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Atrial fibrillation and arterial hypertension: A common duet with dangerous consequences where the renin angiotensin-aldosterone system plays an important role☆

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ABSTRACT

Atrial fibrillation (AF) represents the most common sustained cardiac arrhythmia, as it affects 1%–2% of the general population and up to 15% of people over 80 years. High blood pressure, due to its high prevalence in the general population, is by far the most common condition associated with AF, although a variety of diseases, including valvular, coronary heart and metabolic diseases, are held to create the substrate favouring AF. Due to the concomitance of these conditions, it is quite challenging to dissect the precise role of high blood pressure in triggering/causing AF.

Hence, even though the intimate association between high blood pressure and AF has been known for decades, the underlying mechanisms remain partially unknown. Accumulating evidences point to a major role of the renin-angiotensin-aldosterone system in inducing cardiac inflammation and fibrosis, and therefore electric and structural atrial and ventricular remodelling, with changes in ions and cell junctions leading to AF development. These evidences are herein reviewed with a particular emphasis to the role of the renin-angiotensin-system aldosterone system.

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, with an estimated prevalence of 1%–2% in the general population and up to 15% of people over 80 years [1–5]. These rates likely entail a marked underestimation because AF can be totally asymptomatic (silent AF). Moreover, due to aging of the population, a doubling of the prevalence of AF is expected to occur in the next 50 years thus leading to an epidemic of AF worldwide.

AF doubles the risk of death independently of other known predictors of mortality [6] and represents the major cause of cardio-embolic stroke with ensuing long-term disability [1]. It also worsens the quality of life [7,8] and can lead to cognitive dysfunction and dementia by causing silent and recurring strokes [9].

As AF mandates long-term treatment for heart rate control and anticoagulation and, moreover, accounts for one third of all hospitalizations for arrhythmias, it imposes an enormous burden on the community [1].

Due to the high prevalence of high blood pressure (HBP) in the general population the vast majority of the cases of AF occurs in hypertensive patients, even though many other factors, as valvular and coronary artery diseases, heart failure, metabolic disorders as hyperthyroidism, obesity, and diabetes mellitus, often concur to create the stage favouring and maintaining AF. As HBP involves multiple hormonal and biochemical changes, it has been challenging to disentangle the role of HBP in triggering/causing AF from that of these other factors; therefore the relative weight of different putative mechanisms underlying the association between AF and HBP still remains poorly understood [10]. Nonetheless, there is little doubt that a better identification of the mechanisms and predictors of AF in HBP is key for developing more effective prevention strategies and intervention programmes. The aim of this review is meant to provide updated information on prevalence, predictors, and putative mechanisms of AF in the hypertensive heart disease.

1. Incidence of AF in HT patients

After anecdotal reports of an association between AF and HBP [11], unambiguous evidence that HBP contributes to AF came from the Framingham Heart Study in 1994 [12]. During 38 years of follow-up of 2090 men and 2641 women 562 new cases of AF were observed, with a doubling AF incidence after 50 years of age with each successive decade, leading to almost 10% rate of AF in people who reached age 80 years of age.

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The age-dependency of AF was emphasized by a more recent analysis of a cohort of the Framingham Heart Study: this showed increased age-adjusted AF prevalence rates from 1958–1967 to 1998–2007, which can be explained by the improved medical care leading to increased survival in general, and also after the onset of AF [13]. Of note, in the most recently examined decade of the Framingham Study, i.e. 1998–2007, notwithstanding the reduction over time of the prevalence of most modifiable risk factors for AF [13], it was altogether evident that HBP and antihypertensive treatment carried the greatest population-attributable risk. After age-adjustment, the only predictors of AF were HBP and ECG evidence of hypertensive left ventricular (LVH), besides diabetes mellitus and cigarette smoking (in women). Moreover, hypertensive men and women had 80% and 70% greater risk for AF, respectively, than normotensive subjects; ECG evidence of LVH increased risk of AF by almost a 3- and 4-fold, respectively (Table 1) [12].

Other studies thereafter confirmed the role of HBP in causing AF: for example, in the 30,424 high CV risk participants of the Ontarget study (mean age 66 years), who were in sinus rhythm at enrolment, new AF occurred in 6.8% of the patients during a median follow-up period of 4.7 years. Age, history of HBP, and coronary or cerebrovascular disease, systolic BP, pulse pressure, LVH, body mass index, and serum creatinine predicted incident AF [14], which, in turn, implied an increased risk of congestive heart failure and cardiovascular death. In the PIUMA Study that prospectively examined the determinants of AF in 2482 untreated essential hypertensive patients without valvular or rhythm diseases at baseline, LVMI predicted new onset AF and, alongside left atrial diameter, also chronic AF [15]. BP, EKG evidence of LVH, age, and male gender predicted AF also in the hypertensive patients with echocardiographically determined LVH of the LIFE study [16]. Moreover, regression of LVH with treatment was associated with a lower incidence of AF as compared to persistent LVH [17,18], thus confirming the causative role of HBP-induced LVH in triggering AF. More recent studies showed that the increased risk of AF in hypertensive patients is not confined to those at high CV risk, like the ONTARGET or LIFE Studies patients, but would be shared also by those with BP in the upper normal range [19,20]. Of note, the observation that night-time ambulatory BP correlated with the left atrial size and the plasma levels of natriuretic peptides even in normotensive subjects with AF supported the causative role of BP in AF [21].

Finally, in summarizing the studies reporting an association of AF with HBP the *2012 Position paper of the Working Group on 'Hypertension Arrhythmias and Thrombosis' of the European Society of Hypertension* (*ESH*) [22] overall indicated that from 49% to 90% of AF patients have HBP [23–27].

2. Pathophysiology of AF associated with HT

The major mechanisms underlying AF in HT, although often concomitant, are herein reviewed separately for the sake of clarity.

Table 1
Risk factors for the development of AF in 38-years follow-up of the Framingham Study. Mod. From Kannel W.B. [12].

Risk factors	Age-adjusted OR		Multiple risk factor-adjusted OR	
	Men	Women	Men	Women
Smoking	1.0	1.4*	1.1	1.4
Diabetes	1.7**	2.1***	1.4*	1.6**
EKG-LVH	3.0***	3.8***	1.4	1.3
HT	1.8***	1.7***	1.5**	1.4*
BMI	1.03	1.02	–	–
Alcohol	1.01	0.95	–	–

BMI: body mass index; EKG-LVH: echocardiographic left ventricular hypertrophy; and OR: odds ratio.
Analysis performed using 2-year pooled logistic regression.
* $p < .05$
** $p < .01$.
*** $p < 0.001$.

2.1. Genetic factors

Rare gene mutations predisposing to AF were identified, but they were limited to isolated families without traditional risk factors; their interaction with HBP can be only speculated at this time [28,29]. In 2003 Chen et al. described a gain-of-function mutation in the KCNQ1 gene, which they claimed to be responsible for AF in a Chinese family [30]. This gene encodes the α subunit of the slow component of the delayed rectifier K^+ current (IKs). The variant, as well as others thereafter identified, increases IKs during the action potential (AP) in the atria, thus shortening the atrial AP duration and/or atrial refractoriness [31,32]. Gain of function mutations in other K^+ channels (KCNE2, KCNE5 or KCNJ2), and loss-of-function mutation in the KCNA5 gene, which codes the atrial-specific K^+ voltage gated channel Kv1.5, were also reported to promote AF by inducing early atrial repolarisation [33–37]. Increased susceptibility to AF was also found in patients with mutations in Na^+ or Ca^{2+} channel genes that control ion currents across cell or sarcoplasmic membranes in atrial myocytes [38–40]. Evidence that some mutations specifically increase the susceptibility to AF in hypertensive cardiac disease is, however, lacking. It is nonetheless conceivable that, in the carriers of gene variants predisposing to HBP and AF, an interaction with additional risk factors, particularly in the presence of hypertensive cardiac remodelling, can more easily lead to AF with aging (Fig. 1) [41,42].

2.2. Channels and cell junctions

Mechanic overload, due to HBP or ischemic injury, was found to induce an abnormal expression of ion channels and/or junctional complexes, as connexin 40 and connexin 43, which can enhance myocardium vulnerability by triggering focal ectopic and re-entry activity [43,44]. Whether these alterations play a major role in AF in hypertensive patients has not been specifically investigated and, therefore, is unknown. Undoubtedly, HBP, by causing LVH and impaired LV filling, stretches the atria, thus favouring AF [45]. Moreover, in patients with HBP atrial remodelling and fibrosis can in turn affect channels and/or cell junctions in atrial cardiomyocytes [43].

2.3. Renin-angiotensin-aldosterone system (RAAS)

Activation of RAAS, not only is a feature of high renin essential hypertension, renovascular hypertension and renin secreting tumours, but also represents a common consequence of treatment with diuretics and direct vasodilators. It has electrophysiological effects that can trigger arrhythmias and ultimately induce structural remodelling of the atria, favouring the onset and the perpetuation of AF. For example, angiotensin (Ang) II activates profibrotic pathways via AT1 receptor in myofibroblasts [16,29], thus promoting transformation of resident atrial fibroblasts into myofibroblasts, as well as synthesis of TGFβ1, a major profibrotic cytokine in the atria and the ventricles. Myofibroblasts may in turn release TGFβ1, and other paracrine factors as PDGF, connective tissue growth factor (CTGF), fibroblast growth factor (FGF)-2, and interleukines of the IL-6 family that also affect myocyte electrical function [46,47]. Of note, TGFβ1 released by myofibroblasts differentially regulates the transcription and function of the Na^+ channels [47], while CTGF affects the connexin expression pattern, leading to atrial remodelling and fibrosis (Fig. 2) [46]. Accordingly, some studies reported a lower incident AF in hypertensive patients treated with RAS inhibitors compared to controls [16,48].

Even though atrial wall stretch would be expected to lower aldosterone via enhanced ANP release, plasma aldosterone was found to be elevated in AF patients; conversely, restoration of sinus rhythm lowered its levels [49]. Interestingly, a causative role of aldosterone in the development of AF is supported by the finding of a 12-fold increase of the risk of AF in a large retrospective study of patients with primary aldosteronism, as compared to matched essential hypertensive patients (OR 12,