# Structural and Functional Arterial Properties

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Contributor: Giacomo Pucci , Andrea Grillo , Kalliopi V. Dalakleidi , Emil Fraenkel , Eugenia Gkaliagkousi , Spyretta Golemati , Andrea Guala , Bernhard Hametner , Antonios Lazaridis , Christopher C. Mayer , Ioana Mozos , Telmo Pereira , Dave Veerasingam , Dimitrios Terentes-Printzios , Davide Agnoletti

Atrial fibrillation (AF), the most common cardiac arrhythmia, is associated with adverse cardiovascular (CV) outcomes. Vascular aging (VA), which is defined as the progressive deterioration of arterial function and structure over a lifetime, is an independent predictor of both AF development and CV events. A timing identification and treatment of early VA has therefore the potential to reduce the risk of AF incidence and related CV events.

vascular aging | atrial fibrillation | arteriosclerosis | cardiovascular disease

## 1. Introduction

Atrial fibrillation (AF), the most common sustained cardiac arrhythmia, is associated with a high burden of cardiovascular (CV) morbidity and mortality, mainly related to an increased risk of cardioembolic stroke and heart failure [1]. The global cumulative mortality attributed to AF was 0.51% in 2017, reflecting an 81% relative increase over the past two decades [1]. The prevalence of AF is currently increasing and is expected to rise in the coming years across all age groups and regions [2]. This is primarily attributed to the growing burden of comorbidities, socioeconomic deprivation and AF risk factors such as hypertension, obesity, diabetes and ischemic heart disease [3].

From a pathophysiological point of view, AF is defined as a supraventricular tachyarrhythmia marked by uncoordinated atrial electrical activation, leading to ineffective atrial contraction and causing an irregular heart rhythm. From a clinical perspective, AF is classified as paroxysmal (PAF, episodes lasting less than one week), persistent (continuously sustained beyond 7 days, including episodes terminated by cardioversion) or permanent (stable AF rhythm with no further attempts to restore/maintain sinus rhythm) [4]; long-standing persistent AF (continuously sustained for an extended period, typically lasting beyond 12 months); valvular/non-valvular AF (valvular AF indicates the presence of moderate/severe mitral stenosis or a mechanical prosthetic heart valve(s)). The classification of lone AF, referring to AF without any other cardiorespiratory diseases or risk factors, is now dismissed.

Notably, asymptomatic AF poses a challenge to clinicians, potentially causing delays in establishing preventive strategies [5]. It is estimated that one out of ten ischemic strokes is related to a previously unknown history of AF [6]. This could be prevented by implementing digital systems and mobile health technologies for AF screening and detection, especially in individuals at risk [7].

The term vascular aging (VA) is commonly used to describe the deterioration of both structural and functional components of the arterial tree, although a universally acknowledged definition is still lacking [8].

## 2. Structural Arterial Properties: The Arterial Stiffness

At a structural level, the process of VA is identified with the progressive stiffening of the arterial tree, namely arterial stiffness (AS). This process mainly occurs at the level of large elastic arteries such as the aorta and the carotid arteries, where a mechanical remodeling of the arterial wall is observed [9]. The most commonly used method for the non-invasive estimation of arterial stiffness is the measure of the pulse wave velocity (PWV), which represents the velocity of the pressure waves generated from the systolic contraction along a defined arterial segment. Most commonly, the carotid–femoral PWV (cfPWV) is used as a marker of aortic stiffness. CfPWV has been associated with adverse clinical outcomes in several population settings [10], and predicts CV outcome better than chronological aging [11][12]. Several other methods used for arterial stiffness estimation are summarized in **Table 1**.

**Table 1.** Description of vascular aging biomarkers.

| Vascular Aging Biomarker | Method of Measurement |
|---|---|
| Carotid–femoral pulse wave velocity (cfPWV) | Ratio of traveled distance between the carotid and femoral pulse site and transit time between common carotid and common femoral artery; based on tonometers, piezoelectronic sensors, cuffs or Doppler ultrasound, either simultaneously or sequentially, using ECG for gating. |
| Heart–femoral pulse wave velocity (hfPWV) | Ratio of traveled distance between the heart and femoral pulse sites and transit time starting from second heart sound; based on tonometers, ECG and microphones. |
| Brachial–ankle pulse wave velocity (baPWV) | Ratio between traveled distance and transit time calculated with occlusive cuffs placed at brachial artery and ankle; cardio-ankle vascular index is a variation using a phonocardiogram and occlusive cuffs. |
| Arterial stiffness index (ASI) | Marker of arterial stiffness calculated by dividing height by the timing of reflected waves from finger photoplethysmography |
| Cardio-ankle vascular index | Marker of arterial stiffness based on the stiffness parameter β, reflecting arterial properties from origin of the ascending aorta to the ankle. |

| Vascular Aging Biomarker | Method of Measurement |
|---|---|
| (CAVI) | |
| Brachial pulse pressure (PP) | Measured using validated sphygmomanometers; brachial pulse pressure defined as systolic minus diastolic BP. |
| Central pulse pressure (cPP) | Central pulse pressure based on waveforms recorded at the radial, brachial or carotid artery, mainly using tonometers or cuffs; waveforms are calibrated with measured brachial BP leading to central systolic BP and pulse pressure. |
| Augmentation index (AIx) | The ratio between central augmented pressure and pulse pressure, as a surrogate indicator of wave reflections and left ventricular loading. |
| Pulse pressure amplification (PPA) | Central to peripheral pulse pressure amplification (peripheral PP/central PP) is due to both cardiac and arterial factors: ventricular ejection, arterial stiffness, amplitude and timing of wave reflection. VA reduces PPA values. |
| Brachial artery flow-mediated dilation (FMD) | Flow-mediated dilation induces the release of nitric oxide, resulting in vasodilation that can be measured by ultrasound imaging of the diameter of the brachial artery after an ischemia induced by arterial occlusion using a cuff, which is released after 5 min, leading to reactive hyperemia. |
| Aortic distensibility | Measure of aortic elasticity estimated by the relative change in diameter, area or volume divided by the pulse pressure generating this change; may be measured by echocardiography or by MRI. |
| Carotid artery distensibility | Measure of carotid artery elasticity estimated by the ratio between relative change in diameter or volume and the pulse pressure generating this change; usually measured by carotid ultrasound. |

At a functional level, the hallmark of VA is the impairment of endothelial function, which is the result of a decrease in nitric oxide synthase (eNOS) expression in endothelial cells and that, in turn, promotes the development of a prothrombotic state [13] and atherosclerosis [9]. This process, namely the endothelial dysfunction (ED), is hastened by oxidative stress and occurs in response to both physiological aging and systemic inflammation [14][15]. Flow-mediated dilation (FMD), usually assessed at the brachial artery, has been established as a reliable and reproducible technique for assessment of ED [16][17], and has been independently associated with vascular disease and adverse CV events [18].

The exposure to CV risk factors, including smoking, obesity, hypertension, diabetes and hypercholesterolemia, promotes the development of both early VA and AF. Therefore, measurement of VA biomarkers such as PWV and brachial FMD in people with AF, or at risk for it, has a strong rationale and large expected impact on clinical practice to better characterize the individual CV risk and to provide targeted interventions.

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