Aldosterone and Cardiovascular Damage:

A New Lesson from an Old Study

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Short title: Aldosterone and Cardiovascular Damage

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In a post-hoc analysis of the ARIC Study, which recruited 15,792 adults (18.1% Black and 81.9% Whites), aged 45-64 years, from 4 US communities between 1987 and 1989, Brown et al. collected echocardiographic data, plasma renin and aldosterone values at visit 5 (2011-2013) and incident events at follow-up over 6 to 8 years in 4,457 subjects entailing 28% of the original cohort [1]. They observed an association of renin suppression with greater left ventricular (LV) mass index (LVMI), LV volumes, altered LV filling, and left atrial volume index; of note, this increase of LVMI entailed an eccentric LV remodeling, in line with previous observations in patients with primary aldosteronism, who showed an inward reverse type of remodeling after cure by adrenalectomy[2]. Moreover, the hazard ratio (1.34) for heart failure hospitalization (HF) and for atrial fibrillation (AF) (1.37) raised with renin suppression and higher plasma aldosterone levels, respectively.

In line with a bulk of data, the authors proposed that excess mineralocorticoid receptor activation, via salt retention and intravascular volume expansion as revealed by renin suppression and high plasma aldosterone, would cause a cascade of cardiomyocyte hypertrophy and perivascular inflammation, disproportionate increase of LV mass and fibrosis, altered LV filling and left atrium dilatation, eventually predisposing to AF and to HF (Figure; for review [3]). Key in this process is a high sodium intake, which allows excess aldosterone to exploit its damaging effects; unfortunately, whether their ARIC subjects were on such high sodium intake could not be ascertained. Besides, adjustment for hypertension and anti-hypertensive treatment annulled the statistical significance of the aforementioned hazard ratios; this is not surprising, since cardiac remodeling is determined by both pre- and afterload, i.e. by the concurrence of aldosteronism, a high sodium intake, and hypertension.

Although ARIC was not a hypertension study, at visit 5 data 70% of the participants were on antihypertensive agents, and those featuring renin suppression (33% of the total) showed higher

BP values and a lower rate of antihypertensive treatment than the renin non-suppressed cohort (63% vs 73%), indicating that, for unclear reasons, they had more severe hypertension and/or were less intensively treated. In this retrospective study, unfortunately, their medical history and BP control in over 22-24 years until visit 5 remains a black box.

Overall, 28% of the ARIC patients were on beta-blockers, which blunt renin secretion; unsurprisingly, the proportion of users of these agents was higher in the renin-suppressed than in non-suppressed participants (39% vs 22%, $p<0.001$). Conversely, the rate of treatment with drugs that raise renin (ACE inhibitors, ARBs and/or diuretics) was significantly lower (44% vs 77.4%). Thus, the hormonal differences could simply reflect the effect of treatment and/or cohorts with different comorbidities, thus requiring diverse agents rather than an underlying pathophysiology.

Despite these limitations, the authors could take advantage of a large dataset and perform several sensitivity analyses: reassuringly, they found similar, albeit subtler, LV changes even in patients without treated hypertension. This reinforces their contention that renin suppression, a proxy for excess mineralocorticoid receptor activation, denotes detrimental effects on the heart regardless of BP. Hence, one might speculate that subtle hormonal changes, more accurately revealed by renin than aldosterone, induce adverse LV remodeling even before hypertension occurs. Remarkably, in both ARIC and the Framingham Heart Offspring study [4], the remodeling developed in spite of hormone values considered 'well within the normal range', in line with results of clinical trial in HF where mineralocorticoid receptor blockade was life-saving even without overtly elevated aldosterone.

To depict this combination of renin suppression and higher plasma aldosterone the authors used the term 'primary aldosteronism physiology', since these are the two hallmarks of primary aldosteronism. It's unfortunate that they could not tell us how many of their ARIC participants

had undetected ‘clinical’ primary aldosteronism, which has a long natural history[5] , may mimic essential hypertension and is amenable to cure. Of note, 11.6% of them had both an aldosterone-to-renin ratio $\geq$ 20 (ng/dl)/(ng/ml/h) and plasma renin activity values $\leq$ 0.5 ng/ml/h, consistent with the profile of PA; in this ‘epidemiologic primary aldosteronism' sub-cohort the echocardiographic findings were fully consistent with the overall results, thus further supporting the concept that renin-independent aldosterone production affects cardiac structure and function.

How do these results fit with available knowledge? In the ‘70s, seminal studies from Dr. Laragh’s group [6] identified renin as ‘the cardiovascular damaging hormone’, leading to consider high renin the trademark of severe and/or malignant hypertension and the major target for pharmacological blockade. Conversely, the hyperaldosteronism associated with renin suppression typically seen in PA, was regarded as a benign form of hypertension. This simplistic view disregarded that secondary aldosteronism is a feature of high renin states. It was only after studies by Suzuki et al. in primary and secondary aldosteronism [7] and in larger primary aldosteronism cohorts thereafter, reporting excess LV hypertrophy [8] and fibrosis [9 10] as compared to BP-matched essential hypertensive patients, as well as a 12-fold increased risk of AF in patients with primary aldosteronism [11], that due attention was drawn to the detrimental cardiac effects of hyperaldosteronism. Those observations triggered a broader screening of hypertensive patients for primary aldosteronism and led to appreciate that, under high sodium intake, excess aldosterone damages the heart even when renin is undetectable. Since then, more consideration has been devoted to assessing hypertension-mediated organ damage in low-renin patients and the latest guidelines list ‘hypertension-mediated organ damage in excess of what expected on the basis the degree of BP elevation’ among the conditions that should alert physicians on the presence of primary aldosteronism [12].

Owing to the current aging of the population, the clinical outcomes associated with aldosteronism in the study by Brown et al [1], i.e. AF and HF, contribute substantively to cardiovascular morbidity and mortality. The novel ARIC findings would suggest that renin and aldosterone profiling is valuable for risk stratification in clinical practice. Although available automated chemiluminescent assays are accurate, reproducible, and require plasma collection at room temperature, this approach still faces several challenges, including the need for knowledge of the effect of drugs on renin and aldosterone levels, the common neglect of these measurements even in hypertensive patients, and the fact that sodium intake, a major determinant of their values, is usually overlooked. These challenges must be overcome to navigate out of the perilous sea of un-personalized cardiovascular Medicine.

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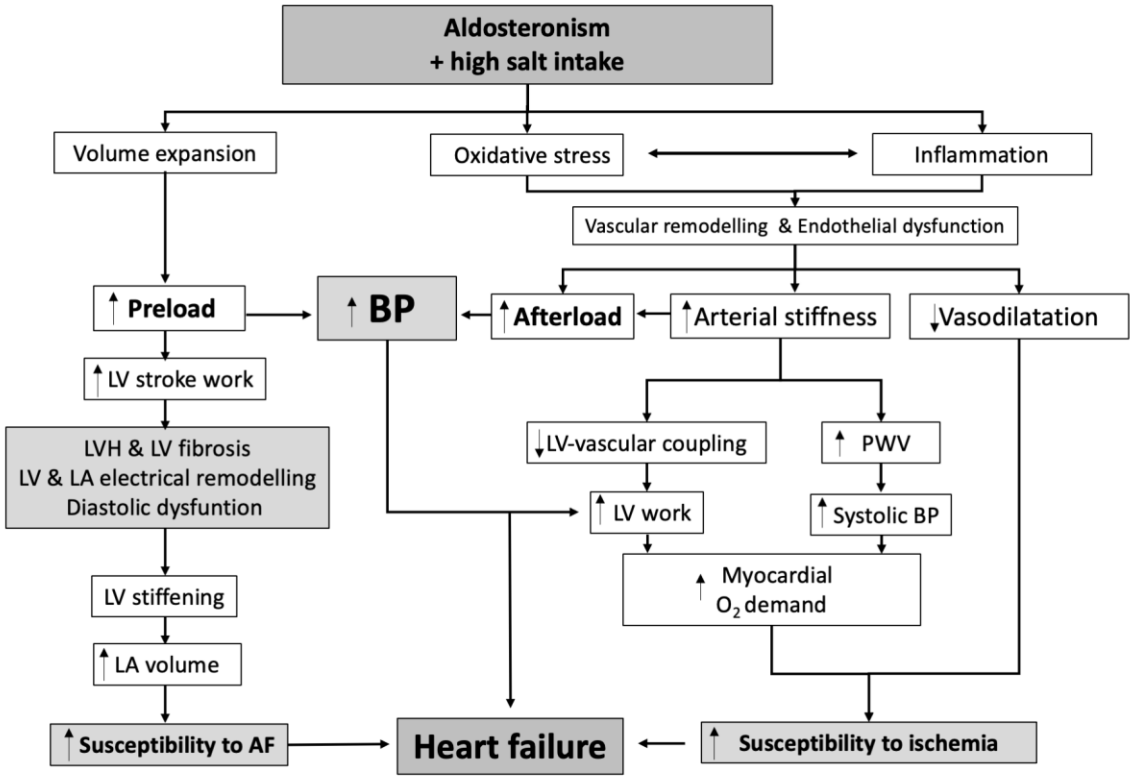

Figure legend: Sequence of events that, starting from a relative or absolute aldosterone excess in the context of a high sodium intake, increase susceptibility to atrial fibrillation (AF) and heart failure; AF itself, in the setting of a stiffer left ventricle with hypertrophy and fibrosis, increases the risk of developing heart failure. Abbreviations: BP= blood pressure, LV= left ventricle; LA= left atrium; PWV= pulse wave velocity.