Chapter 3

Arrhythmia Risk and Arterial Stiffness

Ioana Mozos*

Department of Functional Sciences, “Victor Babes” University of Medicine and Pharmacy, Romania

*Corresponding Author: Ioana Mozos, Department of Functional Sciences, Discipline of Pathophysiology, T. Vladimirescu Street 14, 300173, Timisoara, Romania, Email: ioanamozos@yahoo.de

First Published December 10, 2016

Conflict of Interests: The author declares that there is no conflict of interest regarding the publication of this chapter.

Copyright: © 2016 Ioana Mozos.

This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source.

Abstract

Considering the high prevalence of cardiac arrhythmia, often related to cardiovascular mortality, it was the aim of the present paper to review the type of arrhythmia associated with arterial stiffness, the main mechanisms linking arrhythmia risk and arterial stiffness, focusing on the latest studies in the area, their implications for cardiovascular prevention, clinical practice and therapy.

The relationship between increased heart rate and pulse wave velocity (PWV) is explained by the autonomic tone, functional changes of the elastic fibers in the vascular wall, increased metabolic rate leading to an increased oxidative stress and low grade inflammation. The most important links between PR interval prolongation and increased arterial stiffness are neurohormonal pathways and aging. More links were found between atrial fibrillation and arterial stiffness including: left atrium remodeling, mitral regurgitation, vascular inflammation and smooth muscle cell contraction, gradual ischemic myocardial damage, impaired endothelial function due to increased serum uric acid and homocysteine, neurohormonal factors (aldosterone and natriuretic peptides), hypertension and aging. The association between arterial stiffness and impaired ventricular repolarization may be explained by electrophysiological myocardial remodeling and coronary atherosclerosis.

Risk assessment for the occurrence of rhythm and conduction disorders should include arterial stiffness.
Cardiac Arrhythmia

Introduction

Cardiovascular diseases continue to be the leading mortality causes worldwide. The underlying substrate is, in most cases, atherosclerosis, with a latent evolution and a possible fatal clinical debut. Sudden cardiac death, related to fatal ventricular arrhythmias, is a common mortality cause. Markers of cardiovascular arrhythmia and sudden cardiac death risk deserve special attention.

Arterial stiffness is a noninvasive marker of subclinical atherosclerosis and arteriosclerosis, based on changes of vascular structure (rupture of elastin fibers, accumulation of collagen, fibrosis and necrosis of muscle fibers, inflammation and calcium deposits in the media of the vascular wall) and function [1], reducing distensibility of the arterial wall and impairing the buffering capacity of the arteries to pulsatile cardiac ejection [2].

Arterial stiffness can be assessed by pulse wave velocity (PWV) measurement, the gold standard measure of aortic stiffness [3]. Arterial stiffness and endothelial dysfunction predict, beyond standard cardiovascular risk factors, future cardiovascular events [2, 4-6], especially coronary heart disease and stroke. When arteries stiffen, PWV increases, and excessive aortic stiffness contributes to damage and inflammation in the arterial wall, increasing the likelihood of plaque rupture [7].

Several other markers of atherosclerosis may be used besides PWV, such as intima-media thickness, pulse pressure or ankle-brachial index. Intima-media-thickness (IMT) is a measure of arterial thickening and predictor of myocardial infarction and stroke risk [8] and resting ankle-brachial index (ABI) is the most commonly used test to diagnose lower-extremity atherosclerosis [9]. Pulse pressure, the difference between systolic and diastolic blood pressure, is a surrogate marker of proximal aortic stiffness and vascular aging, linked to cardiovascular morbidity and mortality [10, 11].

The association between endothelial dysfunction and arterial stiffness has been demonstrated by several studies, related especially to reduction of nitric oxide and up-regulation of endogenous endothelin-1 production, explaining why condition exhibiting endothelial dysfunction are also associated with increased arterial stiffness [12, 13].

Objectives

Considering the high prevalence of cardiac arrhythmia, often related to cardiovascular mortality, it was the aim of the present paper to review the type of arrhythmia associated with arterial stiffness, the main mechanisms linking arrhythmia risk and arterial stiffness, focusing on the latest studies in the area, their implications for cardiovascular prevention, clinical practice and therapy.

Heart Rate and Arterial Stiffness

Heart rate, a hemodynamic parameter and marker of sympathetic activity and basal metabolic rate, plays differential roles in the development of arterial stiffness and...
subclinical atherosclerosis during young adults, as reported by Chen et al. in the Bogalusa Heart Study, including 255 Black and 659 White subjects and demonstrating a significant positive association between resting heart rate and PWV, independently of blood pressure and age [14]. A higher heart rate may increase arterial stiffness by accelerating the fatigue of elastic fibers due to increased number of repetitive stretching cycles, impairing relaxation of large arteries due to shorter diastole, enabling vascular smooth muscle cell growth and synthesis of the components of the extracellular matrix [14]. The increase of PWV with heart rate is more important in Blacks than in Whites [14]. Park et al. also reported a gradually increase of brachial-ankle pulse wave velocity with heart rate, independent of classic cardiovascular risk factors, in a study including 641 Korean adults, in a health examination program, concluding that early detection of increased resting heart rate is important for preservation of arterial function and assessment of cardiovascular risk [15]. Several other studies have shown that arterial distensibility varies inversely with heart rate, related to the vagal tone [16,17]. Silva et al. found and tested a formula, related to changes in arterial distensibility and heart rate, demonstrating that reduction of arterial distensibility with heart rate was more important in arteries that supply end capillaries with high permeability and low reflection coefficients [18].

Considering the influence of the sympathetic tone on both heart rate and vascular stiffness, it has been suggested that the change in sympathetic tone determines the heart-rate-dependent PWV variations [14]. An increased sympathetic tone is responsible for an increased vascular tone and resistance and is associated with an increased oxygen consumption and increased production of proinflammatory cytokines able to impair nitric oxide release and cause endothelial dysfunction [15]. A higher heart rate may reflect an increased metabolic rate, leading to increased oxidative stress and low-grade inflammation [15]. Heart rate variability, a measure of autonomic control, was associated with indices of early carotid damage in 100 peri- and postmenopausal women, suggesting that autonomic regulation is involved in vascular damage, together with estrogen level and metabolic changes [19]. Augmentation index, a marker of endothelial dysfunction and arterial stiffness is corrected for heart rate according to several methodologies. Conflicting results have been obtained regarding the association between heart rate and intima-media-thickness [14].

The PR Interval and Arterial Stiffness

PR interval prolongation exceeding 200 ms characterizes the first-degree atrioventricular block and is very common in clinical practice, its prevalence increasing with age and several clinical conditions [20,21]. It is related to increased vagal tone in young and degenerative changes in old subjects, with a prolongation of the interval between the P wave onset and His bundle poten-
tial, reflecting a delay within the atrioventricular junction [20,22]. It was considered “benign” by several authors, but lately it has been associated with a high risk for incident atrial fibrillation and heart failure hospitalization, pacemaker implantation, adverse cardiovascular outcomes and all-cause mortality [23-25].

PR interval length was independently associated with endothelial dysfunction and increased arterial stiffness, in a study including 88 healthy subjects, with no history of cardiovascular diseases, suggesting the presence of a systemic, intermediate, pathological state of the vasculature related to PR prolongation, before clinically manifest cardiovascular events [20]. An association between PR interval duration and arterial stiffness was present even in subjects with a normal PR interval duration (< 200 ms), suggesting the need to redefine the normal range of PR interval [20]. PR prolongation increases intra-atrial pressure and activates neurohormonal pathways, impairing thereby the vascular function [24]. A higher risk of adverse cardiovascular outcomes was also noticed in subjects with a PR interval exceeding 149 ms [24]. Gosse et al. demonstrated a link between baseline increased pulse pressure or arterial stiffness with the prolongation of the PR interval with aging, suggesting that increased arterial stiffness favors the increase in the PR interval with age [21]. PR interval prolongation was associated with endothelial dysfunction assessed by brachial flow-mediated dilatation and endothelial repair activation assessed by measuring circulating endothelial progenitor cells by flow cytometry, in 348 high-risk patients with prior coronary artery disease [25]. PR interval prolongation may be considered as a marker for vascular damage and repair but it could also be an accompanying phenomenon during the atherosclerotic process [25]. PR interval prolongation may be a marker of subclinical cardiovascular disease, mediated through endothelial dysfunction [25].

**Atrial Fibrillation and Arterial Stiffness**

Atrial fibrillation, the most common arrhythmia, is associated with an increased risk of stroke. Conflicting results have been obtained regarding the interaction between atrial fibrillation and arterial stiffness.

Several studies revealed an interplay between systemic atherosclerosis, assessed by different methods, and the occurrence of atrial fibrillation (Table 1). Arterial stiffness was found as an important determinant of left atrium remodeling, considering the association with the left atrial diameter according to a study including 33 patients with atrial fibrillation after external cardioversion [31]. Possible links between arterial stiffness and left atrial diameter might be mitral regurgitation, associated with higher cardio-ankle vascular index values (CAVI), inflammation, vascular smooth muscle cell contraction and stretch-
induced release of metalloproteinase-12 in atrial tissues [31,36]. An elevated aortic stiffness is able to increase the diameter of the left atrium and increase the risk of atrial fibrillation and stroke, suggesting that atrial fibrillation is the pathophysiological link between arterial stiffness and stroke, according to a study including 310 hypertensive patients and reporting significant correlations between left atrial diameter as a determinant of atrial fibrillation risk and PWV, independent of other confounding factors [35]. The aorta may be considered, according to its embryological origin, as a third chamber of the left heart, enabling a continuous flow of the stroke volume [37]. Left atrial diameter was significantly increased and independently associated with arterial stiffness in patients with obstructive sleep apnea, atrial remodeling contributing to the increased risk of atrial fibrillation [33]. Subclinical atherosclerosis may cause gradual ischemic myocardial damage, enabling premature apoptosis of myocytes, arterial fibrosis, structural and electrical remodeling of the atria, due to fibrosis and hypertrophy, and occurrence of areas with impaired or blocked conduction, facilitating reentrant arrhythmias [7,11]. Atrial stiffness was also associated with abnormal microvascular structure and function, with an increased susceptibility to intermittent microvascular ischemia due to abnormal microvascular reactivity and inward eutrophic or hypertrophic vascular remodeling [7].

### Table 1: Studies linking arterial stiffness and arrhythmia risk.

<table>
<thead>
<tr>
<th>Atrial fibrillation or marker of arrhythmia risk</th>
<th>Markers of arterial stiffness</th>
<th>Mechanisms explaining the link, findings</th>
<th>Study population</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation (AF) incidence</td>
<td>Carotid intima-media thickness (cIMT)</td>
<td>Atherosclerosis and arterial stiffness play a role in AF pathophysiology</td>
<td>ARIC Study (13,907 patients) MESA Study (6,640 patients) Rotterdam Study (5,220 patients)</td>
<td>Chen et al, 2010 [11]</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>Radial artery pulse wave velocity</td>
<td>In patients with hypertension, the presence of AF was associated with arterial stiffness, related to serum uric acid and homeostatic levels</td>
<td>267 hypertensive patients before administration of antihypertensive treatment</td>
<td>Crouze et al, 2013 [28]</td>
</tr>
<tr>
<td>Atrial fibrillation subtypes</td>
<td>cAVI (carotid-ankle vascular index)</td>
<td>Atrial stiffness at baseline predicts atrial fibrillation and stroke, suggesting that atrial fibrillation is associated with arterial stiffness</td>
<td>57 patients with both hypertension and atrial fibrillation and 156 hypertensive patients</td>
<td>Tagliabue et al, 2014 [27]</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>Pulse pressure</td>
<td>The prevalence of AF increased with widening PP</td>
<td>6,036 participants from the Multi-Ethnic Study of Atherosclerosis</td>
<td>Kottke-Marchant et al, 2012 [10]</td>
</tr>
<tr>
<td>Atrial fibrillation (AF)</td>
<td>Measurement of timing of Korotkoff sounds</td>
<td>Atrial fibrillation is a strong predictor of future atrial fibrillation in hypertensive patients, independently of age, 24-h pulse pressure and left atrial diameter</td>
<td>387 hypertensive patients before administration of antihypertensive treatment</td>
<td>Crouze et al, 2013 [28]</td>
</tr>
<tr>
<td>Non valvular atrial fibrillation (NVAF)</td>
<td>Carotid intima-media thickness (cIMT)</td>
<td>Nonvalvular atrial fibrillation and systemic arterial stiffness are closely associated; persistent/permanent NVAF was an independent predictor of abnormal cIMT, suggesting a higher atherosclerotic burden in patients with long-standing NVAF</td>
<td>312 patients enrolled in the Atrial Fibrillation Registry</td>
<td>Portrait et al, 2013 [29]</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>Pulse pressure (PP)</td>
<td>PP is a significant risk factor for AF</td>
<td>6,036 participants from the Multi-Ethnic Study of Atherosclerosis</td>
<td>Kottke-Marchant et al, 2012 [10]</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>cAVI (carotid-ankle vascular index)</td>
<td>In patients with atrial fibrillation, arterial stiffness is associated with age and AF duration and other cardiovascular risk factors, and could represent an important factor for left atrial remodeling and AF maintenance</td>
<td>93 patients with atrial fibrillation after external cardioversion</td>
<td>Tagliabue et al, 2014 [11]</td>
</tr>
<tr>
<td>Atrial fibrillation hospitalization</td>
<td>Carotid intima-media thickness (cIMT)</td>
<td>Atrial fibrillation can predict future AF</td>
<td>4,046 middle-aged subjects from the general population</td>
<td>Abraham et al, 2014 [9]</td>
</tr>
<tr>
<td>Prolonged QT and Tpeak-Tend intervals (predictors of ventricular arrhythmia risk)</td>
<td>Pulse wave velocity (PWV), augmentation indices</td>
<td>Myocardial and endomyocardial longitudinal remodeling due to increased ventricular load, or subclinical atrial stiffness due to microvascular ischemia in the coronary artery</td>
<td>58 healthy participants</td>
<td>Mazzu, 2014 [5]</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>Ankle-brachial index (ABI)</td>
<td>ABI is a simple and cheap method to better define the prevalence of vascular disease in patients with nonvalvular atrial fibrillation</td>
<td>2,027 non valvular atrial fibrillation patients</td>
<td>Veratti et al, 2013 [12]</td>
</tr>
<tr>
<td>PP interval</td>
<td>Pulse pressure, QRJ interval (the interval between the QRJ complex on the ECG and the occurrence of the last Korotkoff sound)</td>
<td>Increased atrial stiffness favors the incidence of the PP interval with age</td>
<td>214 untreated hypertensive patients</td>
<td>Giro et al, 2011 [21]</td>
</tr>
<tr>
<td>PR interval</td>
<td>cIMT, carotid-ankle pulse wave velocity (cAVI)</td>
<td>cIMT and carotid-ankle pulse wave velocity are independent predictors of atrial fibrillation</td>
<td>748 middle-aged subjects without obstructive sleep apnea</td>
<td>Singer et al, 2010 [13]</td>
</tr>
</tbody>
</table>

**ARIC Study (6,640 patients)**
**MESA Study (6,640 patients)**
**Rotterdam Study (5,220 patients)**
**ARAPACS Study (6,640 patients)"**
Compared with paroxysmal AF patients, persistent AF patients had higher PWV values, serum homocysteine and uric acid concentrations, and left atrial diameters according to a study including patients with hypertension and atrial fibrillation [26]. PWV was higher in hypertensive patients with atrial fibrillation compared to those without [26]. Increased serum uric acid and homocysteine impair vascular structure and function due to decrease in nitric oxide, increased production of reactive oxygen species, vascular inflammation and proliferation of vascular smooth-muscle cells with inhibition of endothelial cell growth [26,38,39]. However, therapy of hypertension should also consider lowering of arterial stiffness in order to prevent the occurrence of atrial fibrillation [26].

Aldosterone and natriuretic peptides, markers of neurohormonal activation, are increased in atrial fibrillation and influence atrial remodeling [20]. The mentioned markers are reversed on cardioversion [40]. Hypertension and aging, two important risk factors of incident atrial fibrillation, are both associated with an increased arterial stiffness, but arterial stiffness was revealed as a strong predictor of future atrial fibrillation in hypertensive patients, independently of age, 24-h pulse pressure and left atrial diameter in a study including 853 hypertensive patients, before administration of antihypertensive therapy [28]. Low-grade inflammation could be the link between aortic stiffness and left atrium dilation [27].

Higher pulse pressure (PP) was associated with left atrial enlargement [41] and an increased prevalence of atrial fibrillation, especially in adults < 75 years [10]. The link between AF and PP is, probably, arterial stiffness, which increases with age, promoting left ventricular hypertrophy, impairing left ventricular relaxation and enabling left atrium enlargement due to the increase in the intra-atrial pressure, atrial dysfunction and enlargement [10,42]. Yoon et al. went further and assessed echo-doppler derived variables of ventricular stiffness and ventriculo-arterial interaction as predictors of new-onset atrial fibrillation in patients with heart failure [43]. Persistent/permanent non valvular atrial fibrillation (NVAF) was an independent predictor of abnormal intima-media thickness, suggesting a higher atherosclerotic burden in patients with long-standing NVAF and that atherosclerosis might favor the progression of paroxysmal to long-standing atrial fibrillation, as reported by Proietti et al. in a study enrolling 2,027 patients [29]. Intima-media thickness values were predictors of hospitalization for NVAF during a follow up of 15.3 years of 4,846 middle-aged subjects from the general population, suggesting that arterial thickening can predict future atrial fibrillation [8]. A high prevalence of pathological ankle-brachial index was reported among patients with nonvalvular atrial fibrillation, progressively increasing from paroxysmal to permanent AF [32].

After midlife, wave reflection is reduced in the larger muscular arteries, enabling more pulsatile energy to pen-
etrate the small arteries, resulting in damages due to the barotrauma and an increased cardiovascular risk [7]. In elderly atrial fibrillation patients who underwent electrical cardioversion, baseline arterial stiffness predicted atrial fibrillation relapse at follow up in a study including 31 patients with atrial fibrillation [27]. Modulation of vascular properties could represent a possible target to reduce atrial fibrillation in elderly patients [27].

Aldosterone, known for its effect in regulating electrolyte balance, has been shown to impair endothelial function, related to high blood pressure and atherosclerosis [44]. The vascular effects of aldosterone depend on oxidative stress: at low oxidative stress, aldosterone promotes nitric oxide production, enabling vasodilation, but with increased oxidative stress, endothelial dysfunction and vasoconstriction will prevail [45].

On the other hand, Reiffel revealed that the arterial stiffness index and left ventricular hypertrophy cannot be used to predict the risk of atrial fibrillation in hypertensive patients, considering 53 hypertensive patients with or without atrial fibrillation and 17 nonhypertensive controls with AF [46]. Carotid ultrasound or measurement of arterial stiffness were not recommended in prediction of atrial fibrillation by the findings of several large studies (ARIC, MESA and Rotterdam Study), despite the role of atherosclerosis and arterial stiffness in AF etiopathogenesis [11].

The conflicting results of the several studies assessing the relationship between arterial stiffness and atrial fibrillation may be explained by the cross-sectional study designs, inter- and intra-observer method’s variability, different characteristics, size and inclusion criteria of study populations, self-reporting of some data (history of AF), selection biases due to missing data or antihypertensive therapy, use of different and multiple statistical methods [10,26,29].

**Ventricular Arrhythmia Risk and Arterial Stiffness**

The QT interval, the electrocardiographic expression of ventricular depolarization and repolarization, is a predictor, if prolonged, of ventricular arrhythmia [47,48]. The Tpeak-Tend interval, measured as the difference between QT and QTpeak interval, has been accepted as a measure of transmural dispersion of repolarization, related to arrhythmogenesis [49,50].

Prolonged QT and Tpeak-Tend intervals were associated with endothelial dysfunction, arterial stiffness, impaired coronary perfusion and accelerated arterial aging in a study including 54 healthy participants [6]. Several mechanisms may explain the association between subclinical arterial disease and impaired repolarization, such as myocardial and electrophysiological remodeling due to increased ventricular load, or subendocardial ischemia due to microvascular atherosclerosis in the coronary artery, or parallel evolution of subclinical arterial disease and coronary atherosclerosis [6,34].
Conclusions

Arterial stiffness and atherosclerosis play an important role in arrhythmia occurrence and recurrence and it may allow early detection of subjects most susceptible to develop future arrhythmias. The relationship between increased resting heart rate and PWV is explained by the autonomic tone, functional changes of the elastic fibers in the vascular wall, increased metabolic rate leading to an increased oxidative stress and low grade inflammation. The most important links between PR interval prolongation and increased arterial stiffness are neurohormonal pathways and aging. More links were found between atrial fibrillation and arterial stiffness including: left atrium remodeling, mitral regurgitation, vascular inflammation and smooth muscle cell contraction, gradual ischemic myocardial damage, impaired endothelial function due to increased serum uric acid and homocysteine, neurohormonal factors (aldosterone and natriuretic peptides), hypertension and aging. The association between arterial stiffness and impaired ventricular repolarization may be explained by electrophysiological myocardial remodeling and coronary atherosclerosis.

Delaying atherosclerosis progression and controlling atherosclerosis risk factors would result in a lower incidence of persistent atrial fibrillation and ventricular arrhythmia. Risk assessment for the occurrence of rhythm and conduction disorders should include arterial stiffness and other markers of subclinical atherosclerosis. Further follow up studies are needed to find and evaluate new mechanisms linking arterial stiffness and rhythm and conduction disorders.

References


47. Al-Khatib SM, LaPointe NM, Kramer JM, Califf RM. What clinicians should know about the QT interval. JAMA. 2003; 289: 2120-2127.

