**Arterial stiffness: a possible predictor of atrial fibrillation**

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Abstract

Atrial fibrillation (AF) is the most common cardiac arrhythmia, affecting 0.5%–1% of people worldwide. Hemodynamic changes due to stiffening of the arteries may cause cardiac structural and electrical remodeling that induces AF. Pulse wave velocity (PWV) is a direct non-invasive method to measure arterial stiffness (AS). Central pulse pressure (P Pc) describes oscillations around the mean arterial pressure and is increased in more rigid arteries. These two central variables can be considered markers of AF. Sympathetic activity has been reported to be directly related to PWV even in patients without comorbidities. Therefore, in patients with more rigid arteries, sudden changes in pressure could affect the activation of arterial baroreceptors, leading to an acute imbalance between the sympathetic and parasympathetic responses in the heart. The coexistence of AF and AS is common. This critical review aims to bring information about the role of AS in the pathophysiology of AF and discuss results of clinical studies on this topic. Although discussed in the literature, further studies are needed to confirm the predictive role of these variables in AF, and their use in clinical practice.

**Keywords:** Pulse wave velocity; Atrial fibrillation; Arterial stiffness

1. Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia, affecting 0.5%–1% of people worldwide [1,2]. It is associated with increased morbidity from cardiovascular diseases (CVD) such as heart failure, embolic events, and all-cause mortality [3]. The prevalence of AF increases with age, affecting 8% of people older than 80 years [4,5]. Also, its incidence is estimated to double by 2030 [6].

Arterial stiffness (AS), determined by the viscoelastic properties of the arterial walls, represents increased rigidity of arteriosis [7,8]. It results from a degenerative process of the media layer of elastic arteries [9] causing remodeling of the arterial wall [10]. Furthermore, AS increases with age and is associated with several cardiovascular risk factors [11]; it contributes to the development of CVD and is a marker of vascular disease in the elderly population [7,10]. Therefore, AS has important clinical implications [12].

Interestingly, it has been shown that both AF and AS share common risk factors [4], as old age, female sex, smoking, hypertension, heart failure, obesity, dyslipidemia, diabetes mellitus, and other metabolic abnormalities [13–15]. Many studies have shown a correlation between AF and AS [1,5,13,16,17]. This article aims to discuss the association between AF and AS.

2. Arterial stiffness and measurement methods

The arterial wall is composed of collagen and elastin fibers (matrix proteins), smooth muscle cells, and other components [18]. AS is determined by the structural portion of the arterial wall, primarily elastin and collagen [7]. In accordance with the statement “a man is as old as his arteries” made by Thomas Sydenham (1624–1689 AD), it is known that AS is a natural process of aging [19].

In healthy individuals, stiffening and aging have a quadratic, non-linear relationship, with a considerable acceleration around age 50 [20]. Boutouyrie et al. [19] reported the results who showed an increase inwave velocity (PWV) from 520 to 855 cm/s in individuals aged from 5 to 84. This results indicates that AS may increase even in individuals without risk factors or active diseases. However, stiffening may accelerate in the presence of other risk factors and diseases.

Measurement of blood pressure by oscillometry produces valid but questionable estimates of systolic and diastolic pressures. Although the algorithms are sensitive to differences in pulse pressure and AS, the actual measurement of systolic and diastolic pressures feature discussions of biomedical engineering. However, new algorithms based on physics and physiology allow for greater accuracy in estimating systolic and diastolic pressures [21]. Buckling pressure, which represents fluctuations in maximum arterial compliance and maximum cuff pressure (when cuff pres-
sure is almost equal to the mean arterial pressure) [22,23], is around 0–2 mmHg. Jeon et al. [24] analyzed the oscillometric method through computer simulation, and identified errors in blood pressure waveform due to errors in estimating mean arterial pressure. Then, an algorithm independent of the influence of the waveform was studied, and the same results were found in the simulations regardless of the waveform [24].

The accuracy of systolic and diastolic blood pressure levels determined by the oscillometric method is questionable in patients with AF and AS. Heart rate variation affects the accuracy of algorithms in oscillometric devices. In a study of a mathematical model for patients with AF, oscillometric pulses were used in a Kalman filter algorithm. Simulations with hypothetical waveforms with variable systolic and diastolic levels, and heartbeat rhythms associated with AF and rigid arteries demonstrated potential accuracy of blood pressure estimates of 1.5 mmHg with standard deviations of the order of 0.1 mmHg. Variations in heart rate and AS were also observed. Computational analysis of oscillometric cuff pulsations with the Kalman filter has been shown to be useful in detecting variations in heart rate and blood pressure levels associated with AF, quantifying AS, and providing continuous non-invasive blood pressure monitoring [25].

AS can be assessed by invasive and non-invasive methods. PWV is a direct non-invasive method to measure AS. It consists of measuring the velocity in which the pulse wave travels in an arterial segment [26], which, according to the physics of pulsatile flow, a pulse wave travels faster in stiffer arteries [27]. Thus, PWV is considered a predictor of cardiovascular morbidity and mortality [28]. The gold-standard method is the carotid-femoral PWV, which evaluates only elastic arteries, primarily the aorta. Other possible methods to assess AS are the heart-femoral and the brachial-ankle PWV (baPWV) [29]. BaPWV is easily determined, and has been widely used in Asian countries [3]. It is also more reflected than the lower limb arteries [30]. Finally, the cardio-ankle vascular index (CAVI), derived from PWV, is another method to determine AS [31].

Other methods are indirectly correlated to AS index. Central pulse pressure (PPc) describes oscillations around the mean arterial blood pressure [32] and is increased in stiffer arteries [33]. For this reason, PPc is considered a marker of AS [34]. The augmentation index (Aix) is the measure of the enhancement of central aortic pressure by a reflected pulse wave. It is correlated with PWV and is a valid measure of AS [35]. The carotid intima-media thickness (cIMT) does not measure AS itself, but is strongly correlated with changes in PWV [36]. PWV and cIMT are both parameters of functional vascular damage [37].

3. Atrial fibrillation and arterial stiffness

Although the coexistence of AF and AS is common [15], an association between these two conditions has been suggested but not yet established. Reiffel [38] was one of the first to describe the correlation between AF and AS in 2004. Later, Mitchel et al. [33] and Lee et al. [39] found a positive correlation between AF and AS, using different methods to assess AS. Mitchel et al. [33] used a multivariable analysis and found that an increase in pulse pressure (PP) of 20 mmHg was associated with a 34% increased risk of developing AF (95% confidence interval [CI], 22%–47%; p < 0.001) [28]. Lee et al. [39] performed a multivariate linear regression analysis in which the presence of AF was an independent determinant of heart-femoral PWV (p = 0.007). They also found that individuals with AF had higher PWV than the others (1028 ± 222 m/s vs. 923 ± 110 m/s; p = 0.03) [39].

More recently, Chen et al. [40] compared three cohort studies including 25,767 participants of both genders from the United States of America and Europe. PWV was available just in one cohort population, while cIMT was analyzed in all cohorts. In this study, Cox proportional hazards models were used to calculate hazard ratios (HR) and 95% CIs, and 1-standar deviation (SD) increment in the arterial index. PWV was associated with a higher incidence of AF (HR = 1.18; 95% CI, 1.06–1.32; p < 0.004). Also, higher cIMT was associated with higher incidence of AF in all three cohorts (HR = 1.26; 95% CI, 1.21–1.30; p < 0.001; HR = 1.25; 95% CI, 1.15–1.37; p < 0.001; HR = 1.21; 95% CI, 1.09–1.35; p < 0.001).

Similarly, to evaluate the association between AF and AS in the general population without known CVD, Chung et al. [13] performed a cross-sectional study with 8048 participants. AS was measured using CAVI, and the Framingham risk score (FRS) was used to determine the risk for CVD. By univariate analysis, the prevalence of AF was associated with CAVI ≥8 (OR 2.41; 95% CI 1.589–3.359; p < 0.001). In a multivariate analysis adjusted for FRS, AF was also more prevalent in individuals with CAVI ≥8 (OR 2.064; 95% CI 1.397–3.050; p < 0.001). When the study sample was categorized by the FRS in low, intermediate and high-risk for CVD, AS was not an equally significant parameter for the prevalence of AF in the three groups. A CAVI ≥8 was significant only in the intermediate (OR 3.094; 95% CI 1.414–6.769; p = 0.005) and the high-risk groups (OR 3.690; 95% CI 1.090–12.490; p = 0.036).

Lau et al. [41] conducted a study with 68 patients who underwent ablation procedures for symptomatic lone AF and a control group. Lone AF patients had elevated PP basal measures as compared with the control group (38 ± 11 mmHg vs. 33 ± 6 mmHg; p = 0.02). Using Kaplan-Meier statistics, it was found that AS was associated with lower survival free from AF (p = 0.02).

Shaikh et al. [42] analyzed participants from the Framingham Heart Study and found contrasting results between different AS measurement modalities. While PWV was not associated with the occurrence of AF (p = 0.19), the multivariable-adjusted analysis evidenced that an increased
risk of incident AF was associated with increased PP (HR = 1.16; 95% CI, 1.02–1.32; p = 0.02) and AIx (HR = 1.11; 95% CI, 0.98–1.25; p = 0.09).

Another cohort study from China (2016) [5] evaluated 167 individuals with persistent AF. AS was measured using baPWV and then compared with cardiovascular outcomes. Cardiovascular events and baPWV were associated in the multivariable model (HR = 1.045; 95% CI, 1.016–1.075; p = 0.002). Furthermore, the authors compared AS in patients with persistent AF with that reported in non-AF patients in a previous study. In patients with persistent AF, baPWV was higher than in non-AF patients (19.282 ± 5.165 m/s vs. 17.108 ± 41.99 m/s; p < 0.001).

Larstorp et al. [34] found a baseline PP of 76.5 ± 15.5 mmHg in 8810 patients at risk of developing new-onset AF in Sweden. This measure was associated with 39% (95% CI, 22–58%; p < 0.001) increased risk of new-onset AF per SD. Also, PP values during antihypertensive treatment were associated with an increased risk of incident AF (HR = 1.33; 95% CI 1.18–1.50; p < 0.001).

In a cross-sectional study, Miyoshi et al. [43] used CAVI and Augmentation index (AIx) to assess whether AS was associated with paroxysmal AF. CAVI measures were significantly higher in patients with paroxysmal AF than in the control group (9.0 ± 1.0 vs. 8.7 ± 0.8; p < 0.01). The same association was found when the AIx was used (89 ± 12% vs. 83 ± 10%; p < 0.001). A multivariate analysis was performed to evaluate the relative associations of CAVI, blood pressure (BP) and left ventricular (LV) parameters with AF. The analysis revealed that the OR of paroxysmal AF was elevated 1.83 per CAVI unit (95% CI, 1.15–2.92; p = 0.01).

As mentioned before, AS is a natural aging process and may be accelerated by other cardiovascular conditions. To put aside the aging factor, Kilicgedik et al. [17] investigated the association of left atrial (LA) function and AS in middle-aged (48.5 ± 10.4 years) patients with first AF episode. Aortic PP had a positive correlation with LA diameter (r = 0.33; p = 0.01). During the patients’ follow-up, a second AS measure was made, and aortic PP was significantly higher (p = 0.028). These findings demonstrate that AS is associated with reduced LA strain in this population.

On the other hand, Fumagalli et al. [16] found a better LV performance with increased AS in elderly patients (76 ± 8 years) with persistent AF. Despite using a small sample, CAVI measures were associated with a rise in absolute values of longitudinal strain (p = 0.049), which represents a better LV performance.

Finally, several studies have shown an association between heart rate (HR) and AS [39,44–46]. Chu et al. [14] evaluated whether HR was associated with AS only, or whether HR also influenced the relationship between AF and AS. Initially, multivariate analysis evidenced a positive correlation between PWV and AF (p ≤ 0.001). However, after adjusting the analysis for HR, this association disappeared (p = 0.832). These findings indicate that HR is an important influencing factor in the AF and AS relationship.

3.1 Potential role of arterial stiffness in the development of atrial fibrillation

Hemodynamic and nonhemodynamic mechanisms seem to be involved in the pathogenesis of AF [47].

Hemodynamic changes due to the stiffening of the arteries may cause structural and electrical remodeling that induces AF [5]. A more rigid vasculature will result in increased PP and PWV, with an earlier return of the reflected wave from the peripheral arteries during LV systole. Consequently, there will be an elevation of central aortic PP and LV after load [47] and reduction of ejection fraction, leading to LV hypertrophy [5]. Also, ventricular remodeling may cause an increase in LA pressure, with consequent increase in LA wall stress and LA remodeling, ultimately leading to LA dilation [48], which, altogether, leads to triggering of ectopic beats triggers and induction of AF [49].

Nonhemodynamic mechanisms consist mostly of the autonomic system activity [50]. The sympathetic nervous system affects the mechanical properties of the arterial wall decreasing its distensibility [51]. It has been demonstrated that sympathetic system has a direct effect on carotid-femoral PWV, even in patients without comorbidities. Consequently, an increased sympathetic tone shows a negative effect on arterial wall thickness [52]. In addition, changes in the baroreceptor response due to the stiffening of the arterial walls alter the cardiac autonomic drive. Therefore, in patients with stiffer arteries, sudden changes in pressure could affect the activation of arterial baroreceptors, leading to an acute imbalance between the sympathetic and parasympathetic responses in the heart, hence increasing its vulnerability to AF.

3.2 Hypertension, AS and AF

Possible mechanisms for the linkage between hypertension and AF begin with endothelial dysfunction (Fig. 1, Ref. [49]). Ciccone et al. [53] reported the relationship of the inflammatory process with initial damage of the vascular wall. Sympathetic overactivity may precede hypertension and promote AF.

3.3 Genetic influence on arterial stiffness and atrial fibrillation

Genetic predisposition to AS and increased risk for AF risks another interesting aspect that has been studied. Zekvat et al. [50] analyzed patients of the UK Biobank, participants of the genome-wide association study (GWAS), using Mendelian randomization to determine the association of AS index with cardiovascular diseases. In this study, genetic variants linked to AS were identified. In addition, the authors found a genetic causal relationship between AS and increased systolic BP (β = 4.63 mmHg; 95% CI, 2.1–7.2; p = 3.37 × 10⁻⁴) and diastolic blood pressure
Fig. 1. Potential mechanisms linking arterial stiffness and atrial fibrillation. AF, atrial fibrillation; LVH, left ventricular hypertrophy. Adapted from Kjeldsen et al. [49].

($\beta = 2.61$ mmHg; 95% CI, 1.2–4.0; $p = 2.85 \times 10^{-4}$) [47].

Roselli et al. [54], in a meta-analysis of the same dataset, found an increase in the number of loci associated with AF, and identified genes that might be involved in AF etiology. Later, Zekavat et al. [55] conducted another study investigating the association between genetic predisposition to AS and an increased risk for AF. After performing Mendelian randomization with several loci associated with increased AS, the researchers found that genetic predisposition to AS was associated with the incidence of AF (OR 1.8 per SD Arterial Stiffness Index [ASI] phenotype; 95% CI, 1.4–2.2; $p = 3.1 \times 10^{-7}$). These results support a causal relationship between AS and AF. However, due to the lack of genetic studies in this field, further investigations are still required.

3.4 Arterial stiffness as a predictor of atrial fibrillation

Besides the relationship between AS and AF, already described in the literature, it is still unknown whether AS would play a predictive role in AF [40]. Krishnamoorthy et al. [56] found a positive correlation between AS and AF in patients with dual-chamber pacemakers (PWV, $p = 0.004$; PP, $p = 0.001$) and suggested that AS may be an important predictor of AF in this population. Likewise, in a 20-year observational study of 5331 participants of the Framingham Heart Study, Mitchell et al. [33] showed that AS, measured by PP, was a predictor of AF.

As already mentioned, Lau et al. [41] found a positive correlation between AS and AF. In addition, the authors found that AS was an important feature of AF recurrence after cardiac ablation in individuals with AS values $\geq 75$th percentile, but not in the others ($p = 0.008$). Also, Kizilirmak et al. [48] described that AS was significantly correlated to AF occurrence ($p < 0.001$), but not associated with AF recurrence ($p = 0.068$). In this study, only LA size was shown to be a predictor of AF recurrence ($p = 0.02$). This was corroborated by results of the study Chen et al. [40], which also did not support the use of AS as a predictor of AF.

4. Conclusions

This paper brings together available data on AS in attempt to improve the understanding of its pathophysiology, its association and possible predictive role in AF, as well as the use of non-invasive methods to assess AS. Further investigation is needed to confirm the predictive role of the variables described in AF, and their use in clinical practice.

Author contributions

GSF, ECDB—performed discussion. ECDB—review references. CK, JPG—analyzed aspects of arrhythmia. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

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