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MECHANISMS OF HYPERTENSION AND TARGET-ORGAN DAMAGE (JE HALL AND ME HALL, SECTION EDITORS)

Arterial Hypertension, Aldosterone, and Atrial Fibrillation

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Abstract

Purpose Atrial fibrillation is the most common sustained arrhythmia, with a prevalence of 1–2% in the general population and over 15% in people older than 80 years. Due to aging of the population it imposes an increasing burden on the healthcare system because of the need for life-long pharmacological treatment and the associated increased risk of heart failure and hospitalization. Hence, identification of the factors that predispose to atrial fibrillation it is of utmost relevance.

Recent Findings Several conditions exist that are characterized by inappropriately high levels of aldosterone, mostly primary aldosteronism and the severe or drug-resistant forms of arterial hypertension. In these forms, aldosterone can cause prominent target organ damage, mostly in the heart, vasculature, and kidney.

Summary This review examines the experimental data and clinical evidences that support a link between hyperaldosteronism and atrial fibrillation, and how this knowledge should lead to a change in our management of the hypertensive patients presenting with atrial fibrillation.

Keywords Atrial fibrillation · Aldosterone · Hypertension · Arrhythmia

Introduction

Aldosterone, the main mineralocorticoid hormone, plays a life-saving role in preserving body fluid and electrolyte levels, controlling vascular resistance and maintaining blood pressure (BP) under the conditions of hypovolemia and/or salt/water depletion [1••]. However, when inappropriately high, it causes prominent target organ damage, mostly cardiovascular damage [2]. Conditions featuring relative or absolute hyperaldosteronism entail primary aldosteronism (PA), overweight and obesity [3], and severe (stage 2 to 3) or drug-resistant forms of arterial hypertension (HT), besides heart failure. In recent years, a number of clinical and experimental studies have provided compelling evidences that aldosterone plays a role in causing atrial fibrillation (AF) in these conditions.

AF is imposing an increasing burden on the healthcare system, owing to the need for life-long care and pharmacological treatment and the associated increased risk of heart failure and hospitalization [4]. In fact, it is the most common sustained cardiac arrhythmia with an estimated prevalence of 1–2% in the general population, mounting over 15% in people older than 80 years [5].

In several studies, aging and HT were identified as the major risk factors for AF [6]. In the Framingham Study, during 38 years of follow-up of 2090 men and 2641 women, new cases of AF were observed in 11.8%, with AF incidence doubling with each next decade after age 50 years [7].

PA is most common secondary form of hypertension, as it was found to involve from 5 to 20% of hypertensive patients, depending on the cohorts of examined [8–10]. However, it is also the most commonly overlooked such forms because of the misbelief that it is a rare condition and because it can mimic primary (essential) HT and, moreover, requires a complex diagnostic workup [11].

In the present review, we shall examine the experimental data that implicate hyperaldosteronism in atrial arrhythmia and the clinical evidences that support a link between

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hyperaldosteronism and AF. We will also discuss why this novel knowledge should lead to a change in our management of the hypertensive patients.

Experimental Evidences Supporting a Link Between Aldosterone and AF

Three studies have documented that aldosterone induces clear-cut electrophysiological changes in cardiomyocytes, which are held to favor AF [12–14]. One reported increased expression of T-type channels and L-type Ca^{2+} channels in atrial cells and decreased activity of the rapidly activating delayed rectifier potassium current Ikr and transient outward K^+ currents Ito1 [12]. The other two studies described a prolonged release of Ca^{2+} from the sarcoplasmic reticulum induced by activation of ryanodine receptor ultimately resulting in Ca^{2+} overload [13, 14]. Accordingly, in 2012, an in vivo study by Reil et al. showed that rats infused with aldosterone for 8 weeks, at a dose (0.5 μg/h) that did not affect ventricular function or atrial pressure, developed AF after transesophageal atrial burst stimulation [15••]. As the observed changes in BP were minimal, the authors hypothesized that aldosterone per se created a substrate for atrial arrhythmias independent of significant change of left ventricular (LV) afterload [15••].

These findings were consistent with those of another study published in the same year, which showed that, when infused at the same dose but for a shorter time (4 weeks), aldosterone induced shortening of the left atria action potential and doubling of the time occurring for spontaneous conversion of AF to sinus rhythm [16]. Moreover, aldosteronism often causes hypokalemia, which prolongs the atrio-ventricular conduction time, i.e., the ECG PQ interval, and thus facilitates atrio-ventricular reentry mechanisms and the risk of developing AF [17].

Besides electrophysiologic changes, experimentally induced hyperaldosteronism in the setting of high salt intake was shown to exertpressor effects and to promote myocardiocyte growth, inflammation, necrosis, and reparative cardiac collagen deposition, thus leading to left ventricular (LV) hypertrophy and fibrosis [2, 18, 19]. This cardiac remodeling implies stiffening of the LV, impaired LV filling, atrial stretching, left atrial dilatation, and all mechanisms favoring reentry mechanisms [20]. Accordingly, in the setting of hyperaldosteronism, the aforementioned electrophysiologic changes may act as a trigger for AF and/or anticipate its onset during aging [21–24].

Aldosterone increases the levels of proinflammatory genes, as cyclooxygenase-2, osteopontin, tumor necrosis factor-α, monocyte chemotactic protein-1, and NADPH oxidase (nicotinamide adenine dinucleotide phosphate, reduced form). These factors are known to cause oxidative stress, oxidative damage to DNA, endothelial disfunction, and fibrotic tissue deposition [25, 26].

These changes are held to produce discontinuities of gap junctions and muscle bundles with abnormal depolarization waves and reentry circuits [27••, 28]. Moreover, fibroblast–cardiomyocyte coupling can replace cardiomyocyte–cardiomyocyte coupling and, because of the relatively low membrane potential of fibroblasts (− 30 mV), might promote delayed after-depolarization and ectopic firing, thus favoring increased intracellular Ca^{2+} concentrations and spontaneous Ca^{2+} release from the sarcoplasmic reticulum. These changes, in turn, could concur to development and maintenance of AF[27••].

What remains debated is if an abnormal expression of the mineralocorticoid receptor (MR) can raise the risk of AF and/or if the arrhythmia itself induces changes in atrial MR density and/or distribution. However, an increase of MR protein expression was observed after the depolarization of atrial cardiomyocytes with rapid electric field stimulation, which suggested that the electric remodeling affects MR expression [29]. Moreover, since the increase of MR was abrogated either by chelating intracellular Ca^{2+} with BAPTA-AM (bis-ethane-N,N,N′,N′-tetra acetic acid acetoxymethyl-ester) or by blocking L-type Ca^{2+} channels with verapamil, the changes in MR expression likely depend on intracellular Ca^{2+} [29, 30]. However, it has also been contended that the increased MR expression could amplify the effects of aldosterone, as suggested by the observation that T-type Ca^{2+} currents and sarcoplasmic reticulum Ca^{2+} movements are blunted by the MR antagonist spironolactone [29]. Likely, the driver of these effects is blood-borne aldosterone because neither HL-1 nor human atrial cells produce aldosterone [29].

Consistently with these findings, Takemoto et al. reported that in tachypaced sheep eplerenone reduced the left atrial structural remodeling during AF progression, and also the percentage of animals with AF sustained for more than 7 days by 26%. Eplerenone also prevented collagen-III accumulation, interstitial fibrosis, and atrial dilation, prolonged the time to persistent AF, and reduced the percentage of self-sustained AF over a given time (− 42%, $p = 0.03$) [31]. Since it did modify neither the inward rectifier potassium current (IK1) nor the L-type calcium current (ICaL) densities, and the MR (*NR3C2*) expression, it might be that eplerenone minimizes structural but not electrical remodeling, thus highlighting the central role of as an upstream target for reducing AF burden [31].

Clinical Evidences

In 1999, the Randomized Aldactone Evaluation Study (RALES), the first large RCT evaluating spironolactone on top of standard care in New York Heart Association (NYHA) classes III–IV heart failure patients, was stopped prematurely on recommendation of the steering committee because the primary end-point, i.e. decreased mortality, was

reached in the cohort receiving the MR antagonist [32]. In 2005, the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) also found a decreased incidence of sudden death [33]. Unfortunately, data on incident AF were not collected in these trials. However, it was speculated that the lower risk of sudden death seen in the active treatment arm could be related to a decreased onset of arrhythmias, including AF, possibly because of the prevention of cardiac fibrosis.

Some years later, the multicenter Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) study randomized NYHA II class heart failure patients to eplerenone or placebo [34]. During the treatment period (median 21 months), newly detected AF occurred in significantly less patients in the MR antagonist (MRA) group than in the placebo group (2.7% vs 4.5% hazard ratio [HR] 0.58, 95 CI 0.35–0.96), indicating that the MRA was more effective than placebo in preventing AF [34].

Although the results of EMPHASIS-HF were found to be "encouraging,"further more extensive investigations in humans were held to be necessary and therefore no recommendations for use of MRA in the prevention of AF were included in the 2016 ESC guidelines [5]. The issue of use of MRA for preventing AF also neglected by the recent 2019 AHA guidelines [35].

As regards patients with hypertension due to PA, the association between AF and hyperaldosteronism was first reported in 2005 by Milliez et al., based on a retrospective cross-sectional survey of PA patients with matched essential hypertensive patients [36]. On a multivariate analysis, PA independently predicted AF along with age and known duration of hypertension, thus strongly implicating hyperaldosteronism in the pathophysiology of AF. Those results were then confirmed in a larger prospective cohort study of systematically screened patients with HT, where the PA patients exhibited a 7-fold increase of AF, compared with the essential hypertensive patients [37].

Two meta-analyses showed a reduction of AF risk in MRA-treated patients as compared with patients treated with non MRA [38, 39], but they considered patients with a variety of cardiovascular diseases, from heart failure to cardiac surgery and radiofrequency catheter ablation, thus introducing several confounding factors that rendered difficult to draw firm conclusions concerning the role of hyperaldosteronism.

These limitations did affect a long-term (12 years) longitudinal study of hypertensive 204 patients undergoing target treatment for PA [40]. Noteworthy, this study showed that patients with unilateral PA treated with laparoscopic adrenalectomy had their risk of incident AF lowered to the level seen in optimally treated patients with primary hypertension [40]. Moreover, the improved AF-free survival seen in the adrenalectomized PA patients occurred notwithstanding a tapering of the medical therapy. Conversely, in the medically treated PA patients, the risk of AF remained high in spite of an intensified drug treatment, suggesting that removal of the cause of hyperaldosteronism is superior to control the effect of aldosterone through MRA.

Further compelling evidence for a causative role of hyperaldosteronism came from the Prospective Appraisal of the Prevalence of Primary aldosteronism in HYpertensive patients (PAPPHY) Study [41], which will be published early in 2020 (AGGIUNGI VOCE e metti in Press). The study was designed to prospectively assess the prevalence of PA and its subtypes, i.e., aldosterone producing adenoma (APA) and idiopathic hyperplasia (IHA), in consecutive hypertensive patients referred for unexplained ("lone") AF [42].This was a very demanding study that took an enormous effort to be completed, as shown by the fact that of the several centers that initially agreed to take part only three were eventually able to recruit patients. The study recruited a total of 411 patients, of which the majority had AF attributable to valvular and/or coronary heart disease, abnormal thyroid function. Among those with no such obvious causes of AF, 42% were eventually discovered to have PA, which was surgically curable in 48%. The conclusion was, therefore, drawn that AF is a common clinical presentation of PA in hypertensive patients, which lend further support to the view that hyperaldosteronism is causally involved in AF [41].

The appreciation that PA causes AF in many hypertensive patients might eventually change clinical practice in this field because it suggests the need for a systematic screening of these patients for PA. Since PA involves about 6% of the hypertensive patients seen by the general practitioners, more than 11% of those referred to the specialized centers and about 20% of those with resistant hypertension, this piece of information is quite important, also considering that, as mentioned above, surgical cure lowers incident AF, and provides a complete cure or a marked improvement of arterial hypertension in over 80% of the PA patients [8]. Hence, an early diagnosis of PA can change the natural history of the disease and its complications in these patients.

Does AF Raise Aldosterone?

This is still a debated issue because of the lack of ad hoc studies. Few observational studies suggested that in patients with persistent AF, sinus rhythm restoration could be associated with a fall of plasma aldosterone concentration [43–46]. This could be because AF decreases BP and thus activate the renin-angiotensin-aldosterone system implying that cessation of AF can deactivate this system. On the other hand, during AF, the release of atrial natriuretic peptide (ANP) could inhibit aldosterone secretion, thus blunting the effects of AF-induced activation of the renin-angiotensin-aldosterone system activation. However, to date no study answered the questions if AF per se raises aldosterone or alters sensitivity of the cardiac

tissue to the action of aldosterone. Therefore, properly designed studies seem to be necessary to clarify this issue.

Conclusions

Experimental and clinical studies support a causative role of aldosterone excess in the onset of AF, thus suggesting that AF is a preventable complication, at least in a proportion of the hypertensive patients that have excess aldosterone levels, as those with primary aldosteronism. Given the high prevalence of PA and the fact that AF is expected to rise markedly in the next decades because of aging of the population,, thus raising the burden posed by AF on the health care system, research devoted to improve our knowledge of the role of hyperaldosteronism and, at large, of the mechanisms underpinning AF should be promoted. In the meantime, it is altogether evident that better strategies to simplify the screening and subtyping of PA by means of simplified algorithms can allow preventing the development of AF in a multitude of hypertensive patients in whom PA currently goes undetected.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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