin CS, Wu HP. Prognostic significance of central pulse pressure for mortality in patients with coronary artery disease receiving repeated percutaneous coronary intervention. *Medicine (Baltimore)* 2016;95:e3218.
[PUBMED](#) | [CROSSREF](#)
52. Nakayama Y, Tsumura K, Yamashita N, Yoshimaru K, Hayashi T. Pulsatility of ascending aortic pressure waveform is a powerful predictor of restenosis after percutaneous transluminal coronary angioplasty. *Circulation* 2000;101:470-2.
[PUBMED](#) | [CROSSREF](#)
53. Philippe F, Chemaly E, Blacher J, et al. Aortic pulse pressure and extent of coronary artery disease in percutaneous transluminal coronary angioplasty candidates. *Am J Hypertens* 2002;15:672-7.
[PUBMED](#) | [CROSSREF](#)
54. Al-Mashhadi RH, Al-Mashhadi AL, Nasr ZP, et al. Local pressure drives low-density lipoprotein accumulation and coronary atherosclerosis in hypertensive minipigs. *J Am Coll Cardiol* 2021;77:575-89.
[PUBMED](#) | [CROSSREF](#)

55. Safar ME, Blacher J, Jankowski P. Arterial stiffness, pulse pressure, and cardiovascular disease-is it possible to break the vicious circle? *Atherosclerosis* 2011;218:263-71.
[PUBMED](#) | [CROSSREF](#)
56. Kiefer CR, McKenney JB, Trainor JF, Snyder LM. Pulse-pressure-driven neutral lipid accumulation and correlative proinflammatory markers of accelerated atherogenesis. *Atherosclerosis* 2005;183:17-24.
[PUBMED](#) | [CROSSREF](#)
57. Sakamoto H, Aikawa M, Hill CC, et al. Biomechanical strain induces class a scavenger receptor expression in human monocyte/macrophages and THP-1 cells: a potential mechanism of increased atherosclerosis in hypertension. *Circulation* 2001;104:109-14.
[PUBMED](#) | [CROSSREF](#)
58. Lee RT, Schoen FJ, Loree HM, Lark MW, Libby P. Circumferential stress and matrix metalloproteinase 1 in human coronary atherosclerosis. Implications for plaque rupture. *Arterioscler Thromb Vasc Biol* 1996;16:1070-3.
[PUBMED](#) | [CROSSREF](#)
59. Gould KL, Lipscomb K, Hamilton GW. Physiologic basis for assessing critical coronary stenosis. Instantaneous flow response and regional distribution during coronary hyperemia as measures of coronary flow reserve. *Am J Cardiol* 1974;33:87-94.
[PUBMED](#) | [CROSSREF](#)
60. Pijls NH, van Son JA, Kirkeeide RL, De Bruyne B, Gould KL. Experimental basis of determining maximum coronary, myocardial, and collateral blood flow by pressure measurements for assessing functional stenosis severity before and after percutaneous transluminal coronary angioplasty. *Circulation* 1993;87:1354-67.
[PUBMED](#) | [CROSSREF](#)
61. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J* 2020;41:407-77.
[PUBMED](#) | [CROSSREF](#)
62. O'Rourke MF, Hashimoto J. Mechanical factors in arterial aging: a clinical perspective. *J Am Coll Cardiol* 2007;50:1-13.
[PUBMED](#) | [CROSSREF](#)
63. Hoffman JI, Buckberg GD. The myocardial oxygen supply:demand index revisited. *J Am Heart Assoc* 2014;3:e000285.
[PUBMED](#) | [CROSSREF](#)
64. Watanabe H, Ohtsuka S, Kakhana M, Sugishita Y. Decreased aortic compliance aggravates subendocardial ischaemia in dogs with stenosed coronary artery. *Cardiovasc Res* 1992;26:1212-8.
[PUBMED](#) | [CROSSREF](#)
65. Leung MC, Meredith IT, Cameron JD. Aortic stiffness affects the coronary blood flow response to percutaneous coronary intervention. *Am J Physiol Heart Circ Physiol* 2006;290:H624-30.
[PUBMED](#) | [CROSSREF](#)
66. Ikonomidis I, Lekakis J, Papadopoulos C, et al. Incremental value of pulse wave velocity in the determination of coronary microcirculatory dysfunction in never-treated patients with essential hypertension. *Am J Hypertens* 2008;21:806-13.
[PUBMED](#) | [CROSSREF](#)
67. Fukuda D, Yoshiyama M, Shimada K, et al. Relation between aortic stiffness and coronary flow reserve in patients with coronary artery disease. *Heart* 2006;92:759-62.
[PUBMED](#) | [CROSSREF](#)
68. Saito M, Okayama H, Nishimura K, et al. Possible link between large artery stiffness and coronary flow velocity reserve. *Heart* 2008;94:e20.
[PUBMED](#) | [CROSSREF](#)
69. Kingwell BA, Waddell TK, Medley TL, Cameron JD, Dart AM. Large artery stiffness predicts ischemic threshold in patients with coronary artery disease. *J Am Coll Cardiol* 2002;40:773-9.
[PUBMED](#) | [CROSSREF](#)
70. Weber T, Auer J, O'Rourke MF, Punzengruber C, Kvas E, Eber B. Prolonged mechanical systole and increased arterial wave reflections in diastolic dysfunction. *Heart* 2006;92:1616-22.
[PUBMED](#) | [CROSSREF](#)
71. Weber T. The role of arterial stiffness and central hemodynamics in heart failure. *Int J Heart Fail* 2020;2:209-30.
[CROSSREF](#)
72. Weber T, Wassertheurer S, O'Rourke MF, et al. Pulsatile hemodynamics in patients with exertional dyspnea: potentially of value in the diagnostic evaluation of suspected heart failure with preserved ejection fraction. *J Am Coll Cardiol* 2013;61:1874-83.
[PUBMED](#) | [CROSSREF](#)

73. Duman OO, Goldeli O, Gursul E, Baris N, Ozpelit E, Simsek MA. The value of aortic pulse wave velocity in predicting coronary artery disease diagnosis and severity. *Acta Cardiol* 2015;70:315-22.
[PUBMED](#) | [CROSSREF](#)
74. Kim HL, Jin KN, Seo JB, et al. The association of brachial-ankle pulse wave velocity with coronary artery disease evaluated by coronary computed tomography angiography. *PLoS One* 2015;10:e0123164.
[PUBMED](#) | [CROSSREF](#)
75. Kim HL, Kim MA, Shim WJ, et al. Sex difference in the association between brachial pulse pressure and coronary artery disease: the Korean Women's Chest Pain Registry (KoROSE). *J Clin Hypertens (Greenwich)* 2017;19:38-44.
[PUBMED](#) | [CROSSREF](#)
76. Li J, Peng Y, Ji K. Brachial pulse pressure is associated with the presence and extent of coronary artery disease in stable angina patients: a cross-sectional study. *BMC Cardiovasc Disord* 2020;20:143.
[PUBMED](#) | [CROSSREF](#)
77. Tanindi A, Erkan AF, Alhan A, Töre HF. Central pulse pressure amplification is associated with more extensive and severe coronary artery disease. *Scand Cardiovasc J* 2014;48:167-75.
[PUBMED](#) | [CROSSREF](#)
78. Yannoutsos A, Ahouah M, Dreyfuss Tubiana C, Topouchian J, Safar ME, Blacher J. Aortic stiffness improves the prediction of both diagnosis and severity of coronary artery disease. *Hypertens Res* 2018;41:118-25.
[PUBMED](#) | [CROSSREF](#)
79. Calvet D, Touzé E, Laurent S, et al. Aortic stiffness measurement improves the prediction of asymptomatic coronary artery disease in stroke/transient ischemic attack patients. *Int J Stroke* 2014;9:291-6.
[PUBMED](#) | [CROSSREF](#)
80. Cho SW, Kim BK, Kim JH, et al. Non-invasively measured aortic wave reflection and pulse pressure amplification are related to the severity of coronary artery disease. *J Cardiol* 2013;62:131-7.
[PUBMED](#) | [CROSSREF](#)
81. Chung CM, Yang TY, Lin YS, et al. Relation of arterial stiffness assessed by brachial-ankle pulse wave velocity to complexity of coronary artery disease. *Am J Med Sci* 2014;348:294-9.
[PUBMED](#) | [CROSSREF](#)
82. Hayashi S, Yamada H, Bando M, et al. Augmentation index does not reflect risk of coronary artery disease in elderly patients. *Circ J* 2014;78:1176-82.
[PUBMED](#) | [CROSSREF](#)
83. Hofmann B, Riemer M, Erbs C, et al. Carotid to femoral pulse wave velocity reflects the extent of coronary artery disease. *J Clin Hypertens (Greenwich)* 2014;16:629-33.
[PUBMED](#) | [CROSSREF](#)
84. Kim JH, Rhee MY, Kim YS, et al. Brachial-ankle pulse wave velocity for the prediction of the presence and severity of coronary artery disease. *Clin Exp Hypertens* 2014;36:404-9.
[PUBMED](#) | [CROSSREF](#)
85. Bechlioulis A, Vakalis K, Naka KK, et al. Increased aortic pulse wave velocity is associated with the presence of angiographic coronary artery disease in overweight and obese patients. *Am J Hypertens* 2013;26:265-70.
[PUBMED](#) | [CROSSREF](#)
86. Fischer-Rasokat U, Brenck F, Zeiher AM, Spyridopoulos I. Radial augmentation index unmasks premature coronary artery disease in younger males. *Blood Press Monit* 2009;14:59-67.
[PUBMED](#) | [CROSSREF](#)
87. Kotecha D, New G, Collins P, et al. Radial artery pulse wave analysis for non-invasive assessment of coronary artery disease. *Int J Cardiol* 2013;167:917-24.
[PUBMED](#) | [CROSSREF](#)
88. Liu CS, Li CI, Shih CM, et al. Arterial stiffness measured as pulse wave velocity is highly correlated with coronary atherosclerosis in asymptomatic patients. *J Atheroscler Thromb* 2011;18:652-8.
[PUBMED](#) | [CROSSREF](#)
89. Nam HJ, Jung IH, Kim J, et al. Association between brachial-ankle pulse wave velocity and occult coronary artery disease detected by multi-detector computed tomography. *Int J Cardiol* 2012;157:227-32.
[PUBMED](#) | [CROSSREF](#)
90. Oberoi S, Schoepf UJ, Meyer M, et al. Progression of arterial stiffness and coronary atherosclerosis: longitudinal evaluation by cardiac CT. *AJR Am J Roentgenol* 2013;200:798-804.
[PUBMED](#) | [CROSSREF](#)
91. Xiong Z, Zhu C, Zheng Z, et al. Relationship between arterial stiffness assessed by brachial-ankle pulse wave velocity and coronary artery disease severity assessed by the SYNTAX score. *J Atheroscler Thromb* 2012;19:970-6.
[PUBMED](#) | [CROSSREF](#)

92. Alarhabi AY, Mohamed MS, Ibrahim S, Hun TM, Musa KI, Yusof Z. Pulse wave velocity as a marker of severity of coronary artery disease. *J Clin Hypertens (Greenwich)* 2009;11:17-21.
[PUBMED](#) | [CROSSREF](#)
93. Koji Y, Tomiyama H, Yamada J, et al. Relationship between arterial stiffness and the risk of coronary artery disease in subjects with and without metabolic syndrome. *Hypertens Res* 2007;30:243-7.
[PUBMED](#) | [CROSSREF](#)
94. Nair GV, Waters D, Rogers W, Kowalchuk GJ, Stuckey TD, Herrington DM. Pulse pressure and coronary atherosclerosis progression in postmenopausal women. *Hypertension* 2005;45:53-7.
[PUBMED](#) | [CROSSREF](#)
95. Weber T, Auer J, O'Rourke MF, et al. Arterial stiffness, wave reflections, and the risk of coronary artery disease. *Circulation* 2004;109:184-9.
[PUBMED](#) | [CROSSREF](#)
96. Feistritz HJ, Klug G, Reinstadler SJ, et al. Prognostic value of aortic stiffness in patients after ST-elevation myocardial infarction. *J Am Heart Assoc* 2017;6:6.
[PUBMED](#) | [CROSSREF](#)
97. Hwang IC, Jin KN, Kim HL, et al. Additional prognostic value of brachial-ankle pulse wave velocity to coronary computed tomography angiography in patients with suspected coronary artery disease. *Atherosclerosis* 2018;268:127-37.
[PUBMED](#) | [CROSSREF](#)
98. Kaneko H, Yajima J, Oikawa Y, et al. Role of arterial stiffness and impaired renal function in the progression of new coronary lesions after percutaneous coronary intervention. *Cardiovasc Interv Ther* 2013;28:56-62.
[PUBMED](#) | [CROSSREF](#)
99. Kaolawanich Y, Boonyasirinant T. Incremental prognostic value of aortic stiffness in addition to myocardial ischemia by cardiac magnetic resonance imaging. *BMC Cardiovasc Disord* 2020;20:287.
[PUBMED](#) | [CROSSREF](#)
100. Ki YJ, Choi DH, Lee YM, Lim L, Song H, Koh YY. Predictive value of brachial-ankle pulse wave velocity for long-term clinical outcomes after percutaneous coronary intervention in a Korean cohort. *Int J Cardiol* 2014;175:554-9.
[PUBMED](#) | [CROSSREF](#)
101. Lee HS, Kim HL, Kim H, et al. Incremental prognostic value of brachial-ankle pulse wave velocity to single-photon emission computed tomography in patients with suspected coronary artery disease. *J Atheroscler Thromb* 2015;22:1040-50.
[PUBMED](#) | [CROSSREF](#)
102. Maruhashi T, Soga J, Fujimura N, et al. Endothelial dysfunction, increased arterial stiffness, and cardiovascular risk prediction in patients with coronary artery disease: FMD-J (Flow-Mediated Dilation Japan) Study A. *J Am Heart Assoc* 2018;7:e008588.
[PUBMED](#) | [CROSSREF](#)
103. Nakamura M, Yamashita T, Yajima J, et al. Brachial-ankle pulse wave velocity as a risk stratification index for the short-term prognosis of type 2 diabetic patients with coronary artery disease. *Hypertens Res* 2010;33:1018-24.
[PUBMED](#) | [CROSSREF](#)
104. Siasos G, Oikonomou E, Maniatis K, et al. Prognostic significance of arterial stiffness and osteoprotegerin in patients with stable coronary artery disease. *Eur J Clin Invest* 2018;48:e12890.
[PUBMED](#) | [CROSSREF](#)
105. Sugamata W, Nakamura T, Uematsu M, et al. Combined assessment of flow-mediated dilation of the brachial artery and brachial-ankle pulse wave velocity improves the prediction of future coronary events in patients with chronic coronary artery disease. *J Cardiol* 2014;64:179-84.
[PUBMED](#) | [CROSSREF](#)
106. Tokitsu T, Yamamoto E, Hirata Y, et al. Clinical significance of pulse pressure in patients with coronary artery disease. *Int J Cardiol* 2015;190:299-301.
[PUBMED](#) | [CROSSREF](#)
107. Tomiyama H, Koji Y, Yambe M, et al. Brachial -- ankle pulse wave velocity is a simple and independent predictor of prognosis in patients with acute coronary syndrome. *Circ J* 2005;69:815-22.
[PUBMED](#) | [CROSSREF](#)
108. Weber T, O'Rourke MF, Lassnig E, et al. Pulse waveform characteristics predict cardiovascular events and mortality in patients undergoing coronary angiography. *J Hypertens* 2010;28:797-805.
[PUBMED](#) | [CROSSREF](#)
109. Wildman RP, Farhat GN, Patel AS, et al. Weight change is associated with change in arterial stiffness among healthy young adults. *Hypertension* 2005;45:187-92.
[PUBMED](#) | [CROSSREF](#)

110. Ikonomidis I, Mazarakis A, Papadopoulos C, et al. Weight loss after bariatric surgery improves aortic elastic properties and left ventricular function in individuals with morbid obesity: a 3-year follow-up study. *J Hypertens* 2007;25:439-47.
[PUBMED](#) | [CROSSREF](#)
111. Tanaka H, Dinunno FA, Monahan KD, Clevenger CM, DeSouza CA, Seals DR. Aging, habitual exercise, and dynamic arterial compliance. *Circulation* 2000;102:1270-5.
[PUBMED](#) | [CROSSREF](#)
112. Na SH, Kim YS, Bae JH, et al. Effects of physical activity and aerobic exercise capacity on aortic stiffness in patients with untreated hypertension. *Korean Circ J* 2009;39:52-6.
[CROSSREF](#)
113. Oliveira NL, Ribeiro F, Alves AJ, Campos L, Oliveira J. The effects of exercise training on arterial stiffness in coronary artery disease patients: a state-of-the-art review. *Clin Physiol Funct Imaging* 2014;34:254-62.
[PUBMED](#) | [CROSSREF](#)
114. Mahmud A, Feely J. Effect of smoking on arterial stiffness and pulse pressure amplification. *Hypertension* 2003;41:183-7.
[PUBMED](#) | [CROSSREF](#)
115. Takami T, Saito Y. Effects of smoking cessation on central blood pressure and arterial stiffness. *Vasc Health Risk Manag* 2011;7:633-8.
[PUBMED](#) | [CROSSREF](#)
116. Jatoi NA, Jerrard-Dunne P, Feely J, Mahmud A. Impact of smoking and smoking cessation on arterial stiffness and aortic wave reflection in hypertension. *Hypertension* 2007;49:981-5.
[PUBMED](#) | [CROSSREF](#)
117. Lee GB, Shim JS, Kim HC. Dose-response association between smoking cessation and arterial stiffness: the Cardiovascular and Metabolic Diseases Etiology Research Center (CMERC) cohort. *Korean Circ J* 2020;50:361-9.
[PUBMED](#) | [CROSSREF](#)
118. Ferrier KE, Waddell TK, Gatzka CD, Cameron JD, Dart AM, Kingwell BA. Aerobic exercise training does not modify large-artery compliance in isolated systolic hypertension. *Hypertension* 2001;38:222-6.
[PUBMED](#) | [CROSSREF](#)
119. Seals DR, Tanaka H, Clevenger CM, et al. Blood pressure reductions with exercise and sodium restriction in postmenopausal women with elevated systolic pressure: role of arterial stiffness. *J Am Coll Cardiol* 2001;38:506-13.
[PUBMED](#) | [CROSSREF](#)
120. van den Berkmortel FW, Wollersheim H, van Langen H, Smilde TJ, den Arend J, Thien T. Two years of smoking cessation does not reduce arterial wall thickness and stiffness. *Neth J Med* 2004;62:235-41.
[PUBMED](#)
121. Mitchell GF, Dunlap ME, Warnica W, et al. Long-term trandolapril treatment is associated with reduced aortic stiffness: the prevention of events with angiotensin-converting enzyme inhibition hemodynamic substudy. *Hypertension* 2007;49:1271-7.
[PUBMED](#) | [CROSSREF](#)
122. Asmar R. Effect of antihypertensive agents on arterial stiffness as evaluated by pulse wave velocity: clinical implications. *Am J Cardiovasc Drugs* 2001;1:387-97.
[PUBMED](#) | [CROSSREF](#)
123. Williams B, Lacy PS, Cruickshank JK, et al. Impact of statin therapy on central aortic pressures and hemodynamics: principal results of the Conduit Artery Function Evaluation-Lipid-Lowering Arm (CAFE-LLA) Study. *Circulation* 2009;119:53-61.
[PUBMED](#) | [CROSSREF](#)
124. Ait-Oufella H, Collin C, Bozec E, et al. Long-term reduction in aortic stiffness: a 5.3-year follow-up in routine clinical practice. *J Hypertens* 2010;28:2336-41.
[PUBMED](#) | [CROSSREF](#)
125. Ikonomidis I, Pavlidis G, Thymis J, et al. Effects of glucagon-like peptide-1 receptor agonists, sodium-glucose cotransporter-2 inhibitors, and their combination on endothelial glycocalyx, arterial function, and myocardial work index in patients with type 2 diabetes mellitus after 12-month treatment. *J Am Heart Assoc* 2020;9:e015716.
[PUBMED](#) | [CROSSREF](#)
126. Batzias K, Antonopoulos AS, Oikonomou E, et al. Effects of newer antidiabetic drugs on endothelial function and arterial stiffness: a systematic review and meta-analysis. *J Diabetes Res* 2018;2018:1232583.
[PUBMED](#) | [CROSSREF](#)
127. Kato ET, Kimura T. Sodium-glucose co-transporters-2 inhibitors and heart failure: state of the art review and future potentials. *Int J Heart Fail* 2020;2:12-22.
[CROSSREF](#)

128. Lin X, Chen G, Qi J, Chen X, Zhao J, Lin Q. Effect of continuous positive airway pressure on arterial stiffness in patients with obstructive sleep apnea and hypertension: a meta-analysis. *Eur Arch Otorhinolaryngol* 2016;273:4081-8.
[PUBMED](#) | [CROSSREF](#)
129. Sary HC. Macrophages, macrophage foam cells, and eccentric intimal thickening in the coronary arteries of young children. *Atherosclerosis* 1987;64:91-108.
[PUBMED](#) | [CROSSREF](#)